A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis


Standard therapy in the United States for malignancy-associated hyperuricemia consists of hydration, alkalinization, and allopurinol. Urate oxidase catalyzes the enzymatic oxidation of uric acid to a 5 to 7 times increased urine soluble product, allantoin. Rasburicase is a new recombinant form of urate oxidase available for clinical evaluation. This multicenter randomized trial compared allopurinol to rasburicase in pediatric patients with leukemia or lymphoma at high risk for tumor lysis. Patients received the assigned uric acid-lowering agent for 5 to 7 days during induction chemotherapy. The primary efficacy end point was to compare the area under the serial plasma uric acid concentration curves during the first 96 hours of therapy (AUC_0-96). Fifty-two patients were randomized at 6 sites. In an intent-to-treat analysis, the mean uric acid AUC_0-96 was 128 ± 70 mg/dL.hour for the rasburicase group and 329 ± 129 mg/dL.hour for the allopurinol group (P < .0001). The rasburicase versus allopurinol group experienced a 2.6-fold (95% CI: 2.0-3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% versus 12% reduction (P < .0001) of initial plasma uric acid levels. No antirasburicase antibodies were detected at day 14. This randomized study demonstrated more rapid control and lower levels of plasma uric acid in patients at high risk for tumor lysis who received rasburicase compared to allopurinol. For pediatric patients with advanced stage lymphoma or high tumor burden leukemia, rasburicase is a safe and effective alternative to allopurinol during initial chemotherapy. (Blood. 2001; 97:2998-3003)

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Introduction

In patients with myeloproliferative diseases or hematopoietic malignancies, nucleic acids are catabolized as a result of increased turnover of malignant cell populations. This results in an increase in purine metabolism, leading to hyperuricemia. Aggressive cancer chemotherapy regimens cause an increase in cell lysis and release of urine metabolites. Tumor lysis syndrome is characterized by severe hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure. As a consequence of hyperuricemia, renal insufficiency develops when urine becomes supersaturated with uric acid and crystals of uric acid form in the renal tubules and distal collecting system. Moreover, despite management of metabolic abnormalities to reduce the risk of acute renal failure, 25% of children with advanced-stage Burkitt lymphoma and B-cell acute lymphoblastic leukemia still experience acute renal failure at onset of cytoxic chemotherapy. The standard treatment for hyperuricemia in the United States consists of allopurinol, urinary alkalinization, and hydration. By inhibiting the enzyme xanthine oxidase, allopurinol blocks uric acid formation (Figure 1). This increases the plasma concentrations of the uric acid precursors hypoxanthine and xanthine. Patients at high risk for tumor lysis still need to excrete preexisting uric acid, which is not affected by allopurinol treatment. Consequently, a drug that has rapid and highly potent uricolytic properties, reduces metabolic morbidity, and can be conveniently integrated with the initiation of a cancer chemotherapy regimen would be helpful in the supportive management of this patient population.

Urate oxidase catalyzes the enzymatic oxidation of uric acid into allantoin (Figure 1), a readily excretable substance about 5 times more soluble than uric acid. Urate oxidase is an endogenous enzyme found in most mammals, but not in humans because of a nonsense mutation in the coding region in the gene during hominoid evolution. Rasburicase is a recombinant form of the urate oxidase enzyme. A study in healthy adult male volunteers established that single daily intravenous doses of rasburicase were well tolerated and led to dramatic decreases in plasma uric acid levels. A recent multicenter phase II trial of rasburicase in pediatric patients with leukemia and lymphoma (n = 131) demonstrated that 100% of patients achieved uric acid control at a dose of rasburicase of 0.2 mg/kg despite concomitant intensive chemotherapy. The present study reports the efficacy of rasburicase compared to allopurinol in reducing exposure to plasma uric acid in children with leukemia or lymphoma at high risk for developing tumor lysis syndrome.
Eligibility criteria included:

- Murphy stage III or IV non-Hodgkin lymphomas (NHL),
- acute lymphocytic leukemia (ALL) with a uric acid level of 8 mg/dL or higher at presentation, or (3) any childhood lymphocytic leukemia (ALL) with a peripheral white blood cell (WBC) count of 25,000/μL or higher at presentation, or (3) any childhood lymphoma or leukemia with a uric acid level of 8 mg/dL or higher at the time of study entry. Patients must have been scheduled to receive cytoreductive chemotherapy. The primary efficacy end point was the reduction of uric acid at 4 hours after first dose of uric acid-lowering agent therapy (ie, immediately before first dose of study drug administration). A secondary end point was the percent reduction of uric acid at 4 hours after first dose of uric acid-lowering agent therapy (ie, prior to induction chemotherapy).

### Safety and toxicity
Safety analyses were performed in all patients and compared between treatment groups. All adverse events were coded according to the World Health Organization Adverse Reactions Terminology (WHO-ART) and assigned a system-organ class. Antirasburicase antibody determination was performed under the responsibility of Sanofi Research Division, Great Valley, PA via an enzyme-linked immunosorbent assay (ELISA) technique as previously reported.18

### Statistical analysis
The primary efficacy end point was the plasma uric acid \( AUC_{0-96} \). The end point was computed for each patient using the trapezoidal rule. Linear interpolation was used to compute a missing value. Values collected below the limit of quantification (LOQ) were replaced by the LOQ value. Descriptive summary statistics (N, mean, median, SD) were computed for each treatment group. A one-way analysis of variance (ANOVA) model was used to evaluate the treatment effect on plasma uric acid \( AUC_{0-96} \) and percent change from baseline plasma uric acid concentrations at 4 hours. Subgroup analyses were similarly performed by disease (lymphoma or leukemia) or presenting uric acid values (<8 mg/dL or ≥8 mg/dL).

Descriptive statistics and statistical analyses of the safety and efficacy data were calculated using SAS software, Version 6.12 on a Sanofi Alphaserver.

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**Figure 1. Mechanism of action: rasburicase and allopurinol.** Depicted is the pathway of purine catabolism. Rasburicase is a recombinant form of urate oxidase, an enzyme that converts uric acid to allantoin. Allopurinol in comparison acts by inhibiting the endogenous enzyme xanthine oxidase, thereby inhibiting formation of uric acid.

**Materials and methods**

**Study design**

From November 1996 through December 1997, 52 pediatric patients with leukemia or lymphoma were enrolled on this open-labeled, randomized, multicenter, comparative trial of rasburicase versus allopurinol. The study investigational new drug (IND) was approved by the Food and Drug Administration. The Institutional Review Boards of all participating institutions approved the study. Patients or families gave written informed consent before entry into the study and randomization.

**Eligibility criteria**

The study enrolled pediatric oncology patients with leukemia or lymphoma deemed at high risk for tumor lysis syndrome. Eligibility criteria included:

- Murphy stage III or IV non-Hodgkin lymphomas (NHL),
- acute lymphocytic leukemia (ALL) with a peripheral white blood cell (WBC) count of 25,000/μL or higher at presentation, or (3) any childhood lymphoma or leukemia with a uric acid level of 8 mg/dL or higher at the time of study entry. Patients must have been scheduled to receive cytoreductive chemotherapy. The primary efficacy end point was the reduction of uric acid at 4 hours after first dose of uric acid-lowering agent therapy (ie, immediately before first dose of study drug administration). A secondary end point was the percent reduction of uric acid at 4 hours after first dose of uric acid-lowering agent therapy (ie, prior to induction chemotherapy).

**Randomization and treatment**

Via telephone entry, treatment (rasburicase or allopurinol) was randomly allocated to patients according to a computer-generated randomization code schema. Randomization was stratified according to presentation uric acid (<8.0 mg/dL or ≥8.0 mg/dL) and disease (leukemia or lymphoma).

Patients were scheduled to receive 5 to 7 days of either uric acid-lowering agent (rasburicase or allopurinol). The dose and schedule of rasburicase was 0.20 mg/kg intravenously given over 30 minutes daily.16 Oral allopurinol therapy was dosed by the individual investigators accord-
Results

Patients

Fifty-two patients were randomized at 6 sites within the United States between November 1996 and December 1997. Patient baseline demographics and disease type are shown in Table 1. There were no statistical differences in the age, race, male/female ratios, or performance status for patients randomized to rasburicase versus allopurinol. The mean age for patients assigned rasburicase versus allopurinol was 7.1 years versus 7.8 years, respectively. Eighty-nine percent of patients assigned to rasburicase had ECOG scores of one or less compared to 84% assigned to allopurinol. Twenty patients with leukemia received rasburicase and 19 patients received allopurinol. Seven patients with lymphoma received rasburicase versus 6 receiving allopurinol. A similar number of patients with advanced Burkitt leukemia/lymphoma (mature B-cell leukemia or ≥ stage III Burkitt small noncleaved-cell lymphoma) were in each treatment group (5 rasburicase, 4 allopurinol). In addition, there was no significant differences in initial tumor burden markers between treatment arms (ie, WBC count in the leukemia patients and lactate dehydrogenase [LDH] in the lymphoma patients). Patient randomizations were also stratified according to presenting uric acid values. Despite this, mean presenting uric acid values were higher in patients assigned rasburicase by about 1 mg/dL, but this did not reach statistical significance. Rasburicase patients presented with a mean uric acid value ± SD of 7.7 ± 3.5 mg/dL versus 6.8 ± 3.4 mg/dL in allopurinol patients. All other metabolic parameters were similar between treatment groups including calcium, potassium, and phosphorus. Finally, the presentation creatinine levels were nearly identical between groups, with the rasburicase patients presenting with a mean creatinine of 0.60 ± 0.33 mg/dL versus 0.61 ± 0.30 mg/dL in allopurinol patients (Table 1).

Drug administration

All 52 patients randomized received at least one dose of their assigned treatments with rasburicase or allopurinol. Patients assigned rasburicase received a dose every 24 hours, except for one patient with early pre-B cell ALL with a WBC count of 178 × 10^9/L and a uric acid value of 4.1 mg/dL who received every 12-hour dose × 4 because of investigator preference. A total of 387 doses (median number of 3 doses/d) of oral allopurinol were administered with a median dose of 100 mg (1 tablet) per dose. The mean time from study drug administration to start of chemotherapy (excluding intrathecal therapy) was 21 hours in both treatment groups. The treatment protocol was violated in 2 patients in each arm because chemotherapy was started prior to the initiation of the study drug. Four patients withdrew from the study before completion of randomized drug. One patient assigned to rasburicase withdrew after 4 doses because of grade 4 hemolysis; a relationship to the study drug was not known by the investigator (see “Adverse events and mortality”). Three patients assigned to allopurinol withdrew from study prior to completion. Two of these patients suffered unrelated deaths (see below) during induction chemotherapy after 14 and 8 doses of allopurinol, respectively. The third patient was withdrawn after 14 doses of allopurinol because chemotherapy had not been administered. All patient data were used regardless of study completion in an intent-to-treat analysis.

Control of plasma uric acid

The primary end point of this trial was the control of uric acid through the first 96 hours of therapy with concomitant induction chemotherapy appropriate for the specific disease. Patients treated with rasburicase had a more rapid decline and maintained lower plasma uric acid levels throughout induction chemotherapy (Figure 2). The area under the curve for mean uric acid AUC_0-96 was used to quantify the exposure to uric acid during the first 96 hours of induction chemotherapy (Figure 2). In an intent-to-treat analysis, the mean AUC_0-96 was 128 ± 70 mg/dL.hr for the rasburicase group and 329 ± 129 mg/dL.hr for the allopurinol group (P < .0001). Patients receiving rasburicase on average experienced a 2.6-fold less exposure to uric acid during the first 96 hours of therapy. For the subgroup of 19 hyperuricemic patients any time prior to dosing, there was a similar reduction in uric acid exposure during therapy in patients who received rasburicase (Table 2). Although no attempt was made to randomize the small number of patients with Burkitt lymphoma in this trial, these patients are at greatest risk for hyperuricemic nephropathy during initiation of treatment.9,10 As illustrated in Table 2, patients with advanced Burkitt lymphoma had the greatest reduction in exposure to uric acid (~4-fold) when comparing rasburicase treatment to allopurinol during the first 96 hours of therapy. Thus, the advantageous decrease in uric acid was evident across all patients included in the study as well as in treatment subgroups, normouricemic versus hyperuricemic patients, and patients with leukemia or lymphoma.

The rapidity of control of uric acid by study drug was a secondary end point in this trial. We found a striking difference between the single dose of intravenous rasburicase at 0.20 mg/kg versus standard doses of oral allopurinol. For patients randomized to rasburicase, there was an 86% reduction in plasma uric acid

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the patients</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Registered</td>
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<td>WBC—Leukemia patients (10^9/L)*</td>
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<td>Lymphoma</td>
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<tr>
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<td>Phosphorus</td>
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<tr>
<td>Potassium</td>
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*All values are mean ± SD; there were no significant differences comparing baseline values between treatment groups.
levels after 4 hours of the first dose compared to only 12% for allopurinol (P < .0001). Finally, we examined the fall in plasma uric acid in patients who were hyperuricemic (uric acid > 8 mg/dL at T = 0). Patients hyperuricemic at baseline and treated with rasburicase (n = 10) all achieved a uric acid concentration of less than 8 mg/dL in less than 4 hours. In contrast, no patients hyperuricemic at start of allopurinol (n = 5) achieved a uric acid level less than 8 mg/dL by 4 hours (Figure 3).

Renal outcome

The study sample size was too small to determine a difference in the incidence of renal failure or required renal support. One patient who received allopurinol required hemodialysis during the study period. This patient was a 12-year-old with stage IV Burkitt lymphoma who had renal failure, hypocalemia, and a maximum serum phosphorous of 20.2 mg/dL, on day 2 of standard cytoreductive chemotherapy with cyclophosphamide, vincristine, and prednisone. He underwent hemodialysis followed by hemofiltration for 6 days with recovery of renal function. In contrast, a 15-year-old girl with a bulky presentation of pre-B ALL in the rasburicase group presented with frank renal insufficiency with a creatinine of 2.5 mg/dL at baseline and a uric acid concentration of 16.5 mg/dL. This patient’s renal function improved during therapy without the need for any type of dialysis or hemofiltration.

Frequent adverse events were common among the study patients including fever, pain, and mucositis secondary to their disease and chemotherapeutic regimens. Two patients assigned allopurinol died during the study period. A 6-year-old girl with T-cell leukemia died of pseudomonal sepsis on day 11 of study, and a 2-year-old girl with acute myelogenous leukemia died of an intracerebral hemorrhage on day 2 of study. Therapy was discontinued for one patient receiving rasburicase because of hemolysis. This 11-year-old boy with pre-B precursor ALL had evidence of disseminated intravascular coagulopathy, which resolved concomitantly with discontinuation of the rasburicase; the relationship to rasburicase is unknown. Testing of the patient’s blood and the 6 red blood cell donors from underlying G-6-PD deficiency. No patients experienced anaphylactic events due to rasburicase. Predose and end-of-study samples for the qualitative determination of antibodies to urate oxidase protein were received from 23 of 27 patients assigned rasburicase. None

<table>
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<tr>
<th>Patient group number of patients (rasburicase: allopurinol)</th>
<th>Rasburicase mean AUC ± SD</th>
<th>Allopurinol mean AUC ± SD</th>
<th>P value†</th>
<th>AUC ratios‡ (95% CI)¶</th>
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<tr>
<td>Total patients (27:25)</td>
<td>128 ± 70</td>
<td>329 ± 129</td>
<td>&lt; .0001</td>
<td>2.6 (2.0-3.4)</td>
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<td>Leukemia (20:19)</td>
<td>141 ± 75</td>
<td>361 ± 129</td>
<td>&lt; .0001</td>
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<td>Lymphoma (7:6)</td>
<td>92 ± 41</td>
<td>224 ± 55</td>
<td>.005</td>
<td>2.4 (1.6-4.0)</td>
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<td>Hyperuricemic (10:9)</td>
<td>162 ± 87</td>
<td>440 ± 121</td>
<td>.0007</td>
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<td>Normouricemic (17:16)</td>
<td>108 ± 51</td>
<td>266 ± 85</td>
<td>&lt; .0001</td>
<td>2.5 (1.9-3.3)</td>
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<td>Burkitt* (5:4)</td>
<td>90 ± 42</td>
<td>348 ± 200</td>
<td>.02</td>
<td>3.9 (1.2-9.0)</td>
</tr>
</tbody>
</table>

*Burkitt includes children with mature B-cell leukemia, or ≥ stage III Burkitt lymphoma, or ≥ stage III small noncleaved-cell lymphoma.
†The two mean AUCs were compared by two-sided Wilcoxon two-sample tests.
‡Ratio of the two mean AUCs were compared by two-sided Wilcoxon two-sample tests.
¶95% confidence intervals on the ratios of the two mean uric acid AUC (0-96 h) using the Fieller theorem.19

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Figure 2. Mean (± SE) plasma uric acid concentrations over time for all patients. Squares denote patients who received rasburicase (n = 27) and stars allopurinol (n = 25). The 24 hours post levels reflect 24 hours after the last dose of study drug. Patients who received rasburicase demonstrated more rapid decline and maintained lower plasma uric acid levels throughout the study period. The area under the plasma uric acid concentration curve through the first 96 hours of therapy was significantly less for patients receiving rasburicase (P < .0001).

Figure 3. Plasma uric acid concentrations during 24 hours after first dose of study drug for individual patients with uric acid levels more than 8 mg/dL at time 0. Squares (solid lines) denote individual patients who received rasburicase and stars (dashed lines) allopurinol. Hyperuricemic patients who received rasburicase (n = 10) all achieved a plasma uric acid level less than 8 mg/dL within 4 hours of first drug dose. None of the hyperuricemic allopurinol patients (n = 5) achieved control by 4 hours.
of the samples contained detectable amounts of antibodies to rasburicase.

Discussion

The use of urate oxidase is not a new therapeutic modality for the treatment of hyperuricemia associated with hematologic malignancies. The aspergillus-derived protein (nonrecombinant urate oxidase, Uricozyme) has been used in France and Italy for almost 3 decades. A report from France using the nonrecombinant urate oxidase protein in children with advanced Burkitt lymphoma/mature B-cell ALL demonstrated only a 1.7% incidence of dialysis during induction chemotherapy. This compares favorably to a recent report in the United States in which 21% of children with advanced Burkitt lymphoma treated with allopurinol, hydration, and alkalinization required hemodialysis during induction chemotherapy and 6 patients died during induction therapy secondary to renal/metabolic complications. Pui and colleagues treated 134 children with acute leukemia and Burkitt lymphoma with the nonrecombinant urate oxidase. They found a more rapid and significantly greater decrease in blood uric acid levels than historical controls treated with similar chemotherapy and allopurinol. However, 4.5% of the children given aspergillus-purified urate oxidase developed allergic reactions, manifested primarily by urticaria, bronchospasm, and hypoxia. The present study is the first randomized comparison of recombinant urate oxidase (rasburicase) versus allopurinol in pediatric patients with hematologic malignancies at high risk for tumor lysis.

In the present study, mean uric acid AUC\(_{0-96}\) was statistically significantly lower in the rasburicase group (128.1 mg/dL.hr) than in the allopurinol group (328.5 mg/dL.hr, \(P < .0001\)). Mean percent change from baseline uric acid concentration was \(-86.0\%\) for the rasburicase group and \(-12.1\%\) in the allopurinol group at 4 hours following the first dose of the study drug (\(P < .0001\)). In patients with hyperuricemia at baseline, median time to first demonstration of control of uric acid (plasma uric acid concentration < 8.0 mg/dL) was 4.0 hours following the first dose for the rasburicase group (\(n = 10\)) and 23.9 hours after the first dose for the allopurinol group (\(n = 5\)). These results demonstrate that rasburicase is a more potent and faster-acting hypouricemic agent than oral allopurinol. Unfortunately, intravenous allopurinol was investigational at the time of initiation of study and was unavailable for comparison to rasburicase. Future studies may want to compare the intravenous formulation of allopurinol to rasburicase.

Moreover, the incidence of renal failure requiring assisted renal support (dialysis or hemofiltration) during this study was null in the rasburicase group compared to one patient in the allopurinol group. This patient had a plasma creatinine level within normal range at baseline and developed renal failure secondary to tumor lysis syndrome during allopurinol dosing. In contrast, one patient in the rasburicase group, with a serum creatinine level of 2.2 mg/dL, improved without assisted renal support.

Hyperuricemic patients who received rasburicase improved their adjusted creatinine levels from 144% to 102% of mean for age and gender, from baseline through day 4 of study, respectively. In contrast, hyperuricemic patients who received allopurinol had worsening adjusted creatinine levels from 132% to 147% of mean, from baseline through day 4 of study (\(P = .147\) comparing change from baseline through day 4 by treatment group). This corresponds to a period where cytoreductive chemotherapy had begun and suggests that the more rapid control of plasma uric acid may have

Figure 4. Serum creatinine levels for hyperuricemic patients. (A) Serum creatinine levels for hyperuricemic patients who received rasburicase (\(n = 10\)). All serum creatinine levels for patients were plotted in reference to initiation of study drug. No patients received assisted renal support, including a 15-year-old girl whose creatinine level was more than 2 mg/dL at baseline (see text for details). (B) Serum creatinine levels for hyperuricemic patients who received allopurinol (\(n = 9\)). All serum creatinine levels for patients were plotted in reference to initiation of study drug. One patient who began therapy with a normal creatinine for age developed renal failure requiring hemodialysis and hemofiltration for several days (see text for details). (C) Adjusted creatinine levels (percent \(\pm\) SE of age/sex defined mean) for patients who were hyperuricemic at presentation. Squares denote patients who received rasburicase and stars represent allopurinol. Each creatinine level was adjusted by dividing the serum creatinine value by the published mean creatinine for patient’s age and gender \(\times 100\%). Normal mean creatinine levels were the following: less than 1 year = 0.3 mg/dL; 1 to 12 years = 0.5 mg/dL; 12 to 16 years = 0.75 mg/dL; males 16 years or older = 0.95 mg/dL, females 16 years or older = 0.85 mg/dL. The adjusted creatinine declined steadily during initiation of chemotherapy only for the rasburicase group.
translated into superior renal function during chemotherapy for patients treated with rasburicase. The study was not designed to compare renal function outcome, the incidence of renal failure, or the need for assisted renal support between the 2 treatment arms. Therefore, the number of hyperuricemic patients may have been too small to demonstrate any statistically significant differences.

In summary, this study supports the conclusion that rasburicase is a safe and effective alternative to allopurinol to rapidly control plasma uric acid concentrations in patients with hematologic malignancies at high risk for tumor lysis during induction/reduction chemotherapy. A larger number of patients would be required to determine if the more rapid control and reduction of plasma uric acid with rasburicase will also result in a significant decrease in metabolic complications and morbidity due to tumor lysis syndrome, or the need for additional renal support (dialysis or hemofiltration).

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