

COST-MINIMIZATION AND BUDGET IMPACT ANALYSIS OF VENETOCLAX VERSUS ACALABRUTINIB FOR 1L AND R/R CHRONIC LYMPHOCYTIC LEUKEMIA IN THE BRAZILIAN PUBLIC HEALTHCARE SYSTEM

Mattos ER ¹, Follador W ², Campos L ³, Antunes RC ³, Biella C ³

¹Amaral Carvalho Hospital, Jaú, SP, Brazil; ²Sano-Efiko Health Consulting, São Paulo, SP, Brazil; ³AbbVie, São Paulo, SP, Brazil

OBJECTIVE

To demonstrate the economic advantages of using venetoclax (plus obinutuzumab [VenO] or rituximab [VenR]) vs acalabrutinib monotherapy (Acala) in the first line (1L) and relapse or refractory (R/R) chronic lymphocytic leukemia (CLL) treatment under the Brazilian public healthcare system (SUS).

CONCLUSIONS

VenO and VenR have shown evidence of being the only fixed duration treatment regimens that achieve a sustained CLL remission when compared to continuous Acalabrutinib monotherapy, with similar prices and more convenient treatment for patients and healthcare providers.

Ven-based regimens imply in cost-savings when compared to Acalabrutinib, while the clinical outcomes remain favorable.

REFERENCES

- Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification, and treatment. *Am J Hematol.* 2019;94:1266-1287.
- Scarfó L, Ferreri AJM, Ghia P. Chronic lymphocytic leukaemia. *Crit Rev Oncol Hematol.* Elsevier Ireland Ltd; 2016 Aug;104:169–82.
- Rodrigues CA, Gonçalves MV, Ikoma MRV, Lorand-Metze I, Pereira AD, Farias DLC de, et al. Diagnosis and treatment of chronic lymphocytic leukemia: recommendations from the Brazilian Group of Chronic Lymphocytic Leukemia. *Rev Bras Hematol Hemoter.* 2016;38(4):346–57.
- Hallek M, Cheson BD, Catovsky D, Caligaris-cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008 Jun 15;111(12):5446–56.
- Po-Huang Chen 1 , Ching-Liang Ho, et al. Treatment Outcomes of Novel Targeted Agents in Relapse/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Network Meta-Analysis. *J. Clin. Med.* 2019 May, 8:737.
- Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Depto de Regulação, Avaliação e Controle. Coordenação Geral de Gestão dos Sistemas de Informações em Saúde. Manual de Bases técnicas da Oncologia - SIA/SUS Sistema de Informações Ambulatoriais. Oncologia – 30a edição. Agosto de 2022. Available in: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document//manual_oncologia_29a_edicao_junho_2022.pdf
- Molica S, Giannarelli D, Montserrat E. Comparison Between Venetoclax-based and Bruton Tyrosine Kinase Inhibitor-based Therapy as Upfront Treatment of Chronic Lymphocytic Leukemia (CLL): A Systematic Review and Network Meta-analysis. *Clin Lymphoma Myeloma Leuk.* 2020 Oct 29:S2152-2650(20)30579-6.
- Byrd JC et al. Byrd JC, Hillmen P, Ghia P, Kater AP, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol.* 2021 Nov 1;39(31):3441-3452. doi: 10.1200/JCO.21.01210.
- Mato A et al
- Ministério da Saúde (Brasil). Agência Nacional de Vigilância Sanitária (ANVISA). Listas de preços de medicamentos [Internet]. 2020. Available from: <http://portal.anvisa.gov.br/listas-de-precos>.
- Technology appraisal guidance TA663. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia. Published 9December 2020, available in: <https://www.nice.org.uk/guidance/ta663/chapter/1-Recommendations>
- Food and Drug Administration. Gazvya (obinutuzumab) label 2017.
- Ghia P et al., *J Nlin Onc* 2020.
- CALQUENCE ® (acalabrutinib) [Bula]
- Banco Central do Brasil. 2022. Available in: <https://www.bcb.gov.br/>
- Burger, J.A., Barr, P.M., Robak, T. et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia* 34, 787–798 (2020).

DISCLOSURES

Financial support for this study was provided by AbbVie. AbbVie participated in the analysis, interpretation of data, review, and approval of the publication. All authors contributed to the development of the publication and maintained control over the final content.

Ederson Mattos is a speaker for AbbVie, Janssen, BMS Celgene, Amgen, Astellas , Pfizer, Takeda, Farmocômica, MSD, Novartis, EusaPharma and serves as Advisory Board to AbbVie, BMS Celgene, Amgen, Janssen and Novartis. Wilson Follador serves as consultant for Abbott, Abbvie, Pfizer, Sanofi, Merck, AstraZeneca, Janssen, Novartis, GBT, Biontronik, Edwards, Pint Pharma, FIC, Amny e Ultragenyx. Laura Campos, Rafael Antunes Coutinho and Carla de Agostino Biella are employees of AbbVie and may own AbbVie stock.

INTRODUCTION

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative disease characterized by the persistency of a minimum of $5 \times 10^9/L$ type B monoclonal lymphocytes, which can accumulate in peripheral blood, lymph nodes, blood marrow and spleen. More frequent in elders and considered a rare disease, CLL has a global incidence between <1 and 5.5 cases per 100,000 inhabitants. (1,2)

CLL is an indolent disease, in which about 60% of patients at the time of diagnosis may be asymptomatic, while other 40% may have several unespecific clinical and laboratory changes. (3,4) Patients with IGHV unmutated may present faster disease progression compared to IGHV mutated and presence of 17p deletion, TP53 mutation may indicate worse clinical results specially when treated with immunochemotherapy.(1)

METHODS

Similar efficacy between VenO, VenR and Acala on Overall Survival (OS) and Progression-Free Survival (PFS) were demonstrated in both lines (1L and R/R) by two network meta-analysis (7). The same similarity was shown in a head-to-head trial comparing Acala vs ibrutinib (8) and by an indirect comparison of VenR vs B-cell receptor inhibitors (9). Assuming similar efficacy, a cost-minimization model was developed, comparing these treatment options taking the drugs acquisition costs (2022 Brazilian list price [10] – Table 1) and comparing the costs per patient over 60 months. A Budget Impact Analysis (BIA) was developed considering the estimative for the number of high-risk patients to be treated by the Brazilian public healthcare system (SUS) (3,183 patients/year for 1CLL and 694 patients/year for R/R).

Figure 1 demonstrate treatment schemes. Figure 1A - Obinutuzumab starts with 100mg on Day 1, ramping up to 900mg on Day 2 and 1000mg on Day 8 and 15 (cycle 1) and continue with 100mg in each Day 1 until end of the 6th month (cycles 2 to 6).(11) The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400mg daily for 1 week), thereafter continuing at 400mg daily until completion of cycle 12.

Figure 1 A. Treatment scheme: venetoclax + obinutuzumab

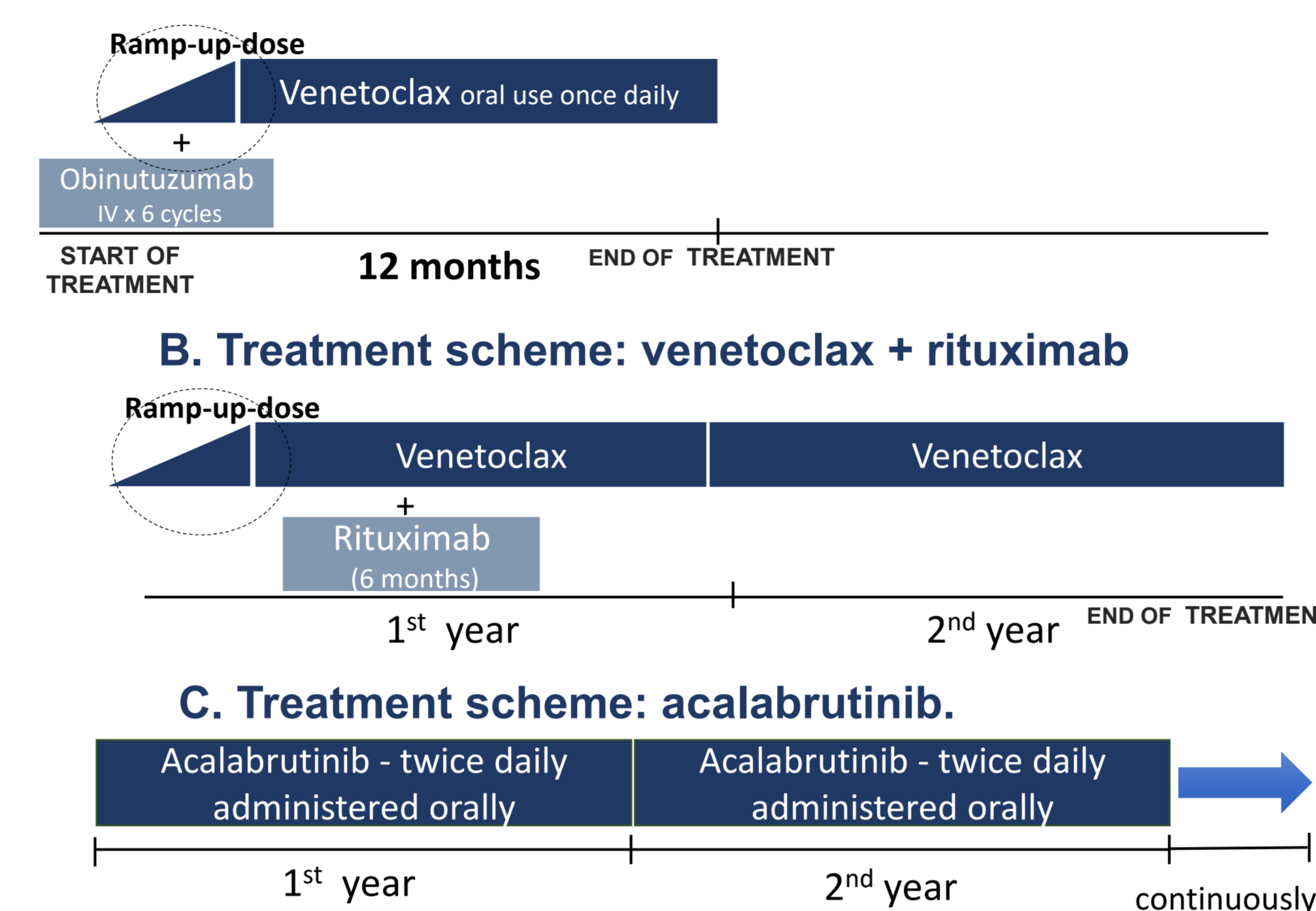


Table 1. Price of drugs and monthly treatment costs.

Drugs	SKU	List Price (PF18%) *	Dosage	Monthly treatment costs **
Venetoclax	10mg, 50mg and 100mg tablets (start-kit)	USD 1,821.46 BRL 9,471.60	1 st month (start-kit)	USD 1,821.46
	100 mg x 120 tablets	USD 8,439.20 BRL 43,883.82	400 mg (maintenance dosage)	USD 8,439.20
Obinutuzumab	1000 mg IV x 40ml per bottle	USD 4,861.30 BRL 25,278.74	1 st Cycle: 3,000 mg (month 1) 2-6 Cycles: 1,000 mg (2-6)	USD 14,583.90 USD 4,861.30
	Rituximab	10 mg/mL x 10 mL per bottle	USD 615.65 BRL 3,201.39	1 st Cycle: 375 mg/m ² 2-6 Cycles: 500 mg/m ²
Acalabrutinib	100 mg x 60 tablets	USD 9,166.70 BRL 47,666.82	200 mg (fixed dose)	USD 7,252.71

*All costs are presented in reais (RBL) and American dollars (USD).**Currency exchange rate used was BRL 5.20 to USD 1.00, according to last 60 days average-price (08/12/2022 to 10/11/2022)(15).

Based on epidemiological parameters, the projection of CLL population eligible for treatment with venetoclax + obinutuzumab and acalabrutinib is shown in Table 2.The projection of CLL population eligible for treatments vs acalabrutinib is shown in Table 2.

Table 2. Projection of eligible population for 1L CLL treatment with venetoclax + obinutuzumab and R/R CLL treatment with venetoclax + rituximab and acalabrutinib (2022-2026)

Year	2022	2023	2024	2025	2026
1L CLL					
General population	5,211	5,245	5,277	5,308	5,338
With 17p deletion or IGHV non-mutated	3,205	3,225	3,245	3,264	3,283
Without 17p deletion or IGHV mutated	2,006	2,019	2,032	2,044	2,055
R/R CLL					
General population	2,347	2,361	2,375	2,388	2,400
With 17p deletion or IGHV non-mutated	704	708	712	716	720
Without 17p deletion or IGHV mutated	1,643	1,653	1,662	1,672	1,680

Table 3. Market share – reference and projected scenarios for 1L or R/R CLL

Year	2023	2024	2025	2026	2027
Reference scenario 1L CLL					
<i>Venetoclax + Obinutuzumab</i>	0%	0%	0%	0%	0%
<i>Acalabrutinib</i>	100%	100%	100%	100%	100%
Projected scenario 1L CLL					
<i>Venetoclax + Obinutuzumab</i>	100%	100%	100%	100%	100%
<i>Acalabrutinib</i>	0%	0%	0%	0%	0%
Reference scenario R/R CLL					
<i>Venetoclax + rituximab</i>	0%	0%	0%	0%	0%
<i>Acalabrutinib</i>	100%	100%	100%	100%	100%
Projected scenario R/R					
<i>Venetoclax + rituximab</i>	100%	100%	100%	100%	100%
<i>Acalabrutinib</i>	0%	0%	0%	0%	0%

Among therapies available for CLL treatment, regimes based on venetoclax (oral therapy), in combination with obinutuzumab for 1L and in combination with rituximab for R/R patients, are fixed duration therapies (Figure 1A-B) that targets the BCL-2 (B-Cell Lymphoma 2) inhibitor, exhibit significant apoptotic activity. Acalabrutinib that is also an oral administered, inhibitor of Bruton's tyrosine kinase, is a continuous treatment used until disease progression or unacceptable toxicity (Figure 1C). (5)

Oncology financing in Brazilian Public Healthcare System (SUS) works through a Diagnosis Related Group reimbursement system (called APAC) defined by cancer type, disease stage and line of treatment. Public hospitals have the autonomy to define their treatment protocols as long as they fit the reimbursement ticket of the APAC. (6)

A Budget Impact Analysis was developed considering the estimative for the number of high-risk patients to be treated (3,183 patients/year for 1CLL and 694 patients/year for R/R).

A yearly discontinuation rate of 10.5% was applied from 2023 to 2027 to acalabrutinib continuous therapy, based on IBTKs phase III randomized trial (16). Discontinuation rate was applied for VenO once the treatment duration is 12 months and authors opted for a more conservative approach on VenO and VenR costs.

RESULTS

Table 4. Annual treatment cost (RBL/USD).

Drugs	Treatment costs of 1 st year		Treatment costs of 2 nd year	
1L CLL				
Venetoclax + obinutuzumab	BRL 650,539.71	USD 125,103.79	-	
Acalabrutinib	BRL 572,001.85	USD 110,000.36	BRL 572,001.85	USD 110,000.36
R/R CLL				
Venetoclax + rituximab	BRL 452,341.47	USD 86,988.74	BRL 413,227.60	USD 79,466.85
Acalabrutinib	BRL 448,849.85	USD 86,317.28	BRL 448,849.85	USD 86,317.28

The cost-minimization analysis in a 24-month period demonstrates VenO as the most economic alternative compared to Acalabrutinib in 1L CLL treatment, with savings of about USD 110,000.36 per patient (100%). In the same period VenR compared to Acalabrutinib in R/R CLL the costs savings were USD 6,850.43 per patient (8%).

Table 5. Results of 1L-CLL cost-minimization analysis (per patient) – 60 months.

	Venetoclax + obinutuzumab	Acalabrutinib	Incremental	% of savings		
Cost of treatment	BRL 650,539.71	USD 125,103.79	BRL 2,860,009.23	USD 550,001.78	-USD 424,897.98	77%

Table 6. Results of R/R-CLL cost-minimization analysis (per patient) – 56 months.

	Venetoclax + rituximab	Acalabrutinib	Incremental	% of savings		
Cost of treatment	BRL900,004.70	USD 173,077.83	BRL3,141,948.94	USD 604,220.95	-USD 431,143.12	71%

For 1L-CLL treatment, the 60 months direct costs of treatment show that VenO results in cost savings up to \$ 424,898 (-77%) per patient; For R/R-CLL, the 56 months direct costs of treatment, VenR results in cost savings up to \$ 431,143 (-71%) per patient, when compared to Acalabrutinib. These savings tend to be higher the longer the duration of treatment.

BIA showed savings of more than 8 billion and 700 million in 5 years, for 1L and R/R-CLL treatments, respectively.

Figure 2. Venetoclax + obinutuzumab vs Acalabrutinib in CLL 1L - accumulated costs (USD) comparison: 1 year and from 1st to 5th year.

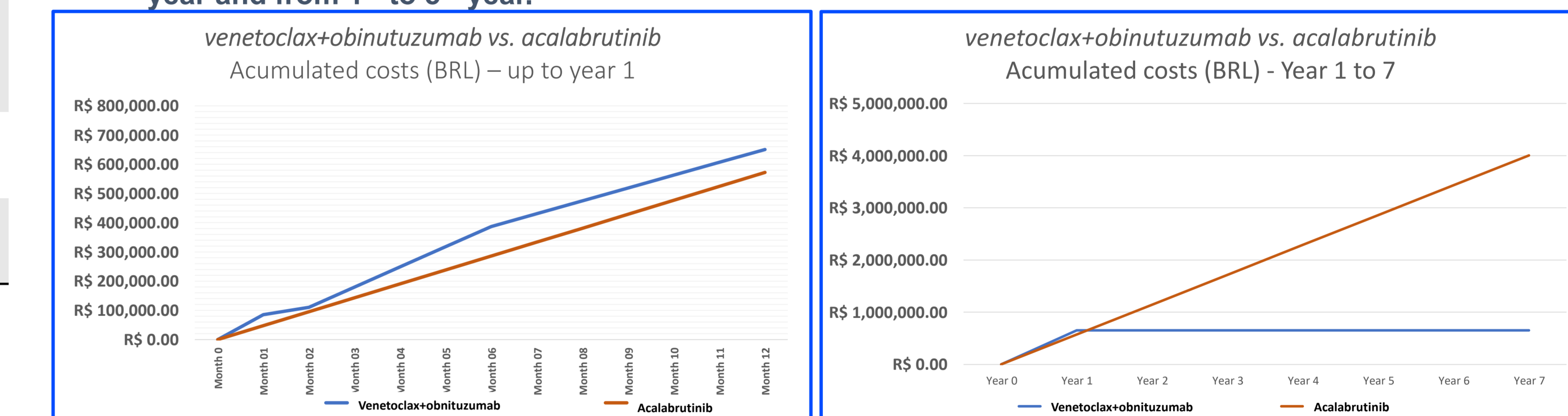


Table 7. Patients in treatment – total population.

Year	2023	2024	2025	2026	2027
Reference scenario 1L CLL					
<i>Ibrutinib</i>	5,211	9,908	14,145	17,968	21,418
Projected scenario 1L CLL					
<i>Acalabrutinib</i>	5,211	9,908	14,145	17,968	21,418
<i>Venetoclax + Obinutuzumab</i>	5,211	5,245	5,277	5,308	5,338
Reference scenario R/R CLL					
<i>Ibrutinib</i>	2,329	2,344	2,359	2,373	2,386
Projected scenario R/R CLL					
<i>Acalabrutinib</i>	2,329	4,359	6,129	7,675	9,024
<i>Venetoclax + rituximab</i>	2,329	4,289	5,940	5,977	6,012

As observed, the number of patients treated with VenO is stable over years, a consequence of its 12-month finite duration dosage, though representing a more predictable and cost-saving treatment option while acalabrutinib presents the cumulative effect related to a continuous treatment (Table 7).

The budget impact analysis showed savings of more than USD 1,6 billion (RBL 8 billion) for 1L CLL treatment and USD 138 million (RBL 700 million) for R/R CLL treatment in 5 years (Table 8).

Table 8. Budget impact (in USD) – High-risk patients.

	2023	2024	2025	2026	2027
1L CLL					
Projected	250,978,151.35	252,602,947.50	254,163,269.04	255,657,222.31	257,083,021.15
Reference	220,678,251.54	419,613,925.77	599,033,302.31	760,927,236.73	907,075,974.04
Incremental	30,299,899.81	-167,010,978.08	-344,870,033.27	-505,270,014.42	-649,992,952.88
R/R CLL					
Projected	60,785,018.85	107,545,206.15	111,449,623.27	112,120,594.04	112,761,968.65
Reference	60,315,819.81	112,879,479.81	158,722,026.92	198,734,861.54	233,688,615.58
Incremental	469,198.85	-5,334,273.65	-47,272,403.85	-86,614,267.31	-120,926,646.92