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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

PHARMACOECONOMIC ANALYSIS OF THE MEDICINAL PRODUCT JAVLOR (VINFLUNINE) IN ADVANCED UROTHELIAL CARCINOMA PATIENTS AFTER FAILURE OF PLATINUM-BASED CHEMOTHERAPY

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Summary: Currently, in treatment of patients with urothelial transitional cell carcinoma resistant to platinum-based regimen, only Javlor (vinflunine) shows the best evidence when using in second-line chemotherapy scheme. Vinflunine shows the advantage over best supportive care during a randomized Phase III study. The aim of this study is to compare Javlor therapy in combination with the best supportive therapy and the best supportive therapy alone in terms of pharmacoeconomic analysis. Budget impact analysis shows that the treatment of urothelial transitional cell carcinoma with Javlor requires additional expenses. Cost-effectiveness analysis shows that the ICER does not exceed "willingness-to-pay" threshold which means that from the point of view of incremental analysis the therapy in patients with urothelial transitional cell carcinoma using Javlor is cost-effective.

Key words: bladder cancer, Javlor, vinflunine, pharmacoeconomic analysis, effectiveness analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, chemotherapy, the best supportive care, resistance to platinum therapy, life years gained, LYG.

Introduction

Urothelial transitional cell carcinoma (UTCC) is a serious health problem worldwide.

Bladder cancer accounts for 4.5% of all cases of cancer incidence. Out of which, 20.8-32.6% of patients have distant metastases. As the first-line chemotherapy, these patients are prescribed treatment with the inclusion of platinum drugs that is not always effective because of resistance. Currently, Javlor (vinflunine) in present time is the only drug of the second-line chemotherapy that has demonstrated its superiority over control group with relation to primary endpoint (overall survival) during a randomized Phase III study [2,26].

Vinflunine is a vinca alkaloid of the third generation that has cytostatic effects associated with the tubulin polymerization inhibition during cell mitosis that is included in the ESMO, EAU, RUSSCO, AOP recommendations as a second-line chemotherapy drug for patients with UTCC.

In this regard, pharmacoeconomic analysis is important. Its results will allow to compare UTCC treatment with Javlor in combination with the best supportive care (BSC) and the BSC alone [1,2,4,5,22, 27].

The objective of this study was to assess the use of vinflunine drug in patients with UTCC resistant to platinum-based regimens in terms of pharmacoeconomic analysis.

To achieve this objective the following tasks were set forward:

1. Collection and analysis of clinical data about compared therapies;
2. Definition of effectiveness criteria of compared treatment regimens;
3. Calculation of total costs that accompany compared treatment regimens;
4. Conduction of cost-effectiveness analysis and budget impact analysis

based on the results of efficiency and cost analysis for compared therapies.

Effectiveness Analysis

At the first stage of the effectiveness analysis, information retrieval associated was carried out. The databases of CSML, Medline, Pubmed and in the Internet using keywords: pharmacoeconomics, urothelial transitional cell carcinoma, cancer treatment, LYG, vinflunine.

As a result in Pubmed database 40 studies were found for last 10 years, and in ClinicalTrials database – 28, in which effectiveness and safety of vinflunine was studied. Among listed studies were chosen the ones with comparison of UTCC therapy regimens: vinflunine + BSC and BSC only. Later the studies with the highest patient cohort were highlighted. (table 1).

Choice of effectiveness criteria depended on the purpose of the study, the studied patient group, peculiarities of UTCC treatment, and the availability of published clinical trials. [15].

After analyzing the data from the selected clinical trials, it was decided to use the results of clinical study (Bellmunt J, 2013) of III phase with 370 patients with follow-up of 45.4 months. [23].

On the basis of information retrieval was defined criterion of effectiveness, allowing to make a pharmacoeconomic evaluation of comparable regimens in patients UTCC resistant to platinum-based regimens. In this study, the criterion of efficiency is the endpoint that reflects the added years of life, which corresponds to 0,54 LYG («life years gained») to therapy with vinflunine + BSC and 0,24 LYG therapy using only the BSC.

Thus, it was found that the use of vinflunine in the second line treatment increases the life expectancy of patients with UTCC resistant to platinum drugs compared with BSC only.

Cost analysis

The following direct costs were included in this study:

- concomitant treatment;
- chemotherapy (CTX);
- BSC.

The costs for concomitant treatment included costs for medical services (MS) and medicinal drugs (MD). The list of MS for diagnostic tests and therapy and the incidence of its usage were taken from the Standard of medical care for patients with malignant tumors of bladder of III-IV stage. Calculations were performed using formula: [7]

$$\text{Cost}(S) = \text{Price}(S) \times Q(S) \times F(S), \text{ where} \quad (1)$$

Cost(S) – cost of medical service, rubles.;

Price(S) – price of medical service, rubles.;

Q(S) – average amount of performed medical;

F(S) – the incidence of performing medical service.



Table 1. Results of information retrieval.

year	Study	Number of patients
2005	Vinflunine in Patients With Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urotelium Phase II	150
2009	Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, Delgado FM, Hurlteloup P, Winquist E, Morsli N, Salhi Y, Culine S, von der Maase H Effectiveness determination at month 22,1.	370
2013	Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy Bellmunt J, Fougeray R, Rosenberg JE, von der Maase H, Schutz FA, Salhi Y, Culine S, Choueiri TK Effectiveness determination at month 45,4.	370
2014	Monotherapy with intravenous vinflunine in patients with advanced or metastatic urothelial cancer after failure of a platinum-containing regimen: a retrospective analysis of German routine data Hegele A, Goebell P, Matz U, Neuhaus T.	21

Information about the cost of healthcare services was taken from the tariffs of the Federal Compulsory Medical Insurance Fund (FCMIF) (2015) [8]

Mean costs for MS per 1 case UTCC were about 5 402 rubles and for patients on the vinflunine + BSC scheme and for patients used only BSC.

Costs for medicinal drugs were calculated for medicinal drugs according the prices taken form state register of maximum sale prices for vital and essential drugs (VED) dated March 1, 2015 [14]. For medicinal drugs that are not included in the list of VED, average retail selling prices for Moscow in rubles (including VAT) dated March 1, 2015 were used [11]. The calculation of costs for drug therapy was performed using the following formulas:

$$\text{Cost}(P) = \text{Price}(P) \times Q(P) \times F(P), \text{ где} \quad (2)$$

Cost(P) – costs for the drug, rubles;
Price(P) – price of 1 unit of activity, rubles;
Q(P) – course dose of the drug;
F(P) – frequency of drug prescription.

$$\text{Price}(P) = C / (Q \times N), \text{ where} \quad (3)$$

Price(P) – price of 1 unit of activity, rubles;
C – the cost of pack of medicinal drug, rubles;
Q – amount of active ingredient in dosage form of MD, mg
N – amount of dosage forms in package of MD, pieces.

Gradually the calculation of costs of MD was performed, including the costs of unit of MD action (formula №3), then of the cost of each MD (formula №2), included in the list of drugs noted in the Standard of medical care for patients with malignant tumors of bladder of III-IV stage. Calculations were performed using formula [3,7]. Mean costs for MD for 1 MD per one case of

UTCC are 10 790 rubles for each of two compared groups.

Based on the above results, the cost of concomitant therapy were about 16 192 rubles. The result of this calculation is the same monetary value for patients treated Vinflunine in conjunction with the BSC, and for patients used only BSC. Equal value of these costs for both compared therapies is due to the use of the standard of care of patients with UTCC, which lists the medical services and medicines, which are received by each patient with that disease [19].

In the present study the first group of patients received vinflunine + BSC in 100% of cases, and the second group – Gemcitabine as part of BSC in 50% of cases, and BSC without Gemcitabine in 50% of cases. [9].

In the Russian Federation (RF) two dosage forms of vinflunine for intravenous administration are registered: 250mg/10 ml и 50mg/2 ml. The price 59 390 rubles и 11 878 rubles, соответственно.

Single dose of Vinflunine depends on the body surface area (BSA) which is on the average 1.82 m2. Distribution of single doses of 320 mg/m2, 280 mg/m2 and 250mg/m2 is performed depending on patient's age and health state (Table 2,3) [1].

Table 2. Distribution of single dose.

Age, years	Health state	Single dose, mg/m2
under 75	Normal	320
75-80	Renal failure	280
Older than 80	Hepatic failure class A	250

Table 3. Price of single dose.

Single dose, mg/m ²	Single dose, mg	Combination of flasks	Price, rubles
320	582,4	2 flasks 250mg/10ml + 2 flasks 50mg/2ml (600mg)	142 536
280	509,6	2 flasks 250mg/10ml + 1 flask. 50mg/2ml (550mg)	130 658
250	455	2 flasks 250mg/10ml (500mg)	118 780
		1 flask 250mg/10ml + 4 flask. 50mg/2ml (450mg)	118 780

The calculation of mean costs of vinflunine course was taken using the following formula:

$$\text{Cost}(B) = C320 \times N320 + C280 \times N280 + C250 \times N250, \text{ где} \quad (4)$$

Cost(B) – mean cost of vinflunine course, rubles
C320 – cost of single dose 320 mg/m2, rubles
N320 – frequency of prescription 320 mg/m2 single dose
C280 – cost of single dose 280 mg/m2, rubles
N280 – frequency of prescription 280 mg/m2 single dose
C250 – cost of single dose 250 mg/m2, rubles
N250 – frequency of prescription 250 mg/m2 single dose

Distribution of administered doses of vinflunine was taken from real clinical practice

and composed 31,37% for 320 mg/m2, 56,87% – 280 mg/m2 and 11,76% – 250 mg/m2[24]. So average cost calculation of one vinflunine cycle was performed using formula №4, and finally cots equaled 132 988 rubles.

According to the clinical trial by Bellmunt (2013) for a course treatment with vinflunine in general three courses are necessary to be performed, in monetary terms it equals about 398 963 rubles [23].

The duration of therapy with gemcitabine is calculated according to the recommendations for 21 day with daily dose (DD) of 1200mg/m². Taking into account BSA mean daily dose was 2 184 mg, and its cost was calculated using formula №8 [2,14]:

$$\text{Cost(DD)} = \text{CД} \times \text{C(1mg)}, \text{ where} \quad (5)$$

Cost(DD) – cost of daily dose, rubles
DD – daily dose, mg
C(1mg) – cost 1 mg of gemcitabine, rubles

The calculation of 1 mg gemcitabine cost was performed according to formula №3.

As for 01.07.2015 gemcitabine was presented at the Russian market in two dosage forms: 200 mg and 1000 mg lyophilisate. Thus, 2 1000 mg flasks and one 200 mg flask were needed for introduction of gemcitabine daily dose. The cost of gemcitabine was taken from the state register of maximum sale prices for vital and essential drugs (VED) and was in general 4 550 rubles per 1 flask on 1000 mg and 901 rubles on 200 mg.

For the calculation of costs of course therapy with gemcitabine the daily dose cost was taken amounted about 10 002 rubles [2,14]. Thus, the course price of gemcitabine, including the frequency of its prescription equaling 50%, was about 105 021 rubles [5].

The part of costs included in BSC were spent on reduction of side effects (SE), appearing with diverse frequency in patients with UTCC in comparing groups. Data on frequency of SE appearing in both groups were taken from clinical trial III phase by Bellmunt (2013) and real-life clinical practice. Also radiation therapy was used in control group, and costs included costs of radiotherapy, hospitalization, and costs of concomitant MS and MD. [6,23,25].

Thus, costs for BSC were composed of costs on reduction of SE, associated with UTCC therapy and also in group of patients taking only BSC was used radiation therapy. During calculation of costs on reduction of SE it was found that usage of vinflunine + BSC scheme that costs amounted 73 038 rubles, and using BSC only were about 12 528 rubles (Table 4).

), and amounted to about 488 192 rubles for the group of patients treated with vinflunine + BSC, and 155,248 rubles for the group of patients who used only the BSC on the course of treatment per patient (Table 5).

Table 5. Total costs per treatment course of one patient.

	Costs of CTX, rubles	Costs of BSC, rubles	Cost on MS and MD, rubles	Total costs, rubles
Vinflunine + BSC	398 963	73 038	16 192	488 192
BSC	105 021	34 035	16 192	155 248

Cost-effectiveness analysis

Cost-effectiveness analysis allows to determine the dominating therapy regime from the pharmacoeconomic point of view, including the ratio of costs to the effectiveness [16,21]. Cost-effectiveness ratio (CER) is calculated with formula № 6:

$$\text{CER} = \text{Cost} / \text{Ef}, \text{ where} \quad (6)$$

CER – cost-effectiveness ratio;
Cost – direct costs, associated with treatment scheme;
Ef – effectiveness of treatment scheme.

Cost-effectiveness ratio reflects the costs of one unit of effectiveness, in this study it is a life year gained. Under the comparison of obtained CER for alternative treatment methods, the therapy is dominating for the one with lower CER. [20].

Using earlier obtained data cost-effectiveness ratio was calculated using formula №6.

Results are presented in the table 6.

Table 6. Results cost-effectiveness analysis.

	Vinflunine + BSC	BSC
Costs, rubles	488 192	155 248
LYG	0,54	0,24
CER, rubles	910 793	654 309

According to the presented results, the costs of unit of effectiveness, i.e. the cost of life year gained is 910 793 rubles for vinflunine + BSC therapy and about 654 309 rubles for BSC only.

Hence, treatment with BSC only requires the lowest costs for reaching the life years gained. On the contrary, the therapy with vinflunine + BSC along with the highest costs, has the highest efficiency, which is expressed as prolongation of life, in this regard, it was further calculated incremental cost-effectiveness ratio using formula №. 7 [14,17]:

$$\text{ICER} = (\text{Cost 1} - \text{Cost 2}) / (\text{Ef1} - \text{Ef2}), \text{ где} \quad (7)$$

ICER – incremental cost-effectiveness ratio;
Ef1 – effectiveness of treatment method 1;
Ef2 – effectiveness of treatment method 2;
Cost 1, Cost 2 – costs for treatment methods 1 and 2.

This indicator reflects the cost of an additional unit of effectiveness, i.e. a life year gained while using the combination of vinflunine + BSC instead of BSC-only mode [10,18].

As a result of calculations it was found that the additional cost per a life year gained for patients receiving Vinflunine + BSC, is 1 114 504 rubles. When compared ICER c GTP for 2015 (1 629 765 rubles), it is determined that the costs of achieving additional units of effectiveness are below the level of GTP for the Russian Federation that allows to make a conclusion that the treatment of patients with UTCC, resistant to platinum-based scheme, vinflunine + BSC is cost-effective (figure 2) [12,13].

Table 4. The costs of reduction of side effects, associated with UTCC therapy.

Side effect	Frequency, %		Cost of reduction of side effect, rubles	
	Vinflunine + BSC	BSC	Vinflunine + BSC	BSC
Abdominal pain	15,7	17,9	110,58	126,07
Asthenia/ fatigue	50	60,7	159,7	193,87
Constipation	47,6	24,8	20	10,42
Local reaction in injections	27,4	0	40,83	0
Muscle ache	16,1	6,8	62,63	26,45
Nausea	39,1	21,4	46,41	25,4
Vomit	29	14,5	34,42	17,21
Sensory neuropathy	12,1	11,1	752,73	690,52
Canker sore	28,6	1,7	60,35	3,59
Anemia	93,1	61,3	2 399,3	1 579,77
Neutropenia	12,8 (III-IVcr)	0,9 (III-IVcr)	9 088,13	639,01
Neutropenia	48,1	2,7	30 390,54	1 705,91
Febrile neutropenia	6	0	6 137,76	0
Thrombocytopaenia	51,2	16,2	23 734,27	7 509,67

Radiation therapy used in patients taking only BSC, required hospitalization, that fact was included in costs' calculation amounting 21 508 rubles [6,23,25].

Thus, costs on BSC in Vinflunine + BSC group were about 73 038 rubles, in BSC only group – about 34 035 rubles.

The level of total costs on compared treatment schemes was formed from the cost of CTX, BSC and concomitant therapy including MD and MS (according to the standard of medical care for patients with cancer of the bladder stage III-IV

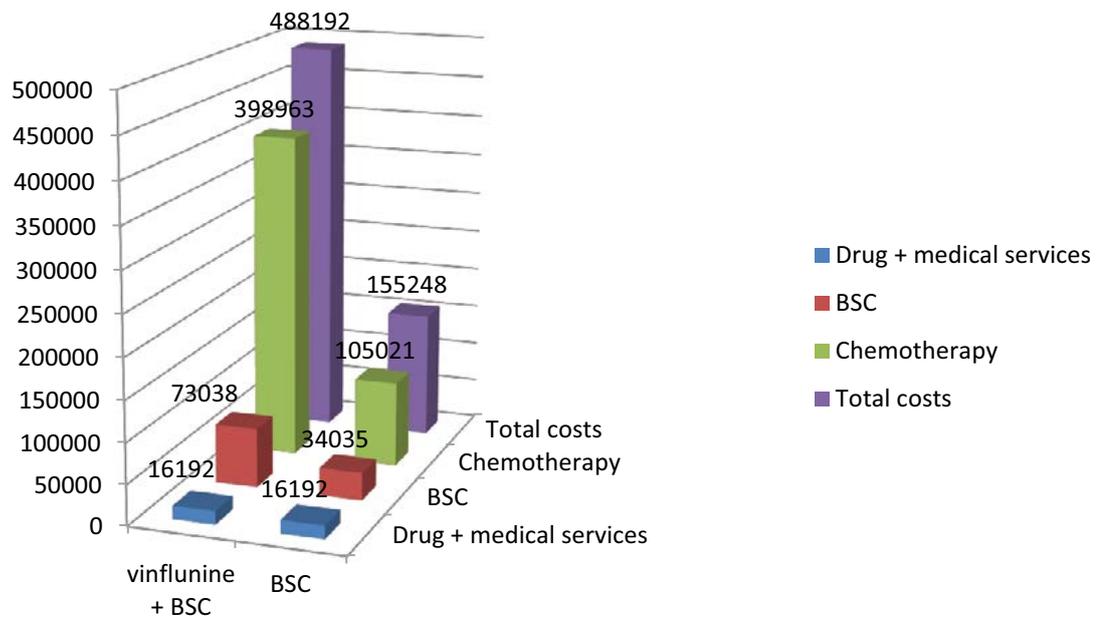


Figure 1. Total costs per treatment course.

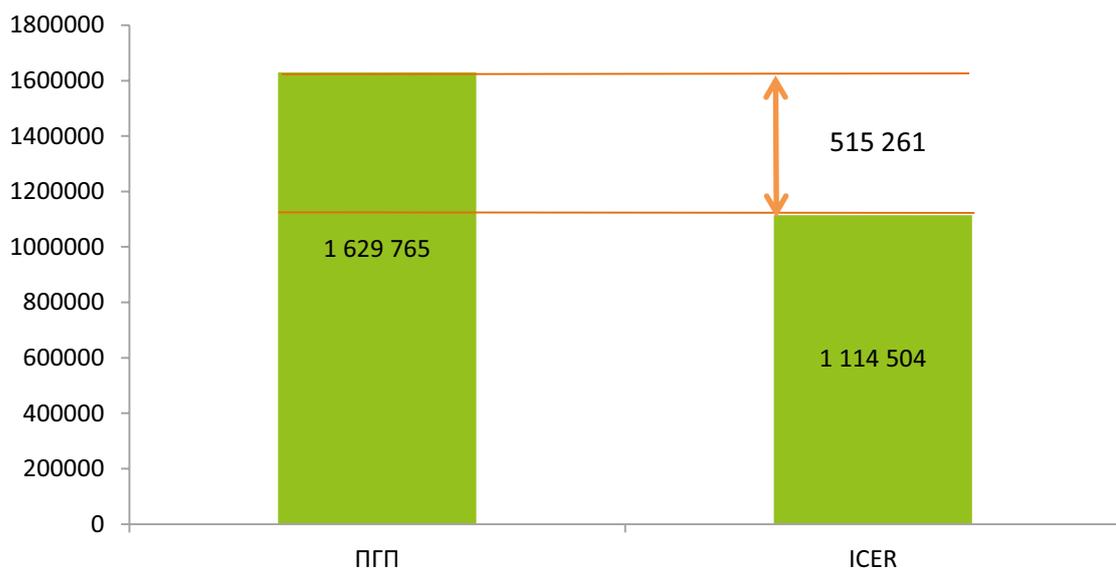


Figure 2. Results of incremental cost-effectiveness analysis.

Budget impact analysis

Budget impact analysis allows to determine the financial consequences for healthcare budget after change of standard care to the innovative cancer therapy. The calculations are made using following formula [10,19].

$$BIA = Cost1 - Cost2, \text{ где} \tag{8}$$

BIA (Budget Impact Analysis) – result of budget impact analysis, rubles;
 Cost1 - total economic effect of treatment 1, rubles;
 Cost2 - total economic effect of treatment 2, rubles

Budget impact analysis includes the costs of primary therapy (chemotherapy), BSC, concomitant therapy, including MS and MS, noted in the Standard of medical care to the patients with UTCC, and the number of patients with such disease, resistant to platinum-based regimens are presented in Table 7.

Table 7. Total costs per treatment course for patients in Russia with UTCC resistant to platinum-based regimens.

	Costs for CTX, rubles	Costs for BSC, rubles	Costs for MS and MD, rubles	Total costs, rubles
Vinflunine + BSC	289 248 014	52 952 283	11 739 101	353 939 398
BSC	76 140 221	24 675 686	11 739 101	112 555 007
Additional costs				241 384 391

According to the budget impact analysis we can conclude that when patients with UTCC resistant to treatment based on platinum are transferred from only BSC to the treatment vinflunine + BSC it requires additional costs

about 332 944 rubles for one patient or 241 384 391 rubles for treatment of all patients with this diagnosis in Russia.

Results

1. During effectiveness determination of vinflunine + BSC and BSC only according to the results of clinical trials it was calculated the most important effectiveness criteria, reflecting life years gained, which amounted 0,54 LYG and 0,24 LYG, respectively.

2. During cost analysis it is determined that for course treatment of one patient with UTCC resistant to the treatment based on platinum during vinflunine + BSC costs amount 488 192 rubles, and during BSC only – about 155 248 rubles

3. The result of cost-effectiveness analysis is the determination of incremental cost-effectiveness ratio, reflecting the cost one additional unit of effectiveness and amounting about 1 114 504 rubles for Vinflunine in combination with BSC.

4. Budget impact analysis reveals that for vinflunine + BSC treatment additional costs are necessary in amount of 241 384 391 rubles for treatment course of the whole Russian patients population.

Conclusions

1. The usage of medicinal drug Javlor (Vinflunine) in the second line chemotherapy compared with BSC in patients with USCC resistant to platinum-based therapy increases the life duration, which is measured in LYG (life years gained) and amounts 0,54 LYG in Vinflunine + BSC and 0,24 LYG in BSC group.

2. During cost-effectiveness analysis it is determined that therapy using scheme vinflunine + BSC is cost-effective, as incremental cost effectiveness ratio was 1 114 504 rubles per 1 added LYG, that does not exceed willingness-to-pay threshold for the Russian Federation and in total is cost is lower per LYG, that for other modern used medicinal drugs in chemotherapy of oncology.

3. Budget impact analysis shows that vinflunine therapy requires additional costs equaling 332 944 rubles per 1 patient or 241 384 391 for all patients in the Russian Federation for full treatment course for patients for whom such therapy is prescribed based on the needs of 725 per year.

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