ARTIGO ORIGINAL
ORIGINAL ARTICLE

Cost-effectiveness analysis of biologics in the treatment of moderate to severe psoriasis in the private healthcare system of Brazil

Análise de custo efetividade dos medicamentos biológicos no tratamento da psoríase moderada a grave no sistema de saúde suplementar brasileiro

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Keywords:
psoriasis, biologic treatment, cost-effectiveness, private healthcare market.

ABSTRACT

Objetive: to estimate the cost per responder of biologic treatment of moderate to severe psoriasis in the Brazilian private healthcare system. **Methods:** Four biologics are approved in Brazil for the treatment of moderate to severe psoriasis, adalimumab, etanercept, infliximab, and ustekinumab. Considering the on-label dosing, yearly treatment costs were calculated based on the official CMED price per vial. A recent metanalysis by Reich *et al*. was used to gather the probability of achieving a PASI 75 response for each treatment, considering the 95% confidence interval. To estimate the impact of biologic treatment of moderate to severe psoriasis, it was assumed a hypothetical budget of R$ 1 million. **Results:** Ustekinumab has the lowest treatment cost, even considering the higher incidence of tax, in both induction and maintenance years compared to the remaining biologics. Etanercept has the second lowest treatment cost (79% higher than ustekinumab), followed by adalimumab (90%) and infliximab (94%) in the maintenance year. Considering the probability of PASI 75 response, ustekinumab is the most cost-effective with a cost per PASI 75 response of R$ 44.362, followed by infliximab (R$ 80.802/PASI 75 response), adalimumab (R$ 107.008/PASI 75 response) and etanercept (R$ 114.251/PASI 75 response). Considering a budget of R$ 1 million, ustekinumab and infliximab result in a higher number of PASI 75 responders. **Conclusion:** Of all biologic treatments approved in Brazil for psoriasis, ustekinumab represents the least costly treatment option and the most cost-effective. Despite higher cost, infliximab is the second most cost-effective biologic followed by adalimumab and etanercept from a private payer perspective.

Palavras-chave:
psoríase, tratamento biológico, análise de custo-efetividade, sistema suplementar.

RESUMO

Objetivo: Estimar o custo por resposta dos tratamentos biológicos da psoríase moderada a grave no sistema de saúde suplementar. **Métodos:** Quatro medicamentos biológicos encontram-se aprovados no Brasil para o tratamento da psoríase moderada a grave, adalimumabe, etanercepte, infliximabe e ustequinumabe. Considerando a dosagem e posologia, o custo de tratamento anual foi calculado com base no preço da CMED considerando um paciente de 70 kg. A probabilidade de resposta PASI 75 para cada tratamento foi retirada da metanálise de Reich *et al*., considerando o intervalo de confiança de 95%. Para estimar o impacto orçamentário da incorporação dos tratamentos biológicos, assumiu-se um orçamento hipotético para uma operadora de saúde de R$ 1 milhão. **Resultados:** Ustequinumabe apresenta o menor custo de tratamento por paciente no ano de indução e na manutenção. Etanercepte tem o segundo menor custo de tratamento (79% mais que ustequinumabe), seguido por adalimumabe (90%) e infliximabe (94%) por ano de manutenção. Considerando a probabilidade de resposta PASI 75, ustequinumabe é o tratamento mais custo-efetivo (R$ 44.362 por resposta PASI 75), seguido por infliximabe (R$ 80.802), adalimumabe (R$ 107.008) e etanercepte (R$ 114.251). Assumindo um orçamento hipotético de R$ 1 milhão, ustequinumabe e infliximabe resultariam no maior número de pacientes com resposta PASI 75. **Conclusão:** Entre os tratamentos biológicos para psoríase moderada a grave, ustequinumabe apresenta o menor custo e o menor custo por resposta. Infliximabe apresenta o segundo menor custo por resposta, seguido por adalimumabe e etanercepte sob a perspectiva do sistema de saúde suplementar brasileiro.

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Introduction

Psoriasis is an autoimmune inflammatory disease mediated by a cascade of cytokines that culminates in the formation of lesions in the surface of the skin. (Luba & Stulberg, 2006; Mrowietz U *et al*., 2006) These lesions vary in size and cause life debilitating consequences as demonstrated by its impact on the quality of life. (Rapp *et al*., 1999) The most common form of psoriasis is characterized by the formation of plaques, occurring in 75-80% of all cases. (Annon, 2006) Plaque psoriasis varies in severity, with moderate to severe psoriasis accounting for 25-33% of all cases. (National Psoriasis Foundation, 2002; Sterry, 2004) Severity can be measured by the PASI score (Psoriasis Area and Severity Index), an important tool that combines both the body surface area affected and the severity of the plaques. (Feldman & Krueger 2005)

The current treatment algorithm for psoriasis includes a large number of therapies, ranging from topical agents, phototherapy, and systemic treatments. (Menter A, *et al.* 2008) Treatment is usually defined by disease severity as mild patients use topical agents, such as corticosteroids, and moderate to severe patients are more likely to advance to systemic treatments. Systemic treatments include agents such as methotrexate, cyclosporine and biologics. Methotrexate and cyclosporine, however, can have serious adverse events resulting in treatment discontinuation. (Griffiths *et al.,* 2000; Bangert and Costner, 2007) Biologics are a new class of treatments that present a strong efficacy and low adverse events for patients with moderate to severe psoriasis.

In Brazil, the Brazilian Society of Dermatology has defined a treatment algorithm that stages the treatment of psoriasis. (Amaral Maia *et al.,* 2009) Initially patients are treated with phototherapy, after treatment failure patients undergo systemic treatment with methotrexate or acytretine, after which patients receive either cyclosporine or biologic treatment. There are four biologic treatments in Brazil for the treatment of moderate to severe psoriasis: adalimumab (HUMIRA™), etanercept (ENBREL™), infliximab (REMICADE™) and ustekinumab (STELARA™).

Access to biologic treatments in Brazil differs depending on whether a patient has supplementary health insurance or not. Around 20% of the Brazilian population (48 million) contracted supplementary private health insurance in 2012, with 80% of Brazilians relying on treatments available in the Brazilian public healthcare system (SUS). (ANS, 2012) The SUS is a tax-based healthcare system based on universal access to care, where biologics are not reimbursed for the treatment of moderate to severe psoriasis, as these have not been included in the national clinical protocol (PCDT). (PCDT, 2004)

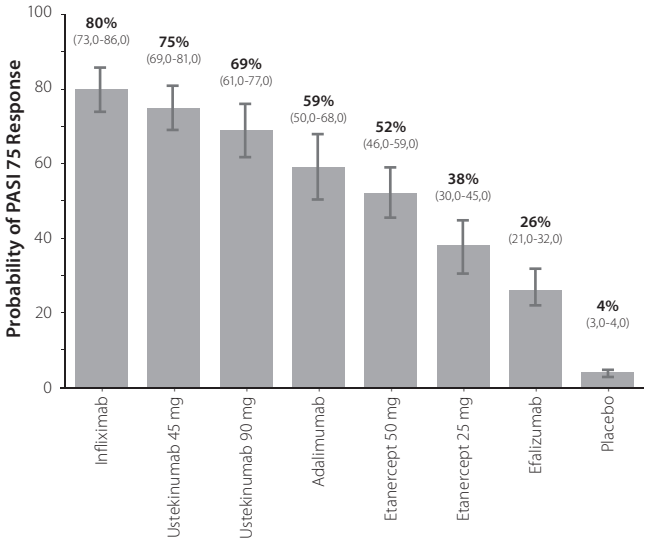
Besides universal coverage by the SUS, around 42 million individuals, about 20% of the population, contract supplementary health insurance. (ANS, 2009) In this context, minimum coverage to care is defined by law, and includes all inpatient drugs. Private payers can also opt to expand coverage to interventions they find beneficial. Access to biologic treatment of psoriasis is also limited in this context, relying on individual decisions by each health insurance companies.

The aim of this study is to investigate the cost-effectiveness of biologic treatment of moderate to severe psoriasis from a private payer perspective in Brazil. This study can help private health insurers decide which biologic treatments to reimburse for this condition. This is particularly important for payers given the number of co-morbidities in these patients and the resulting burden of this disease. (Mrowietz U *et al*., 2006, Neimann *et al.* 2006)

Methods

Efficacy

Efficacy estimates were gathered from a recent metanalysis from Reich *et al., 2012*. Effectiveness was defined as the probability of a PASI 75 response of each biologic at week 12 of treatment. The PASI 75 response represents a 75% improvement over the baseline PASI score of a patient, used as the primary endpoint all clinical trials in psoriasis. This endpoint is also considered a clinically relevant outcome by physicians. This mixed treatment comparison across biologics gathers all phase III clinical trials in psoriasis and compares PASI 75 responses for etanercept, adalimumab, infliximab and ustekinumab (Figure 1).



Baesyian P Value = 0,04
Etanercept 50mg, twice a week for the first 12 weeks
Etanercept 25mg, twice a week for the first 12 weeks
Ustekinumab 45mg is adminstered in patients with less than 100kg

Figure 1 Efficacy results across biologics for the treatment of moderate to severe psoriasis (adapted from Reich *et al*., 2012)

Costs

Only aquisition costs of biologics were considered in the analysis. The price of each biologic was defined as the list price, defined by the national price regulatory body, CMED, and published on the agency's website (Table 1). (CMED, 2012)

The dosing scheme considered for each biologic was defined by label, assuming an average patient weight of 70kg. The number of vials needed in the first year of treatment, induction year and any subsequent year of treatment, maintenance year, is shown in Table 2. It was considered that one year of treatment represents 52 weeks.

Table 1 Price per vial per treatment considering the private payer perspective

	N. of vials/ put up	Price/put up (tax free)	Price/ vial (tax free)
Ustekinumab 45mg	1	R$ 7.678,09	R$ 7.678,09
Etanercept 25mg	2	R$ 4.856,52	R$ 2.428,26
Adalimumab 40mg	4	R$ 2.285,02	R$ 571,26
Infliximab 100mg	1	R$ 2.486,22	R$ 2.486,22

Table 2 Number of vials per year of treatment as defined by label

	Posology (according to label)	Number of Vials (induction year)	Number of vials (maintenance year)
Adalimumab	80 mg at week 0, then 40 mg at week 1 and every other week	27,5	26
Etanercept	100 mg every week for 12 weeks, followed by 50mg a week	128	104
Infliximab	5mg/kg at week 0, 2, 6, followed by every 8 weeks	31	26
Ustekinumab	45mg at week 0, 4 and then every 12 weeks	5	4,3

Results

Cost of treatment

Each biologic has a distinct price and posology, which results in different yearly treatment costs. In induction and maintenance years, ustekinumab has the lowest treatment cost. In the induction year, for example, ustekinumab has the lowest treatment cost followed by adalimumab (74% more expensive), etanercept (85% more expensive), and infliximab (101% more expensive) (Table 3).

In the maintenance year, ustekinumab still represents the lowest treatment cost, followed by etanercept (79% more expensive), adalimumab (90% more expensive), and infliximab (94% more expensive). (Figure 2)

Cost per response

By combining both costs and efficacy data, the cost per PASI 75 response was estimated for each biologic treatment. Combining the lowest treatment cost and a high efficacy, ustekinumab was the most cost-effective treatment at R$ 44.362 per clinical success, or PASI 75 response. Infliximab represented the second most cost-effective treatment, R$ 80.802/PASI 75. Adalimumab had the third most cost-effective with R$ 107.008 per clinical success; followed by etanercept, the least cost-effective biologic treatment for moderate to severe psoriasis (R$ 114.251/PASI 75) (Figure 3 and Table 4).

Incremental cost-effectiveness ratio

By ordering each treatment from lowest to highest efficacy and corresponding treatment costs it is possible to compare treatments in terms of incremental cost-effectiveness. Compared to ustekinumab, infliximab is the only treatment with a higher efficacy, but with a very large incremental cost. As a result, the incremental cost-effectiveness ratio (ICER) between infliximab and ustekinumab is over R$ 773.647 per gain of 1% in clinical response per year (Table 5). It is clear, that ustekinumab is a cost-saving or dominant treatment over both etanercept and adalimumab, offering a gain in efficacy at a lower treatment cost.

Table 3 Treatment costs across biologics in both induction and maintenance years from a private payer perspective

		Induction year		Maintenance year	
	List Price/vial (tax free) (A)	N. of vials (B)	Treatment cost/ patient (A*B)	N. of vials (C)	Treatment cost/ patient (A*C)
Ustekinumab	R$ 7.678,09	5,0	R$ 38.390,45	4,33	R$ 33.271,72
Adalimumab	R$ 2.428,26	27,5	R$ 66.777,15	26,00	R$ 63.134,76
Etanercept	R$ 571,25	124,0	R$ 70.835,62	104,00	R$ 59.410,52
Infliximab	R$ 2.486,22	31,0	R$ 77.072,82	26,00	R$ 64.641,72

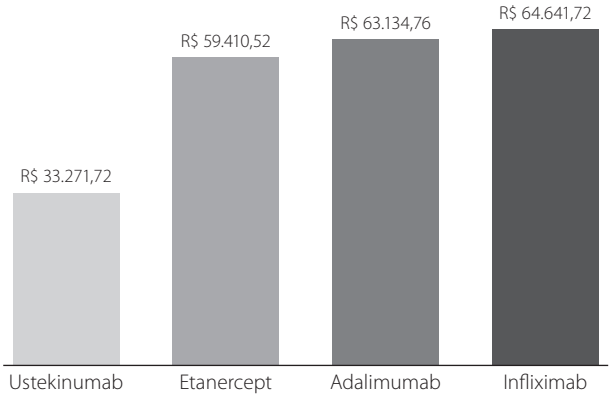


Figure 2 Treatment costs across biologics in the maintenance year

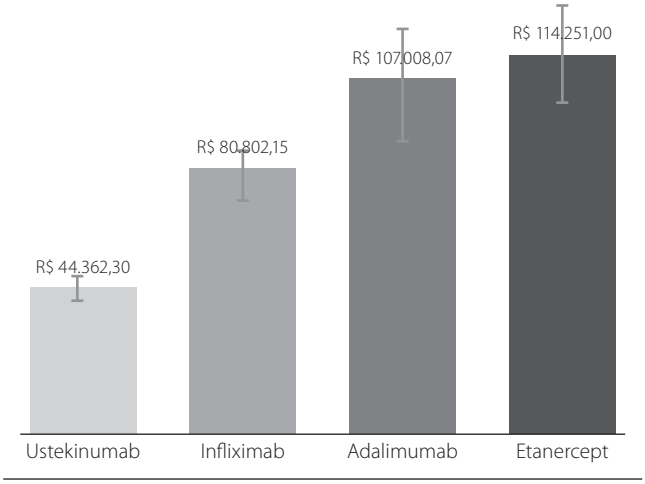


Figure 3 Cost per response across biologics during maintenance year

Sensitivity analysis

Considering the 95% credible intervals (Bayesian equivalent to 95% confidence intervals) for the probability of PASI 75 response, ustekinumab remains the most cost-effective treatment with a cost-PASI 75 between R$ 47.514,40 and R$ 55.777,78, considering the probability of a PASI 75 response between 69% and 81%. Infliximab, adalimumab and etanercept have similar cost-PASI 75 when considering the credible intervals. Infliximab has a cost per patient with PASI 75 response between R$ 109.565,90 and R$ 129.077,63 followed by adalimumabe with a cost-PASI 75 between R$ 120.058,53 and R$ 163.279,60. Etanercept has the highest cost-PASI 75 response, from R$ 146.781,85 to R$ 188.263,67. (Table 6)

Budget use

Considering a hypothetical budget of R$ 1 million for a private health insurance, around 26 patients are treated with ustekinumab, 15 with adalimumab, 14 with etanercept and 13 with infliximab. Of these patients, around 20 will achieve a PASI 75 response with ustekinumab, 10 will respond with infliximab, 9 with adalimumab and 7 with etanercept (Figure 4).

Discussion

A cost comparison across biologics needs to consider a variety of variables including label dosing and treatment duration. In this analysis, treatment duration was defined yearly by induction year and maintenance year. The induction year includes the initial induction dose of each biologic, which re-

Table 4 Cost-Effectiveness results for biologics during induction and maintenance years

	Probability PASI 75 Response (Reich *et al*, 2012)	Induction Year		Maintenance Year	
		Treatment costs	Cost/PASI 75	Treatment costs	Cost/PASI 75
Ustekinumab	75%	R$ 38.390,45	R$ 51.187,27	R$ 33.271,72	R$ 44.362,30
Infliximab	80%	R$ 77.072,82	R$ 96.341,03	R$ 64.641,72	R$ 80.802,15
Adalimumab	59%	R$ 66.777,15	R$ 113.181,61	R$ 63.134,76	R$ 107.008,07
Etanercept	52%	R$ 70.835,62	R$ 136.222,35	R$ 59.410,52	R$ 114.251,00

Table 5 Incremental cost-effectiveness ratio between ustekinumab and each biologic at week 12 (Base case)

	Cost/patient	Incremental Cost	Probability PASI 75 Response (Reich *et al*. 2012)	Incremental Effectiveness	ICER (vs. ustekinumab)
Ustekinumab	R$ 38.390,45	-	75%	0%	-
Infliximab	R$ 77.072,82	R$ 38.682,37	80%	5%	R$ 773.647,40
Adalimumab	R$ 66.777,15	R$ 28.386,70	59%	-16%	DOMINATED
Etanercept	R$ 70.835,62	R$ 32.445,17	52%	-23%	DOMINATED
Placebo		R$ 38.390,45	4%	71%	R$ 54.071,06

Table 6 Sensitivity analysis of PASI 75 response and resulting Incremental Cost-Effectiveness Ratio (ICER) compared to ustekinumab

	Probability of PASI 75 Response, Reich *et al*., 2012			Cost/Patient
	Average (Base Case)	Higher C.I./ Lower C.I.	Lower C.I./ Higher C.i.	
Ustekinumab	75%	81%	69%	R$ 38.390,45
Infliximab	80%	73%	86%	R$ 77.072,82
Incremental	5%	-8%	17%	R$ 38.682,37
ICER	R$ 773.647,40	Dominated	R$ 227.543,35	

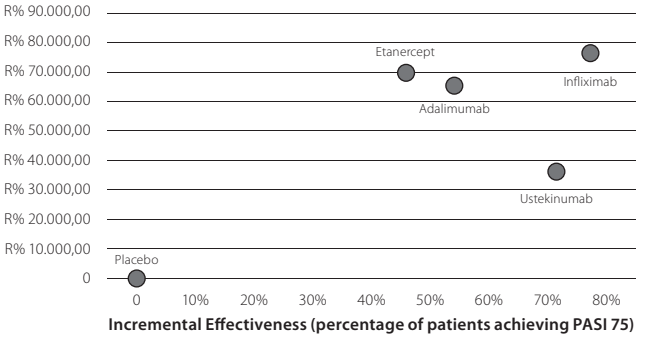


Figure 4 Cost-effectiveness plane of biologic treatments compared to placebo from a Brazilian private health insurance perspective

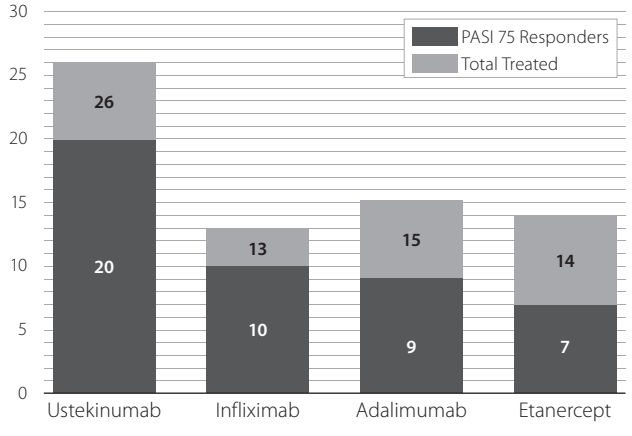


Figure 5 Number of treated patients and PASI 75 responders considering a R$ 1 million

presents a higher cost than seen in the following treatment period. As the induction period varies across treatments, from 4 weeks in the case of ustekinumab to 12 weeks for etanercept, an induction year time horizon allows payers to compare easily across treatments. A more complete costing study would need to consider the cost of treating adverse events, cost of administration (e.g. infusion costs) and the cost of time loss during administration.

The differing dosing schedules results in quite different treatment costs. There is not a clear relationship between the number of vials and treatment costs, while treatment with ustekinumab requires the least number of vials and has the lowest costs, infliximab is the most expensive treatment despite requiring fewer vials than etanercept. Given the significantly lower treatment costs, ustekinumab remains the least costly biologic treatment even considering the shorter dosing interval of 8 weeks, which results in an average treatment cost of R$ 50.032,66 per patient.

Ustekinumab represents a rare case for new technologies as it brings a high efficacy at a lower treatment cost compared to other biologics treatments. This is clear from the cost--response of ustekinumab, well below all other treatments. Considering the credible intervals between ustekinumab and infliximab, the ICER of adopting infliximabe can vary between from R$ 327.882 per gain in 1% probability of PASI 75 to a negative value, with ustekinumab being a dominant intervention.

Given the lack of head-to-head clinical trials between all biologics, a mixed treatment comparison metanalysis is a valuable tool to compare treatment efficacy. It is important to note the uncertainty around the efficacy results from Reich *et al.* 2012, since the results were compared at week 10 and week 16 of treatment. This early time-point may not be representative of the long-term efficacy of these treatments. This is especially important in psoriasis, a chronic condition with indefinite treatment duration. Nonetheless, long-term data for ustekinumab has shown maintenance of treatment response over 152 weeks. (Gordon *et al.,* 2010) Using other endpoints such as DLQI (Dermatology Life Quality Index) or QALYs (quality adjusted life years) offer a more long-term and comprehensive view of the treatment outcomes, however due to the lack of local data of these endpoints, PASI 75 was considered the most meaningful.

With only one head-to-head trial comparing biologic treatments, proving the superiority of ustekinumab to etanercept, it is difficult to observe incoherence between direct evidence and the metanalysis results. (Griffiths *et al.,* 2010) However, due to the large differences in cost, ustekinumab remains the most cost-effective treatment, as demonstrated by the sensitivity analysis. Adalimumab has the largest credible interval when considering the cost-PASI 75 response, around R$ 35.000 per response, followed by etanercept. As discussed earlier, the results cannot distinguish which treatment is the least cost-effective due to overlapping cost-PASI 75 between infliximab, adalimumab and etanercept (Figure 3).

A study by Nelson *et al*., used similar methodology to calculate the cost-PASI 75 response and showed infliximab and adalimumab to be the most cost-effective treatments from an American payer perspective. (Nelson *et al*., 2008) The Nelson *et al*. study did not include ustekinumab, as it was not ap-

proved at the time and considered 12-week treatment costs. Adopting 12-week treatment costs, does change the results presented above in relative terms, but brings the cost-PASI 75 response to a smaller scale. The costs considered by Nelson *et al*. included laboratory costs, physician costs and infusion costs for each treatment. In Brazil, there is no official source for these costs and these vary greatly between private health insurers. As a result, the study was limited to the cost of acquiring each biologic.

As reimbursement of biologic treatments of moderate to severe psoriasis is not mandatory for private health insurers in Brazil, it is important to consider the incremental cost effectiveness ratio (ICER) of each biologic compared to placebo. Considering the probability of PASI 75 response of placebo (4%) from Reich *et al*., ustekinumab has the lowest ICER at R$ 54.206. Followed by infliximabe with an ICER of R$ 123.982, adalimumab at R$ 148.436 and etanercept with an incremental cost of R$ 180.419 for an increase of 1% of patients achieving PASI 75 response. (Figure 4) Private payers in Brazil have mandatory coverage of phototherapy for the treatment of psoriasis. (RN Nº 262, 2011) However, comparing phototherapy is not an appropriate comparator for this study, as patients eligible for biologic treatment have either failed phototherapy or are not able to undergo this treatment. The same is true for systemic therapy, a prerequisite for patients eligible for biologic treatment, despite not being covered by private health insurance in Brazil.

Despite the limitations presented above, this study brings forward useful data for decision-makers in the Brazilian private healthcare system.

Conclusion

Private payers in the Brazilian health insurance market need to consider an array of evidence when reimbursing biologic treatments for moderate to severe psoriasis. Besides the clinical data supporting the use of biologics for moderate to severe psoriasis, this analysis is a useful tool comparing the cost-effectiveness ratio of these interventions. With a significant efficacy and lowest treatment cost, ustekinumab is an important treatment option for both patients and payers. This study concludes that ustekinumab is a dominant intervention over etanercept and adalimumab, with the sensitivity analysis suggesting this to be the case over infliximab as well.

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