Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study

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Background: Sublingual immunotherapy (SLIT) has been proved to be effective in allergic rhinitis and asthma, but there are few data on its preventive effects, especially in children.

Objective: To evaluate the clinical and preventive effects of SLIT in children by assessing onset of persistent asthma and new sensitizations, clinical symptoms, and bronchial hyperreactivity.

Methods: A total of 216 children with allergic rhinitis, with or without intermittent asthma, were evaluated and then randomized to receive drugs alone or drugs plus SLIT openly for 3 years. The clinical score was assessed yearly during allergen exposure. Pulmonary function testing, methacholine challenge, and skin prick testing were performed at the beginning and end of the study.

Results: One hundred forty-four children received SLIT and 72 received drugs only. Dropouts were 9.7% in the SLIT group and 8.3% in the controls. New sensitizations appeared in 34.8% of controls and in 3.1% of SLIT patients (odds ratio, 16.85; 95% confidence interval, 5.73–49.13). Mild persistent asthma was less frequent in SLIT patients (odds ratio, 0.04; 95% confidence interval, 0.01–0.17). There was a significant decrease in clinical scores in the SLIT group vs the control group since the first year. The number of children with a positive methacholine challenge result decreased significantly after 3 years only in the SLIT group. Adherence was 80% or higher in 73.8% of patients. Only 1 patient reported systemic itching.

Conclusions: In everyday clinical practice, SLIT reduced the onset of new sensitizations and mild persistent asthma and decreased bronchial hyperreactivity in children with respiratory allergy.

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INTRODUCTION

Since its introduction in 1986,[1] sublingual immunotherapy (SLIT) has been a promising alternative to traditional subcutaneous immunotherapy (SCIT). During the past 20 years, numerous controlled trials and several meta-analyses[2–5] have confirmed its efficacy in respiratory allergy in adults and children. In addition, studies have demonstrated the satisfactory safety profile of SLIT and the low occurrence of adverse effects,[6–8] even in children younger than 5 years[9,10] or with accelerated build-up regimens.[11] For these reasons, SLIT has been included as a viable alternative to SCIT in the recent guidelines.[12] On the other hand, several important additional effects have been reported with SCIT, including the reduction of asthma onset[13–16] and of new sensitizations[17,18] as evaluated by means of skin prick testing. Some of these effects have been reported with SLIT as well,[19–22] but it has been said that more data are needed to confirm those observations. As with SCIT, the preventive effects can be reliably evaluated only in long-term trials involving many patients. The less restrictive open randomized trials can provide supportive results in this sense.

Based on this background, we aimed to assess the additional effects of SLIT (ie, prevention of persistent asthma onset, prevention of new sensitizations, and reduction of bronchial hyperreactivity) in a large cohort of allergic children with rhinitis with or without intermittent asthma in a real-life setting. Clinical efficacy, safety, and adherence to treatment were evaluated as secondary outcomes.

METHODS

General Plan

This study was designed to compare SLIT added to drug therapy with drug therapy alone in preventing the onset of (1) persistent asthma and (2) new sensitizations. Secondary objectives were to evaluate the magnitude of the clinical effect, the effect on bronchial hyperreactivity, the safety, and the adherence to SLIT. The study was designed to be open, controlled, and randomized. Pediatric outpatients fulfilling the inclusion criteria were evaluated during a baseline 1-year period and then were randomized (1:2) to receive either standard drug therapy or drug therapy plus SLIT for the responsible allergen. The patients were followed up for the onset of persistent asthma and new sensitizations at 3 years. Pulmonary function tests with methacholine challenge were also performed at baseline and at the end of the study. The

symptom plus medication score (SMS) was recorded yearly during the study period. The study design is summarized in Figure 1. All the parents signed an informed consent form, and the trial was approved by the internal ethical committees of Macchi Hospital Foundation, and S. Pertini Hospital.

Patients and Diagnosis

Children attending the Outpatient Department at Cuasso al Monte Hospital were screened for inclusion in this trial. The inclusion criteria were (1) both sexes and age of 5 to 17 years, (2) rhinitis with or without intermittent asthma according to Global Initiative for Asthma guidelines[23] for at least 2 years, and (3) a confirmed allergic etiology of the disease, including mites, grasses, trees, or weeds. The exclusion criteria were (1) persistent asthma or a forced expiratory volume in 1 second less than 80% of predicted, (2) previous courses of immunotherapy, (3) anatomical abnormalities of the upper airways, (4) chronic systemic disorders (malignancies or autoimmune diseases), and (5) sensitization to pets or molds.

The diagnoses of rhinitis and asthma were made according to current guidelines.[12,23] Skin prick tests were performed using a standard panel including the relevant allergens: house dust mites, grasses, birch, olive, ragweed, mugwort, Parietaria, cat and dog dander, Alternaria, and Cladosporium. The same batch of standardized, commercial extracts (Alk-Abellò, Lainate, Milan, Italy) was used throughout the study. Positive (histamine, 1%) and negative (saline) controls were also applied. Positivities were expressed as the mean of the major diameter of the wheal and its orthogonal diameter, and reactions greater than 5 mm were considered positive.

Pulmonary Function and Methacholine Challenge

Full lung function tests were performed at baseline and during the study. A computerized spirometer with a plethysmographic cabin (Masterlab, Jaeger, Wurzburg, Germany) was used. The nonspecific bronchial challenge with methacholine (Lofarma SpA, Milan, Italy) was performed during the period of maximal exposure to the relevant allergen (November-February for mites, March-April for birch, and May-June for grasses and Parietaria) using a constant-pressure dosimeter activated by inhalation, with fixed delivery times and a variable number of doses.[24] The doses were 30, 60, 120, 240, 390, 690, and 1,290 μg. The test results were considered to be methacholine positive when there was a 20% decline in forced expiratory volume in 1 second at a cumulative dose of 1,290 μg or less. Patients with negative methacholine challenge results were considered to have rhinitis only.

SLIT and Drug Treatment

The SLIT was prescribed according to current guidelines.[12] In addition to the Allergic Rhinitis and its Impact on Asthma recommendations, in polysensitized individuals, a nasal provocation test[25] was performed to select the relevant allergen. The prescribed SLIT (Anallergo, Florence, Italy) was prepared as a glycerinated solution to be administered as sublingual drops in the morning, with the patient fasted, that are kept there for at least 1 minute before being swallowed. The extract was standardized through a combined radioallergosorbent test inhibition and bioequivalence method: the potency was expressed as radioallergosorbent test units per milliliter (RU/mL). The build-up phase (approximately 50 days) involved the administration of increasing concentrations (100–3,000 RU/mL). In the maintenance phase, 5 drops from the 10,000 RU/mL vial were given 3 times a week. In patients receiving pollen SLIT, a dose reduction by one-third was performed in the pollen season. According to the manufacturer, the mean cumulative dose of major allergen per year was approximately 480 μg of Der p 1 and Der p 2, 40 μg of Phl p 1 and Par j 1, and 100 μg of Bet v 1. The cumulative yearly dose was, on average, 5 times greater than the dose of
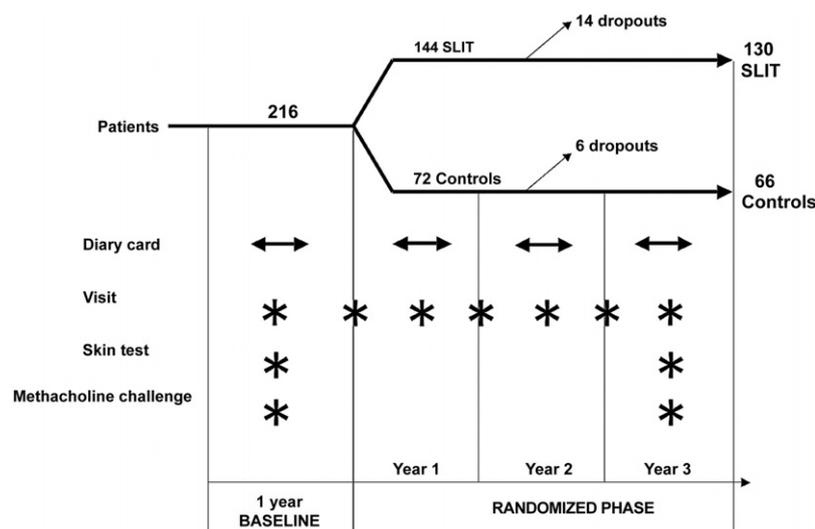

Figure 1. The study design. SLIT indicates sublingual immunotherapy.

the same product administered subcutaneously. A physician was always available at the clinic for telephone contact.

The following drugs were allowed by protocol in all patients: nasal cromolyn (10 mg/d), oral antihistamines (loratadine or cetirizine, 1 drop or 2.5 kg daily), intranasal beclomethasone dipropionate (2 puffs per nostril twice daily, or 400 μg/d), and inhaled salbutamol (100 μg or 1–2 puffs on demand). House dust mite avoidance measures were suggested to mite-sensitized patients.

Symptom plus Medication Score

Parents were instructed to keep a clinical diary of symptoms and drug intake. The clinical efficacy of treatment was analyzed on the basis of this record using the following items: nasal itching, sneezing, rhinorrhea, obstruction, cough, wheezing, and conjunctival itching or redness. Each symptom was rated as follows: 0, absent; 1, mild; 2, moderate; and 3, severe. The diaries were recorded in November to February for mites, March to April for birch, and May to June for grasses and *Parietaria*; 1 point was added for each daily use of any of the permitted drugs (maximum available SMS = 750). The monthly sum of SMSs was obtained; the mean sum of the months in each period of observation (2–4 months depending on the allergen) was used for statistical analysis.

Safety and Adherence

Parents were required to record, at each dose administration, local and systemic adverse reactions (rhinitis, asthma, urticaria, angioedema, generalized itching, diarrhea, vomiting, oral itching or swelling, and edema of the tongue). Any other suspected event was described in free text. Adherence was evaluated at each visit by measuring the remaining volume of the extract in the returned vials and comparing it with the expected amount of extract consumed during the treatment period. The volume of extract actually consumed by each patient was expressed as a percentage of the expected consumption.

Statistical Analysis

No a priori sample size calculation was performed because the study was conducted in real life. The statistician received the codes of the clinical records of the eligible patients and performed the randomization according to an algorithm implemented in the statistical software. For ethical reasons (the expected better outcome of SLIT), the randomization ratio was set at 1:2 in favor of SLIT.

Equality of sex ratios in different treatment groups at baseline were tested using the Fisher exact test, and differences in SMSs at baseline and after 1, 2, and 3 years of treatment were tested using the Mann-Whitney test.[26,27] The different effects of treatments on SMSs were tested using the Mann-Whitney test. To increase the statistical power to reach the same level gained by the corresponding parametric statistics computed when all the assumptions are met, the probability levels for the Pearson, χ^2, and Mann-Whitney tests were computed using a complete randomization method (permutation or exact test) or a Monte Carlo simulation[28] based on a 100,000 sampled table when computation by the permutation method was not possible. All the statistical analyses were computed using a software program (SPSS version 13.01; SPSS Inc, Chicago, Illinois).

RESULTS

Of 216 children (147 boys; mean age, 10 years) fulfilling the inclusion criteria and enrolled in this trial, 144 were allocated to receive SLIT in addition to drug therapy. All these children were prescribed SLIT for a single allergen, as follows: 98 for
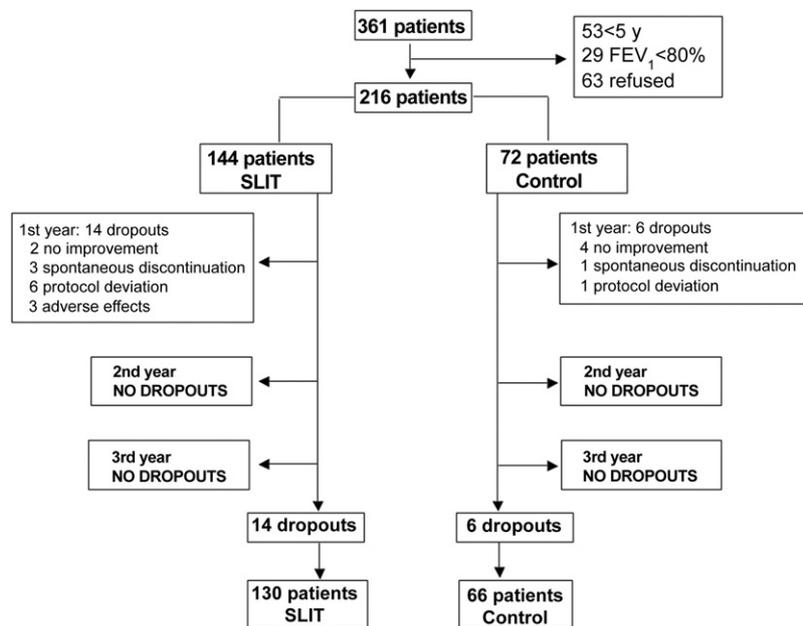

Figure 2. Flowchart of the study population. FEV_1 indicates forced expiratory volume in 1 second.

Table 1. Demographic and Clinical Data at Baseline

	SLIT plus drugs group (n = 144)	Drugs-only group (n = 72)	P value
Male sex, No. (%)	104 (72.2)	43 (59.7)	.09
Age, mean (SD), y	10.7 (0.43)	10.0 (0.3)	.30
Family history of atopy, % (No./total No. of relatives)[a]	42.7 (224/524)	36.9 (93/252)	.60
Any family history of asthma, % (No./total No. of relatives)[b]	17.4 (91/524)	15.1 (38/252)	.70
Rhinitis and intermittent asthma, No. (%)	86 (59.7)	45 (62.5)	.60
Rhinitis only, No. (%)[c]	58 (40.3)	27 (37.5)	.70
SMS, mean (range)	146.4 (106–189)	136.7 (110–178)	<.001
MCh positive, No. (%)[d]	82 (56.9)	42 (58.3)	.80
SPT monosensitized, No. (%)	81 (56.3)	38 (52.8)	.60
SPT polysensitized, No. (%)	63 (43.7)	34 (47.2)	.70
HDM SPT positive, No. (%)	98 (68.1)	48 (66.7)	.60
Pollen SPT positive, No. (%)	46 (31.9)	24 (33.3)	.80

Abbreviations: HDM, house dust mite; MCh, methacholine; SLIT, sublingual immunotherapy; SMS, symptom plus medication score; SPT, skin prick test.
[a] Family history of atopy is defined as at least 1 first-degree relative with inhalant or food SPT positivity.
[b] Any family history of asthma is defined as at least 1 first-degree relative with physician-diagnosed asthma.
[c] No symptoms of asthma and negative MCh challenge results.
[d] Methacholine challenge positive for a forced expiratory volume in 1 second decline of at least 20% at a cumulative dose of 1,290 μg or less.

Table 2. Asthma, Rhinitis, Positive MCh Challenge, Monosensitization, and Polysensitization in the Control and SLIT Groups at Baseline and After 3 Years of Treatment

	SLIT, No. (%)			Control, No. (%)			SLIT vs control (year 3)	
	Baseline (n = 144)	Year 3 (n = 130)	P value	Baseline (n = 72)	Year 3 (n = 66)	P value	P value	OR (95% CI)
Asthma								
Intermittent	86 (59.7)	15 (11.5)	<.001	45 (62.5)	11 (16.7)	<.001	NS	0.65 (0.28–1.51)
Mild persistent	0	2 (1.5)	.60	0	19 (28.8)	<.001	<.001	0.04 (0.01–0.17)
Rhinitis only	58 (40.3)	113 (86.9)	<.001	27 (37.5)	36 (54.5)	.20	<.001	5.54 (2.74–11.19)
MCh positive	82 (56.9)	23 (17.7)	<.001	47 (65.3)	31 (47.0)	.50	<.001	0.24 (0.12–0.47)
Monosensitized	81 (56.2)	72 (55.4)	.50	38 (52.8)	19 (28.8)	.04	<.001	3.07 (1.63–5.80)
Polysensitized	63 (43.8)	58 (44.6)	.70	34 (47.2)	47 (71.2)	.006	<.001	0.33 (0.17–0.61)

Abbreviations: CI, confidence interval; MCh, methacholine; NS, not significant; OR, odds ratio; SLIT, sublingual immunotherapy.

mites, 41 for grasses, 4 for birch, and 1 for *Parietaria*. During the 3-year randomized trial, 20 patients dropped out, but the dropout frequency did not differ in children undergoing SLIT (14 of 144) vs controls (6 of 72) (P = .76) (Fig 2). Four of 6 controls (66.7%) and 2 of 14 SLIT patients (14.3%) dropped out because of intolerable worsening of symptoms requiring more aggressive drugs, including systemic corticosteroids. The 3 dropouts due to adverse events in the SLIT group were for oral itching, asthma, and abdominal pain. According to this, 130 children in the SLIT group and 66 in the control group could be analyzed at the end of the 3 years of observation. Adherence to SLIT was satisfactory, with 73.8% of the patients having adherence of 80% or higher.

During the 3 years of SLIT, only 1 of 130 patients reported 1 episode of generalized itching (without skin lesions) within 30 minutes of taking the dose. This adverse event appeared during the maintenance phase, self-resolved without therapy, and was managed with a temporary dose halving.

The baseline characteristics of the 2 groups are reported in Table 1. There was no statistically significance difference be-

tween the groups, also considering the possible confounders (ie, actual or asthma ever and allergic rhinitis and atopic dermatitis, passive smoking, and pets in the house; data not shown). Only the SMS was slightly higher in the SLIT group at baseline.

In children who had asthma, its characteristics were different after 3 years of treatment, showing a lower occurrence of persistent asthma (that was mild only) in SLIT patients (2/130, 1.5%) than in controls (19/66, 28.8%) (odds ratio [OR], 0.04; 95% confidence interval [CI], 0.01–0.17) (Table 2), with a number needed to treat of 4 (95% CI, 3–5) (Fig 3). Similarly, after 3 years of treatment, a significant difference was seen in the overall occurrence of intermittent and persistent asthma, which was considerably more frequent in the control group (30/66, 45.4%) than in the SLIT group (17/130, 13.1%) (OR, 5.54; 95% CI, 2.74–11.19) (Table 2). The percentage of methacholine-positive patients became significantly different after 3 years (OR, 0.24; 95% CI, 0.12–0.47) (Table 2). The occurrence of new sensitizations was lower in the SLIT group (4 of 130) than in controls (23 of 66), (OR, 0.06; 95% CI, 0.02–0.17). Conversely, an increased rate of
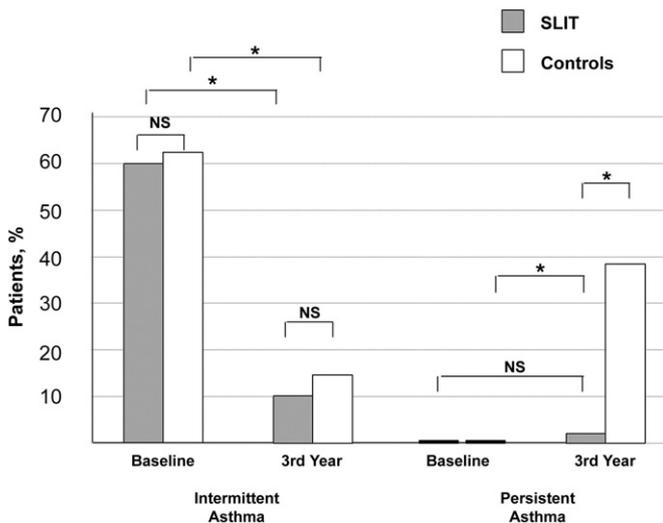
Figure 3. Asthma prevalence at baseline and after 3 years of sublingual immunotherapy (SLIT). *P < .001. NS indicates not significant.

polysensitizations was seen only in the control group (Table 2). The evolution of the SMS showed that the SLIT group had significantly fewer symptoms after 1 year of treatment, and this difference persisted at the second and third years (Fig 4).

DISCUSSION

Although the clinical efficacy of SLIT has been confirmed in several studies, concerns still exist about its preventive effects (eg, on new skin sensitizations and asthma onset). Indeed, the literature includes some positive results concern-
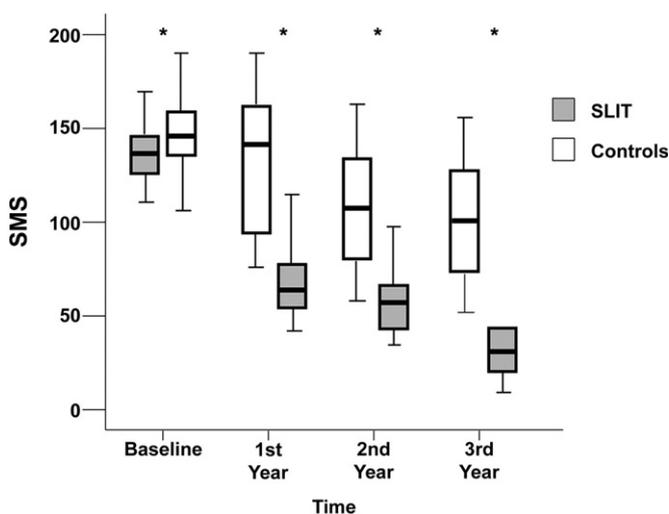

Figure 4. Monthly symptom plus medication scores (SMSs) in patients undergoing sublingual immunotherapy (SLIT) and controls at baseline and after 1, 2, and 3 years of treatment. The horizontal line in the middle of each box indicates the median, whereas the top and bottom borders of the box mark the first and third quartiles, respectively. The whiskers represent the extreme values. *P < .001, Mann-Whitney test (Monte Carlo method).

ing the prevention of asthma onset,[22] bronchial hyperresponsiveness,[29] and asthma worsening,[30] but these trials usually involved few patients, and the results could be questioned from a methodological point of view.[31]

In the present study, we aimed to assess the preventive effect of SLIT on persistent asthma, pulmonary function, and bronchial reactivity by following up allergic children for several years in an open controlled study. This study shows a preventive effect on the onset of mild persistent asthma, and this result remained statistically significant even after the worst-case analysis (SLIT group: 16/144 [11.1%]; control group: 19/72 [26.4%]; OR, 0.35; 95% CI, 0.17–0.72). Prevention of the onset of new sensitizations suggests that SLIT, similar to SCIT, acts as a biological response modifier. Also, for this result, the sensitivity analysis did not modify the significance. In the present study, all the children received symptomatic medications, but there was a significant improvement in nasal and bronchial symptoms in the SLIT group compared with the control group since the first year of treatment. Indeed, the patients and the investigators knew that a new treatment was added, and, therefore, an observer bias and a placebo effect[32] can be hypothesized. Nevertheless, in this study, the change in clinical scores was greater than 50%, and this cannot be explained only by a placebo effect. Another bias could be represented by the statistically significant difference in the baseline clinical scores between the SLIT group and controls that could justify the better result in the SLIT group during the 3 years. Nonetheless, this difference, although statistically significant, is expected to be clinically irrelevant (SLIT vs control: mean SMS, 146.4 vs 136.7) considering that the maximum available score was 750. A double-blind, placebo-controlled design would have enhanced the robustness of the trial, but it was not allowed by local ethics committees based on the duration of the study and the ascertained clinical effect of the treatment. On the other hand, the open design allowed us to expand patients to a greater degree than would have been possible in clinical trials involving selected individuals. In addition, the objective variables, such as pulmonary function, methacholine challenge results, and skin prick test findings, can be only partially affected by patients' or investigators' expectations.

Finally, these data confirm that SLIT is safe in childhood at the recommended doses. Sublingual immunotherapy also represents an advance in immunotherapy because it relies completely on patient self-administration, whereas SCIT is administered by a health care professional. Therefore, sociologic factors, such as the educational and economic status of the family, should be taken in consideration when prescribing SLIT because successful adherence depends on the parents' understanding and motivation.[33] Furthermore, in the controlled trials, adherence to SLIT was generally reported as "satisfactory," but no systematic evaluation was performed. In a recent survey involving a large sample of children in real life confirmed that compliance with SLIT was good, despite that the therapy is self-managed at home.[34] The present quantitative data did not substantially differ from that study. Of course, measuring the

volume of remaining extract does not prove that the patients actually took the vaccine, but this approach avoids an overestimation of the adherence: if the remaining volume of the vaccine is higher than expected we can be assured that the patient has not fraudulently discharged the extract.

In conclusion, this prospective, randomized, open trial in pediatric patients showed that SLIT can exert a preventive effect on the onset of persistent asthma and new skin sensitizations. In addition, these results confirm that SLIT reduces the SMS and nonspecific bronchial hyperresponsiveness.

ACKNOWLEDGMENTS

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