

# Budget Impact Analysis of the use of emicizumab for bleeding prophylaxis in patients with Hemophilia A with inhibitors in the Brazilian Health System

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**Abstract:** Hemophilia A is a hereditary hemorrhagic disorder characterized by deficiency or dysfunction of the coagulation protein factor VIII. The standard therapy consists of factor VIII replacement, which can lead to the development of neutralizing antibodies (inhibitors), a major complication that implies a burden on patient health and the healthcare system because of the decreased quality of life and further costs with treatment. The current work was to assess the budget impact of a bispecific monoclonal antibody, for patients with inhibitors, considering the Brazilian Public System perspective. Results demonstrated high efficacy on preventing bleeds and savings of R\$ 1.5 billion in five years.

**Keywords:** Blood coagulation disorders; budget impact analysis; factor VIII; hemophilia A; public health system; resource allocation.

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## Introduction

Coagulation processes, a cascade of reactions that involve coagulation factors, is a major component of blood homeostasis, the maintenance of blood fluidity inside intact blood vessels. Blood homeostasis can be disturbed in several ways, including by the presence of hemorrhagic disorders, many of which are due to alterations in the coagulation cascade.<sup>1</sup> Congenital hemophilias are rare, inherited hemorrhagic disorders characterized by deficiency or dysfunction of specific coagulation factors that play an important role in the coagulation cascade.<sup>2</sup> Hemophilia A, the most common of these disorders, is a hereditary hemorrhagic disorder characterized by deficiency or dysfunction of the coagulation protein factor VIII and predominantly occurs in males because of its transmission through the X chromosome inherited from mothers.<sup>2,3</sup> Factor VIII deficiency or dysfunction are associated with bleeding episodes that occur after trauma or spontaneously, depending on disease severity, and that typically affect joints, muscles and other tissues.<sup>2,3</sup> The clinical severity of hemophilia A is ascertained based on standardized plasma levels of factor VIII activity, and bleeding patterns generally correspond to the degree of severity.<sup>3,4</sup> Based on levels of factor VIII activity, the severity of hemophilia A can be classified as mild, moderate, or severe. Although not as frequent as musculoskeletal bleedings, life-threatening hemorrhagic events also occur; including gastrointestinal and urinary bleedings, as well as those from central nervous system, which are the leading cause of death in patients with hemophilia.<sup>3,5</sup> In addition to these direct medical consequences, hemophilia A negatively impacts physical, psychological and social aspects of quality of life, both for patients and for their caregivers.<sup>6</sup>

Research is underway in the attempt to address the genetic defect in hemophilia A through gene therapy, but currently the disease remains incurable. Standard treatment for hemophilia A essentially consists in replacement of plasma-derived or recombinant factor VIII concentrates, which can be done episodically – also known as on-demand treatment, after the occurrence of bleedings – or prophylactically, with the appropriate dose, frequency, and number of infusions depending on the type and severity of the bleeding.<sup>2,3</sup> The major

complication of such therapy is the development of neutralizing antibodies (also called inhibitors), which is most frequent in haemophilia A.<sup>2</sup> The latter strategy is associated with reduced bleeding in comparison with the on-demand treatment,<sup>7</sup> and is also generally considered cost-effective.<sup>8</sup> Despite significant clinical gains from the use of concentrate replacement therapy over the past 20 years, the development of inhibitors is the chief complication of replacement therapy. The development of inhibitors varies according to disease severity and potentially with the source of factor VIII, but is reported to occur in 25-30% of patients with severe hemophilia A.<sup>9-11</sup> Inhibitors may lead to greater requirements or even render replacement therapy ineffective,<sup>2,12</sup> leading to medical complications, further decreasing health-related quality of life,<sup>13</sup> and substantially increasing the cost of treatment for patients with hemophilia A.<sup>14,15</sup> Immune tolerance induction (ITI), which consists in regular infusions of factor VIII to induce tolerance, is often used in the attempt to eradicate inhibitors in patients with low-titers of these antibodies.<sup>2,16</sup> For patients with high titers, the so-called bypass agents (activated prothrombin complex concentrate [aPCC] and recombinant activated factor VII concentrate [rFVIIa]) may be used; such agents circumvent the need for factor VIII by promoting coagulation through alternative pathways.<sup>12</sup> However, these strategies remain suboptimal on bleeding control, and novel agents are needed. One such agent is the bispecific monoclonal antibody emicizumab, which bridges two coagulation factors (IX and X) to restore the function of factor VIII missing in patients with hemophilia A.<sup>17</sup>

Emicizumab thus provides additional option for bleeding prophylaxis in pediatric and adult patients with or without inhibitors,<sup>18-20</sup> with potential improvement in quality of life for patients and caregivers.<sup>21</sup>

The World Federation of Hemophilia (WFH) identified 165,379 individuals with hemophilia A worldwide in 2020.<sup>22</sup> Brazil ranked third in absolute number of cases among the 120 countries submitting data to the latest WFH report, with 10,984 patients, almost 99% of whom males and nearly 21% younger than 14 years of age.<sup>22,23</sup> The

prevalence of hemophilia and the existence of specialized centers for their treatment in Brazil have served as the basis for a wealth of local publications investigating disease biology and treatment, as well as the creation of a nationwide information system dedicated to coagulation disorders.<sup>23-25</sup> Nevertheless, there is a relative paucity of information on health-economic aspects associated with hemophilia A in Brazil.<sup>26</sup> In this country, healthcare is a constitutional right provided to a large majority of the population through the Brazilian Unified Health System, *Sistema Único de Saúde* (SUS), a Universal Public Health coverage. The incorporation of novel healthcare technologies in SUS is done after a Health Technology Assessment (HTA) process, a systematic approach to evaluate the properties, effects, and impacts of health technologies in the System. One component of this assessment is budget impact analysis (BIA), which can help policy makers to evaluate the role and value of new technologies and ensure their sustainability when introduced into the Brazilian Public System, SUS.<sup>27</sup> The current study was conducted to estimate the BIA of including emicizumab for bleeding prophylaxis in patients aged up to 99 years with FVIII inhibitors in Brazil.

## Methods

### Overview of the analytical framework

The current work was done following the Guidelines for Budget Impact Analysis of Health Technologies in Brazil.<sup>28</sup> Official recommendations for BIA in Brazil include, among other provisions, the adoption of the budget administrator's perspective; a timeframe of 1 to 5 years; a comparison of reference and alternative scenarios; the expected rate of incorporation of the technology; an estimation of the target population by an epidemiological approach or by actual demand; consideration of potential factors restricting or increasing the indication; consideration of direct and averted costs, and with no adjustment for inflation or discounting.<sup>28,29</sup>

The BIA was performed considering only patients with inhibitors and developed as a macro-enabled MS Excel workbook. The analyses were carried out

through the comparison between the current scenario (Scenario 1), representing fixed distributions of therapeutic options already available in SUS, and an alternative scenario (Scenario 2), in which emicizumab becomes available for bleeding prophylaxis and has a progressively increasing uptake. The perspective considered is that of the Brazilian SUS over a 5-year horizon (2022 to 2026).

### Target population

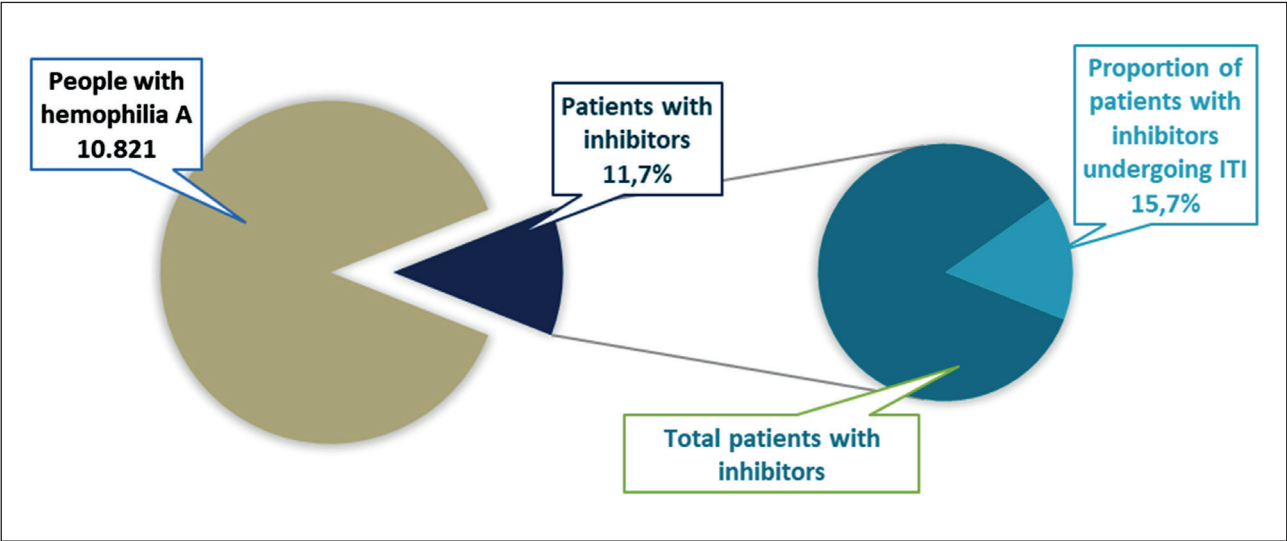
The target population is the one treated under the SUS network, and numbers of individuals are based on the data available from 2019 applicable to individuals aged 0 to 99 years old.<sup>23</sup> The prevalence of hemophilia A in Brazil in that year was 1.0/10,000 male individuals; moreover, 71.6% of cases of hemophilia A with information in Brazil are moderate or severe, 11.7% of patients have inhibitors, and 1.44% are subjected to ITI (15.7% of patients with inhibitors), as shown in figure 1. Based on these data, the following assumptions were made to quantify the target population for:

(1) In the model, 100% of patients with inhibitors were assumed to be the proportion of moderate or severe cases, a decision made after consultation with hemophilia experts based on pathophysiological and clinical knowledge.

### Comparators and treatment mix

The model for patients with inhibitors assumed patients could receive one of the following options: prophylactic and/or on-demand treatment with the bypass agents aPCC (FEIBA<sup>®</sup>, Baxter) or rFVIIIa (NovoSeven<sup>®</sup>, NovoNordisk); prophylaxis with emicizumab before initiating ITI; ITI with octocog alfa, a recombinant factor VIII concentrate (Advate<sup>®</sup>, Takeda); for ITI responders, prophylaxis and/or on-demand treatment with octocog alfa; and for ITI non-responders, prophylaxis with emicizumab and on-demand treatment with the same bypass agents as above. The specific choice of octocog alfa was made in consultation with a hematologist specialized in the treatment of pediatric hemophilia A. Moreover, this has been the preferred factor VIII concentrate under SUS.

**Figure 1.** Number of patients undergoing ITI



**Table 1.** Numerical assumptions regarding the target population (see text for data sources).

| Population (00-99 years)                                           | 2022        | 2023        | 2024        | 2025        | 2026        |
|--------------------------------------------------------------------|-------------|-------------|-------------|-------------|-------------|
| Males                                                              | 103.527.689 | 104.271.843 | 105.681.529 | 106.345.043 | 106.981.304 |
| Patients with hemophilia A                                         | 10980       | 11056       | 11129       | 11198       | 11265       |
| Patients with hemophilia A with inhibitors                         | 1.282       | 1.291       | 1.299       | 1.307       | 1.315       |
| Estimative of hemophilia A patients with inhibitors undergoing ITI | 201         | 202         | 203         | 205         | 206         |
| ITI non-responders                                                 | 60          | 61          | 61          | 62          | 62          |

ITI, immune tolerance induction.

(2) The annual population growth based on official nationwide projections for the Brazilian population by sex and age between 2010 and 2060.<sup>30</sup> Table 1 presents the estimates of the number of patients considered by the model.

For the Scenario 1, it was assumed that bypass agents (57.6% of cases with aPCC, and 42.4% with recombinant activated factor VII concentrate - rFVIIa) were used prophylactically in 75% and upon demand in 25% of cases, whereas Scenario 2 considered gradual incorporation of emicizumab from 60% to 80% in 5 years, gradual decrease in prophylactic use of bypass agents from 30% to 10% over 5 years, and fixed rate of use of these agents at 10%. Among patients using emicizumab, it was considered 100%

to be treated with factor VII concentrate when bleeding.

Sensitivity analyses were conducted considering a more conservative scenario with a fixed incorporation of emicizumabe 30% in 5 years and a more aggressive scenario one with fixed 80% among the 5 year span, to highlight the difference in budget impact depending on the adherence of prophylaxis with emicizumab.

### Resource utilization and costs

Quantification of annual units of infusion products took into account the administration schedule recommended in each label, as well as the average

annual use of each product and the average weight for each age group, the latter shown in Table 2.<sup>31</sup> Since bleeding events require on-demand treatment with bypass agents, the estimation of resource utilization was also based on expected annualized bleeding rates (ABR) (treated bleeds), a common metric used to assess treatment outcomes in hemophilia A. For the pediatric population, the HAVEN 2<sup>32</sup> was used to determine the ABR under emicizumab for the prophylactic treatment of patients with hemophilia A inhibitors, and for adults, the HAVEN 1<sup>18</sup>. For ABR values for other types of prophylactic and on-demand treatment, besides HAVEN 1 and 2, data from the non-intervention study nested within the HAVEN 2 trial were also used.<sup>33</sup> The ABR values used in the models are shown in Table 3.

All costs were modeled in Brazilian Reais (BRL). Only direct costs of infusion products were considered, since these are usually provided to patients or guardians for administration at home. Regarding the cost for emicizumab, the models considered the price listed with the ministry of health with tax exemption. For the costs of comparators, prices paid in the latest procurement available were identified in the Health Price Database (Table 4).<sup>34</sup> No discounting or adjustments for inflation were applied, since these economic adjustments are not justified in this short-time horizon, in agreement with the Guidelines for Budget Impact Analysis of Health Technologies in Brazil.<sup>28</sup>

**Table 2.** Average weight in each age group considered in the model.<sup>30</sup>

| Age group (only for males) | Average weight (Kg) |
|----------------------------|---------------------|
| 0 to 99 years              | 61.93               |
| <1 year                    | 8.1                 |
| 1 year                     | 11.5                |
| 2 years                    | 13.9                |
| 3 years                    | 16.0                |
| 4 years                    | 18.0                |
| 5 years                    | 19.9                |
| 6 years                    | 22.2                |
| 7 years                    | 25.1                |
| 8 years                    | 27.7                |
| 9 years                    | 31.6                |
| 10 years                   | 33.4                |
| 11 years                   | 36.8                |
| 12 years                   | 42.0                |
| 13 years                   | 47.40               |
| 14 years                   | 52.30               |
| 15 years                   | 57                  |
| 16 years                   | 60.10               |
| 17 years                   | 63.10               |
| 18 years                   | 65.30               |
| 19 years                   | 65.90               |
| 20 - 24 years              | 69.40               |
| 25 - 29 years              | 72.70               |
| 30 - 34 years              | 74.20               |
| 35 - 54 years              | 74.60               |
| 55 - 64 years              | 73.10               |
| 64 - 74 years              | 70.30               |
| 75 years or more           | 66.80               |

**Table 3.** Annualized bleeding rates (ABR) used in the models - treated bleeds

| Intervention                           | ABR       |        | Source                                           |
|----------------------------------------|-----------|--------|--------------------------------------------------|
|                                        | Pediatric | Adults |                                                  |
| Emicizumab                             | 0.3       | 2,9    | HAVEN 1 <sup>18</sup> , HAVEN 2 <sup>31</sup>    |
| Prophylaxis with bypass agents         | 21.1      | 15,7   | HAVEN 1 <sup>18</sup> , HAVEN 2 <sup>31,33</sup> |
| On-demand treatment with bypass agents | 23.3      | 23.3   | HAVEN 1 <sup>18</sup>                            |

**Table 4.** Unit cost of infusion products considered in the models.

| Product    | Purchasing Institution                     | Date of Purchase | Unit Cost (BRL) | Unit |
|------------|--------------------------------------------|------------------|-----------------|------|
| NovoSeven® | Hospital Naval de Recife*                  | 30 June 2020     | 3.59            | µg   |
| FEIBA®     | Hospital de Clínicas do Triângulo Mineiro* | 28 July 2021     | 1.64            | U    |
| Advate®    | Departamento de Logística em Saúde*        | 28 December 2021 | 1.10            | U    |
| Hemcibra®  | -                                          | -                | 174.05**        | mg   |

\* Source, Health Price Database.<sup>35</sup> \*\*considering tax exemption

## Results

The number of patients treated per therapeutic option in each scenario are shown in Table 5.

**Table 5.** Number of patients treated per therapeutic option by year

| Product                                       | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|-----------------------------------------------|--------|--------|--------|--------|--------|
| <i>Scenario 1</i>                             |        |        |        |        |        |
| aPCC prophylaxis                              | 467    | 471    | 473    | 476    | 479    |
| aPCC on demand                                | 156    | 157    | 158    | 159    | 160    |
| rFVIIa prophylaxis                            | 344    | 346    | 349    | 351    | 353    |
| rFVIIa on demand                              | 114    | 115    | 116    | 117    | 117    |
| FVIII concentrate (ITI)                       | 201    | 202    | 203    | 205    | 206    |
| FVIII (ITI responders)                        | 141    | 141    | 142    | 144    | 144    |
| emicizumab with rFVIIa for bleeding treatment | 0      | 0      | 0      | 0      | 0      |
| <i>Scenario 2</i>                             |        |        |        |        |        |
| aPCC prophylaxis                              | 187    | 126    | 94     | 63     | 64     |
| aPCC on demand                                | 62     | 63     | 63     | 63     | 64     |
| rFVIIa prophylaxis                            | 137    | 92     | 70     | 47     | 47     |
| rFVIIa on demand                              | 46     | 46     | 47     | 47     | 47     |
| FVIII concentrate (ITI)                       | 201    | 202    | 203    | 205    | 206    |
| FVIII (ITI responders)                        | 141    | 141    | 142    | 144    | 144    |
| emicizumab with rFVIIa for bleeding treatment | 649    | 762    | 822    | 822    | 877    |

**Table 6.** Annual and accumulated projected expenditures (BRL) for patients with hemophilia A aged 0-99 years with inhibitors.

| Scenarios and products                                      | Year 1                  | Year 2                  | Year 3                  | Year 4                  | Year 5                  | TOTAL                   |
|-------------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| <i>Scenario 1 (base case)</i>                               |                         |                         |                         |                         |                         |                         |
| Bypass agents – Prophylaxis plus bleeding episodes (75%)    | R\$1.253.384.421        | R\$1.261.637.396        | R\$1.271.010.029        | R\$1.278.511.297        | R\$1.286.012.565        | R\$6.350.555.708        |
| Bypass agents – On-demand treatment (25%)                   | R\$206.502.972          | R\$208.203.248          | R\$209.903.524          | R\$211.603.799          | R\$211.905.503          | R\$1.048.119.046        |
| Factor VIII concentrate – For ITI, prophylaxis and bleeding | R\$80.597.772           | R\$80.898.766           | R\$81.342.299           | R\$82.530.358           | R\$82.530.358           | R\$407.899.553          |
| Emicizumab (before ITI) plus bypass agents for bleeding     | 0                       | 0                       | 0                       | 0                       | 0                       | 0                       |
| Emicizumab (after ITI) plus bypass agents for bleeding      | R\$57.781.957           | R\$58.744.989           | R\$58.744.989           | R\$59.708.022           | R\$59.708.022           | R\$294.687.980          |
| <b>Total</b>                                                | <b>R\$1.598.267.122</b> | <b>R\$1.609.484.399</b> | <b>R\$1.621.000.841</b> | <b>R\$1.632.353.477</b> | <b>R\$1.640.156.448</b> | <b>R\$8.101.262.287</b> |
| <i>Scenario 2 (emicizumab incorporated gradually)</i>       |                         |                         |                         |                         |                         |                         |
| Bypass agents – Prophylaxis plus bleeding episodes          | R\$499.930.266          | R\$336.037.836          | R\$254.275.596          | R\$170.641.991          | R\$171.393.698          | R\$1.432.279.387        |
| Bypass agents – On-demand treatment                         | R\$83.039.936           | R\$83.341.640           | R\$84.740.212           | R\$84.740.212           | R\$85.041.916           | R\$420.903.915          |
| Factor VIII concentrate – For ITI, prophylaxis and bleeding | R\$80.597.772           | R\$80.898.766           | R\$81.342.299           | R\$82.530.358           | R\$82.530.358           | R\$407.899.553          |
| Emicizumab (before ITI) plus bypass agents for bleeding     | R\$658.584.296          | R\$731.282.895          | R\$784.861.369          | R\$841.867.298          | R\$843.060.999          | R\$3.859.656.857        |
| Emicizumab (after ITI) plus bypass agents for bleeding      | R\$57.781.957           | R\$58.744.989           | R\$58.744.989           | R\$59.708.022           | R\$59.708.022           | R\$294.687.980          |
| <b>Total</b>                                                | <b>R\$1.379.934.227</b> | <b>R\$1.290.306.126</b> | <b>R\$1.263.964.465</b> | <b>R\$1.239.487.881</b> | <b>R\$1.241.734.993</b> | <b>R\$6.415.427.692</b> |

ITI, immune tolerance induction.

These results indicate that, at the moment, the projected yearly expenditure will be more than 1.5 billion reais, with a total of R\$ 8.101.262.287 over the 5-year period modeled. With the gradual incorporation of emicizumab this value will be R\$6.415.427.692, representing a reduction of 20%. The BIA comparing both scenarios each year is depicted in Figure 2.

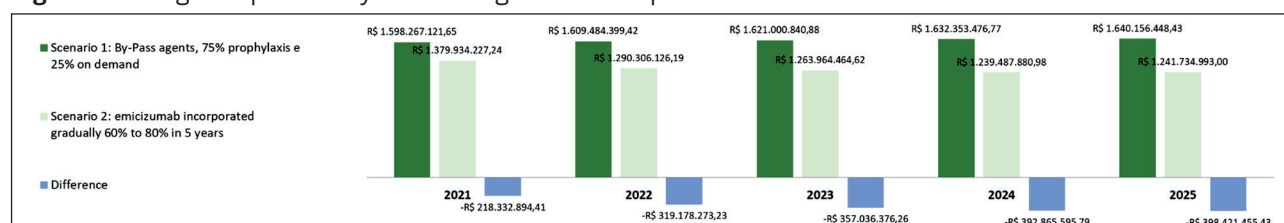
The results from the model for Scenario 1, representing the current reimbursement situation for the treatment of hemophilia A with inhibitors, and Scenario 2, considering the gradual incorporation of

emicizumab are shown in Table 6.

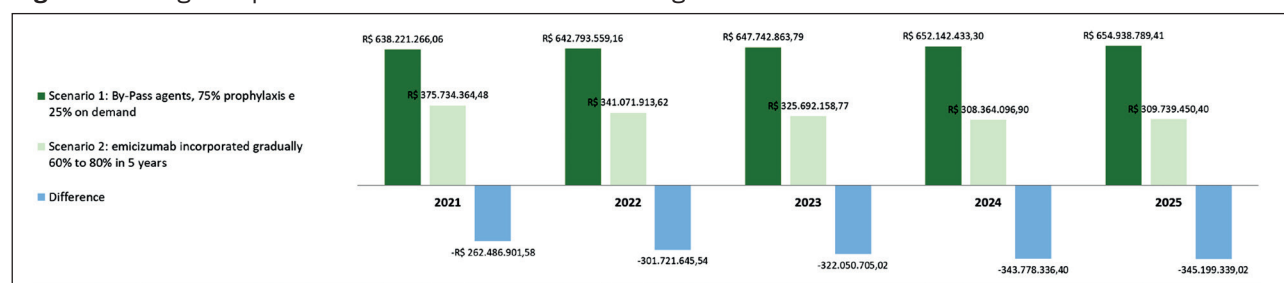
When analyzing only costs incurred with the treatment of bleeding, the incorporation of emicizumab would result in a projected accumulated savings of R\$1.575.236.927 in 5 years (Figure 3).

Sensitivity analysis for Scenario 2, considering a conservative and an aggressive market share is available on table 7. Both are cost-saving when compared to the base case, but the aggressive market share scenario represents further saving with a difference of 1.379 billion reais.

**Figure 2.** Budget impact analyses of the gradual incorporation of emicizumab



**Figure 3.** Budget impact attributable to avoided bleeding



**Table 7.** Annual and accumulated projected expenditures (BRL) for patients with hemophilia A aged 0-99 years with inhibitors, sensitivity analyses (conservative and aggressive scenario).

| Scenarios and products                                      | Year 1                  | Year 2                  | Year 3                  | Year 4                  | Year 5                  | TOTAL                   |
|-------------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| <i>Conservative Scenario</i>                                |                         |                         |                         |                         |                         |                         |
| Bypass agents – Prophylaxis plus bleeding episodes (55%)    | R\$918.850.000          | R\$925.599.560          | R\$932.349.121          | R\$936.475.608          | R\$943.225.169          | R\$4.656.499.458        |
| Bypass agents – On-demand treatment (15%)                   | R\$124.559.904          | R\$124.861.608          | R\$126.260.180          | R\$126.561.884          | R\$126.863.587          | R\$629.107.163          |
| Factor VIII concentrate – For ITI, prophylaxis and bleeding | R\$80.597.772           | R\$80.898.766           | R\$81.342.299           | R\$82.530.358           | R\$82.530.358           | R\$407.899.553          |
| Emicizumab (before ITI) plus bypass agents for bleeding     | R\$328.784.764          | R\$310.876.321          | R\$312.711.850          | R\$314.612.048          | R\$316.512.245          | R\$1.583.497.228        |
| Emicizumab (after ITI) plus bypass agents for bleeding      | R\$57.781.957           | R\$58.744.989           | R\$58.744.989           | R\$59.708.022           | R\$59.708.022           | R\$294.687.980          |
| <b>Total*</b>                                               | <b>R\$1.510.574.397</b> | <b>R\$1.500.981.245</b> | <b>R\$1.511.408.439</b> | <b>R\$1.519.887.920</b> | <b>R\$1.528.839.382</b> | <b>R\$7.571.691.382</b> |
| <i>Aggressive Scenario</i>                                  |                         |                         |                         |                         |                         |                         |
| Bypass agents – Prophylaxis plus bleeding episodes (10%)    | R\$167.267.210          | R\$168.018.918          | R\$170.641.991          | R\$170.641.991          | R\$171.393.698          | R\$847.963.808          |
| Bypass agents – On-demand treatment (10%)                   | R\$83.039.936           | R\$83.341.640           | R\$84.740.212           | R\$84.740.212           | R\$85.041.916           | R\$420.903.915          |
| Factor VIII concentrate – For ITI, prophylaxis and bleeding | R\$80.597.772           | R\$80.898.766           | R\$81.342.299           | R\$82.530.358           | R\$82.530.358           | R\$407.899.553          |
| Emicizumab (before ITI) plus bypass agents for bleeding     | R\$877.774.139          | R\$827.924.087          | R\$833.624.680          | R\$838.310.505          | R\$843.060.999          | R\$4.220.694.409        |
| Emicizumab (after ITI) plus bypass agents for bleeding      | R\$57.781.957           | R\$58.744.989           | R\$58.744.989           | R\$59.708.022           | R\$59.708.022           | R\$294.687.980          |
| <b>Total</b>                                                | <b>R\$1.266.461.014</b> | <b>R\$1.218.928.400</b> | <b>R\$1.229.094.170</b> | <b>R\$1.235.931.088</b> | <b>R\$1.241.734.993</b> | <b>R\$6.192.149.665</b> |

ITI, immune tolerance induction.

## Discussion

Hemophilia is a rare disease associated with a high financial burden on healthcare systems. Despite significant advancements of replacement therapy over the past 20 years, the development of inhibitors is the main complication that can increase up to 3 times the cost of patient management and impacts the quality of life of patients and caregivers<sup>35</sup>.

The reimbursement of approved agents under the Brazilian SUS is dependant on many factors and conditioned on economic consideration, including the results of a BIA, which provides the required operational financial forecasts.<sup>36</sup>

With this study we aimed to understand what an extension of the availability of emicizumab to all patients with inhibitors would mean to the budget.

The results of the current study can be summarized as follows: with the gradual incorporation of emicizumab to the inhibitor population under SUS, there is a saving of 20% on the predicted value over the next 5 years. Also, the sensitivity analysis of a conservative scenario and an aggressive one shows that in any case, the adoption of emicizumab results in cost saving that is proportional to its adherence. The bigger the market share among the inhibitor population, the smaller the budget needed.

These findings are in line with various studies, with different analytical frameworks and target populations, demonstrating emicizumab's potential in financial sustainability. From the perspective of payers and the society in the US, and considering clinical outcomes beyond bleeding as well as the direct and indirect costs from prophylaxis with emicizumab in hemophilia A, an economic model suggested that in addition to lower costs, emicizumab confers additional clinical benefits – fewer bleeding events and delayed onset of arthropathy and of inhibitors – when compared with factor VIII concentrate for children starting prophylaxis at 1 year of age.<sup>37</sup>

In a study under the perspective of the Italian National Health Service, emicizumab prophylaxis was considered a cost-saving intervention for patients with inhibitors, with predicted reduction of costs in all scenarios within de probabilistic sensitivity analysis.<sup>38</sup> Similarly, in France, emicizumab was found to be cost-effective among patients with

hemophilia A with inhibitors as well, with the only non-dominant scenario of patients were 100% on demand treatment with by-pass agents but associated with ABR increased up to 104.6.<sup>39</sup> Positive results were also reported using national insurance claims and epidemiological data from Korea, as well as information obtained from the literature and from expert surveys with hematologists in that country.<sup>40</sup> In the study from Korea, emicizumab was found to be dominant over comparators, with predicted prevention of bleedings, QALY gains and reduced costs in base-case and sensitivity analyses. A BIA conducted considering the public healthcare system in Malaysia, concluded that the 5-year budget impact was reasonable and possibly cost-saving.<sup>41</sup> Finally, dominance for emicizumab over bypass agents was also reported in a study from Iran, although in this case for a more selected target population of patients with factor VIII inhibitors and an estimated ABR of 18 and above.<sup>42</sup>

Limitations of the study: the present BIA was carried out using what we believe to be the most accurate and updated epidemiological data available from Brazil. Nevertheless, BIA is predicated on models, which in turn are based on assumptions. As a result, differences between the current estimates and historical budget records may occur, and they may reflect several sources of inconsistencies, particularly underdiagnosis or poor therapeutic adherence in the healthcare setting investigated.

In conclusion, the current study provides important information on the projected budget impact of extending reimbursement of emicizumab patients hemophilia A aged 0-99 years old treated under the Brazilian SUS. The results suggest that the adoption of emicizumab would result in cost savings due to the additional efficacy on preventing bleeds, as shown in figure 2.

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