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# A study comparing six month treatment effects of Intranasal Mometasone, Azelastine and Oral Cetirizine in patients with persistent allergic rhinitis.

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## ABSTRACT

*Objectives: Allergic rhinitis is an allergen induced upper airway inflammatory disease. This one-year study was taken up to compare the efficacy of intranasal azelastine, intranasal mometasone and oral cetirizine in patients of allergic rhinitis during the six months treatment period and in the six month follow up period after treatment cessation.*

*Methods: In this open label, three-arm study, patients aged 18- 60 yrs, with at least one month history of persistent allergic rhinitis were enrolled and eligible patients were randomized into Group I -Intranasal Azelastine/ Group II-Intranasal Mometasone/ Group III- Oral Cetirizine. Primary outcome measure was reduction in total symptom score at 14 days from baseline.*

*Results: Each group had 15 patients with median baseline symptom scores of 10, 9 and 9 in Groups I, II and III respectively. There was significant reduction in total nasal symptom scores in Group II when compared to Groups I ($p<0.01$) and III ($P<0.0001$) and between Groups I & III, the reduction in total nasal symptom scores was non-significant at day 14. The number of recurrent episodes of rhinitis during follow up period were significantly less in group II when compared to Groups I ($p<0.0001$) and III ($p<0.0001$) and were significantly less in Group I when compared to Group III ($p<0.001$).*

*Conclusions: Mometasone nasal spray when used for longer duration despite resolution of symptoms, is effective in prevention of recurrent episodes after treatment cessation, when compared to azelastine nasal spray and oral cetirizine.*

**KEYWORDS : Mometasone furoate nasal spray, Azelastine Nasal spray, Cetirizine, Allergic Rhinitis.**

**Introduction:**

Allergic rhinitis, is clinically defined as a symptomatic disorder of the nose, induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose, which represents a global health problem. It is an extremely common disease worldwide affecting 10 to 25 % of the population. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment. Although allergic rhinitis is not usually a severe disease, it significantly alters the social life of patients and affects school learning performance as well as work productivity. Moreover, the costs incurred by rhinitis are substantial.[1]

Allergic rhinitis is classified into "intermittent" and "persistent" rhinitis. If symptoms are present for less than 4 days a week or for less than 4 weeks it is intermittent rhinitis; if symptoms are present for more than 4 days a week and for more than 4 weeks then it is persistent rhinitis.[1]

A clinical history is essential in making an accurate diagnosis of rhinitis, assessing its severity and its likely response to treatment. Clinical classification of rhinitis given by International consensus on rhinitis (1994) classifies patients into either sneezers and runners or blockers. Sneezers and runners are characterized by paroxysmal sneezing with watery nasal discharge associated with itching, worse during day unlike blockers who have severe nasal blockage associated with thick nasal discharge worse at night.[2]

The management of allergic rhinitis includes allergen avoidance, medication (pharmacologicaltreatment), immunotherapy, and education. Surgery may be used as an adjunctive intervention in a few highly selected patients.[1]

Medications used for rhinitis are most commonly administered either intranasally or orally. There are several advantages of intranasal medication. High concentrations can be delivered directly into the nose, thus avoiding or minimizing systemic effects. However, in patients with allergic rhinitis who have conjunctivitis and/or asthma, medications may need to be administered systemically to various target organs.[1]

Medications for treatment of allergic rhinitis include oral and topical (intranasal) H1-antihistamines (H1-receptor antagonist/blockers), intranasal corticosteroids, oral corticosteroids, intranasal chromones, oral and intranasal decongestants, oral decongestants combined with H1-receptor antagonists, intranasal anticholinergics, and leukotriene receptor antagonists.[1]

H1-antihistamines are medications that block histamine at the H1-receptor level. Oral H1-antihistamines are effective against symptoms mediated by histamine (rhinorrhoea, sneezing, nasal itching and eye symptoms) but are less effective on nasal congestion. Although first-generation oral H1-antihistamines are effective, they cannot be recommended when second generation drugs are available, because of their sedative and anticholinergic effects. Intranasal H1-antihistamines are effective at the site of administration.[3]

Intranasal glucocorticoids are the most efficacious medication available for the treatment of allergic and nonallergic rhinitis. The rationale for using intranasal glucocorticoids in the treatment of allergic rhinitis is that, high drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects. These medications are effective in relieving all symptoms of allergic rhinitis as well as ocular symptoms. If nasal congestion is present or symptoms are frequent, an intranasal glucocorticoid is the most appropriate first-line treatment as it is more effective than any other treatment.[3]

Although many agents have proved to be effective in management of allergic rhinitis, medications have no long-lasting effect when stopped, so maintenance treatment is required for persistent disease. Tachyphylaxis does not usually occur with prolonged treatment. In asthma, it has convincingly been shown that long term controller therapy is required to maintain control of the disease and prevent exacerbations. However, in rhinitis, a minimal persistent inflammation has been shown in the nasal mucosa of symptom-free patients allergic to house dust mites or pollens, the clinical relevance of these findings has to be better established. Thus, although it is recommended to continue the treatment of patients with controlled persistent rhinitis for some time, guidelines for the duration and cessation of treat-

ment have to be developed and tested.[1]

As the benefit of outcome of long term treatment in allergic rhinitis is still not known and in current scenario, the treatment of allergic rhinitis is generally given on p.r.n (as required) basis, due to uncertainity of outcome of long term treatment and fear of side effects of these agents when used for prolonged periods, we have taken up this long term study of one year duration, to compare the efficacy and safety of intranasal Mometasone, Azelastine and oral Cetirizine and to assess the clinical outcome of six month treatment in patients of persistent allergic rhinitis and and in the six month follow up period after treatment cessation.

**Patients and Methods**

This study was a prospective, randomized, open label, parallel group, three arm study, conducted in accordance to principles of Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by Institutional Ethics Committee and all the patients gave written informed consent before the start of the study.

Patients aged 18-60 yrs of either gender with history of persistent allergic rhinitis of atleast one month and those who have agreed to follow all trial related procedures were included in the study. Patients with history of upper and/or lower respiratory tract infections, diabetes, acid peptic disease; those who have taken antihistamines and/or topical corticosteroids in past 2 wks and systemic corticosteroids in past 4 wks were excluded from the study. Patients undergoing desensitization (immunotherapy), pregnant and lactating women and patients with any history of drug hypersensitivity especially to study medications were also excluded from the study.

Study comprised of altogether 8 visits, which included, Screening visit, Treatment period which included Randomization visit (0 day), visits at 2wks, 6 wks, 18 wks and 24wks (end of treatment visit) and follow up period which included review visit (36 wks) and end of study visit (48wks). All patients were screened in the screening period (1 wk), and then the eligible patients were randomized to any one of the three study groups, group I received intranasal azelastine, group II received intranasal mometasone and group III received oral cetirizine for a period of 24 wks, then the treatment was stopped for all the patients and they entered follow up period from 24wks to 48 wks during which number of recurrent episodes were recorded in each patient. Each patient was given a card in which the patient details, treatment regimens, adverse events, treatment compliance, review dates were recorded and was instructed to get the card at each visit. At all the visits, clinical examination and local examination of nose was done. Symptoms of sneezing, discharge, obstruction and itching and any other relevant medical details were recorded in the card and the case record form.

The following was the treatment schedule followed- Patients of group I received intranasal azelastine (137mcg/spray) 2 sprays/nostril, twice daily from 0- 4wks; then 2sprays/nostril, once daily from 4-6 wks; 1 spray/nostril, twice daily from 6 -12 wks; 1 spray/nostril, once daily from 12-18wks and 1 spray/nostril, thrice weekly from 18-24 wks. Patients of group II received Mometasone nasal spray (50 mcg/spray) 2 sprays/nostril, once daily from 0- 6 wks; 1 spray/nostril, once daily from 6-18 wks;1 spray/nostril, thrice weekly from 18-24 wks. Patients of Group III received Tablet Cetirizine (each tablet containing10mg) 1 tablet/day from 0-18 wks and 1 tablet thrice weekly from18- 24 wks.

The primary outcome measure of the study was change in total nasal symptom scores at day 14 from baseline and secondary outcome measures included comparison of the mean total nasal symptom scores between successive periods of the study (2 wk, 6 wk, 18 wk and 24 wk) between treatments, number of recurrences in the follow-up period and safety and tolerability of study medications.

Assessment of efficacy was done by recording the severity of nasal symptoms, sneezing, nasal discharge, nasal congestion, nasal itching by using a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe); total symptom score which was obtained by adding the individual symptom scores at baseline, 2 wks, 6wks, 18 wks and 24 wks; and by recording the number of recurrent episodes during follow up period per patient. Safety was monitored throughout the study by recording adverse events at each visit.

The primary efficacy variable was analyzed using one-way ANOVA. The secondary efficacy variables were analyzed using two-way ANOVA for comparison of the mean total nasal symptom score between successive periods between treatments, one way ANOVA for number of recurrences during follow up period. All these analyses were done on SPSS software.

Sample size calculation: 54 patients were needed to be enrolled to randomize 15 subjects per group to detect a reduction of total symptom scores at day 14 by 2.8 units at an estimated standard deviation of 2.3 considering 80% as power of study and 5% level of significance with a screen failure rate of 10% and dropout rate of 10%.

**Results:**

In this study, 50 patients were screened, of which 45 patients were randomized, 15 into each group. Of the 50 screened patients, five were not randomized as two patients were found to be diabetic and three patients had history of intake of H1-antihistamines. All the 45 patients completed the study.

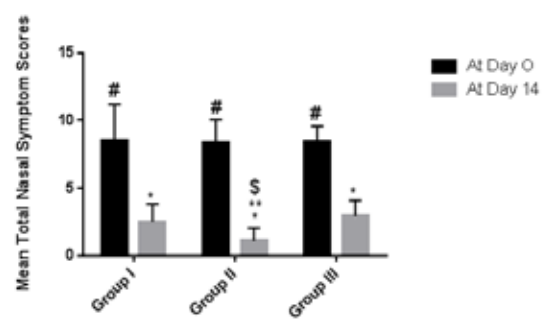
The patient characteristics are as shown in the table no 1. No significant difference was found in total symptom scores at baseline between the groups (p>0.05) (Table No 1).

**Table No 1 shows patient characteristics at baseline (randomization visit).**

| | Parameter | Group I | Group II | Group III | p value |
|---|---|---|---|---|---|
| 1 | Age (in yrs) (mean±SD) | 29.2 ± 6.9 | 30.5 ± 7.8 | 31.3 ± 7.7 | ns |
| 2 | Gender<br>Male,n(%)<br>Female,n (%) | <br>6(40)<br>9(60) | <br>6 (40)<br>9 (60) | <br>8 (53)<br>7(47) | |
| 3 | Median Total Symptom Scor (TSS) | 10 | 9 | 9 | ns |
| 4 | Mean AEC (per cu.mm) | 497 | 451 | 479 | ns |

Note: AEC- Absolute Eosinophil count, ns- non-significant (p>0.05)

In all the three treatment groups, the total symptom scores have significantly decreased at day 14 when compared to baseline (p<0.0001). At day 14 from baseline, the total symptom scores in Group II were significantly less when compared to Group I (p<0.01) and Group III (p<0.0001) and that in group I did not differ significantly from group III (p>0.05) (Fig No 1)




* indicates p<0.0001 compared to Day 0 within group
\# indicates p>0.05 for comparison of between group Day 0 scores
** indicates p<0.01 when compared to group I
$ indicates p<0.0001 when compared to group III

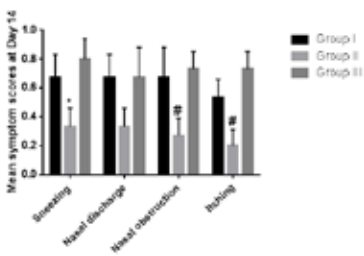
**Fig No 1- showing mean total symptom scores at day 0 (baseline) and day 14 of all the treatment groups.**

In all three groups, the individual symptom scores for sneezing, nasal discharge, nasal obstruction and itching have significantly decreased at day 14 when compared to baseline. (p≤0.001). (Table No 2). At day 14, among the individual symptom scores, sneezing, nasal obstruction and itching significantly decreased in group II when compared to group III (p<0.01, p<0.01, p<0.05 respectively); there was no significant difference seen between group I and group III and between group I and

group II in any of the individual symptoms reduction. (Fig No 2)

**Table No 2 showing mean symptom scores for individual symptoms at baseline and day 14.**

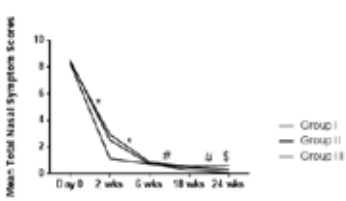
| S.No | Symptom | Group | Mean Symptom score At baseline | Mean Symptom score At Day 14 | p-value (Day 14 compared to baseline) |
|---|---|---|---|---|---|
| 1 | Sneezing | I | 2.47±0.5 | 0.67± 0.6 | <0.0001 |
| | | II | 2.27± 0.5 | 0.33± 0.5 | <0.0001 |
| | | III | 2.33± 0.6 | 0.8± 0.6 | <0.0001 |
| 2 | Nasal Discharge | I | 2.33±0.9 | 0.67±0.62 | <0.0001 |
| | | II | 2.2±0.9 | 0.3± 0.5 | <0.0001 |
| | | III | 2.27± 0.7 | 0.67± 0.8 | <0.0001 |
| 3 | Nasal obstruction | I | 1.6±0.8 | 0.67±0.8 | =0.001 |
| | | II | 1.8 ± 0.4 | 0.27± 0.5 | <0.0001 |
| | | III | 1.53±0.6 | 0.73±0.5 | <0.0001 |
| 4 | Itching | I | 2.13±1.2 | 0.53±0.5 | <0.001 |
| | | II | 2.07±0.1 | 0.2±0.4 | <0.0001 |
| | | III | 2.27 ±0.6 | 0.73±0.5 | <0.0001 |




* indicates p<0.05 between Group II & Group III
# indicates p<0.01 between Group II & Group III

**Fig No 2 showing mean individual symptom scores for sneezing, nasal discharge, nasal obstruction and itching at day 14 of treatment of all the groups.**

In all the three treatment groups, comparison of the mean total nasal symptom score between successive periods showed that, there was significant decrease in symptom scores at day14 from day 0 (p<0.05) and at wk 6 from day14 (p<0.05), there was no significant decrease in symptom scores at wk 18 from wk 6 and at wk 24 from wk 18 (p>0.05) and no statistically significant difference was found between treatments at end of six month treatment period. (Fig No 3)




* - p<0.05 between two successive periods independent of treatment.
# - p>0.05 between two successive periods independent of treatments.
$ - p>0.05 between treatment differences at end of treatment from baseline.

**Figure No 3 showing reduction in mean total nasal symptom scores in the three treatment groups between successive periods during the study.**

Mean number of recurrent episodes of rhinitis during the follow up period of 6 months (from wk 24 weeks to wk 48) were significantly less in group II when compared to Group I (p<0.0001) and Group III (p<0.0001) and were significantly less in Group I when compared to Group III (p<0.001). (Table No 3).

**Table No 3 showing total number of recurrent episodes of allergic rhinitis during the follow up period.**

| S.No | Number of recurrent episodes | Group I | Group II | Group III |
|---|---|---|---|---|
| 1 | Total No. of episodes per group | 77 | 25 | 113 |
| 2 | Mean ± SD | 5.13# | 1.67* | 7.53 |

*p<0.0001 when compared with group I and group III; # p<0.001 when compared to group III

In group I, most commonly reported adverse effect was bitter taste by 5 patients followed by headache in 3 patients; in group II, most commonly reported adverse effect was dry cough in 6 patients followed by headache in 4 patients and in group III most commonly reported adverse effect was sedation in 7 patients followed by headache in 4 patients and lethargy in 4 patients. However, none of the patients have discontinued the study due to adverse effects. (Table no 4)

**Table No 4 showing adverse effects experienced in each of the treatment groups**

| S. No | Adverse effect | I (Azelastine) | II (Mometasone) | III (Cetirizine) |
|---|---|---|---|---|
| 1 | Bitter taste | 5 | 0 | 0 |
| 2 | Sedation | 1 | 0 | 7 |
| 3 | Dry Cough | 0 | 6 | 1 |
| 4 | Headache | 3 | 4 | 4 |
| 5 | Lethargy | 0 | 0 | 4 |
| 6 | Throat irritation | 1 | 0 | 0 |
| 7 | Dryness of throat | 1 | 1 | 1 |
| 8 | Stinging sensation | 1 | 2 | 0 |
| 9 | Nasal irritation | 1 | 1 | 0 |

## Discussion

Allergic rhinitis, is an extremely common, highly prevalent, IgE mediated hypersensitivity disease of mucous membranes of nasal airway characterized by sneezing, watery nasal discharge, sensation of nasal obstruction and itching, causing significant discomfort to sufferers. In this study, which was aimed to compare the efficacy and safety of Intranasal Mometasone, Azelastine and oral cetirizine and to assess the clinical outcome of six month treatment in patients of persistent allergic rhinitis, the allergic rhinitis symptoms decreased in all three groups significantly by day 14 with sustained improvement at 6 wks, 18wks and 24 wks. There was significant symptomatic improvement seen in all three treatment groups at wk 2 when compared to baseline (p<0.00001).The mean total nasal symptom scores at 2wk have significantly decreased in group II when compared to group I (p<0.01) and group III (p<0.0001).

The results of our study are in agreement with results of 3 month, randomized, double blind, double dummy, parallel group study done in 550 patients by Mandl et al, in which the eligible patients were randomized to one of the three treatment groups, Mometasone 200mcg , fluticasone 200mcg or placebo. The mean percent reduction in combined morning and evening total nasal symptom score (from baseline) was significantly more effective in mometasone furoate and fluticasone propionate group when compared to placebo and there was no statistically significant difference seen between mometasone furoate and fluticasone propionate. [4]

The efficacy of Mometasone Furoate nasal spray (MFNS) in the treatment of allergic rhinitis has been demonstrated in several clinical studies, particularly in a review performed by Italian researchers, who carried out a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. In this analysis, 1534 subjects and 1464 subjects represented MFNS and placebo-group, respectively. A significant reduction in total nasal symptom scores such as congestion, rhinorrhea, sneezing, and nasal itching was observed in the MFNS partici-

pants. This evaluation provided a level Ia evidence for the efficacy of MFNS in the therapy of allergic rhinitis vs placebo. Finally, such topical nasal steroid is also effective in preventing the onset of symptoms in patients with Allergic Rhinitis.[5]

In a review done by Davies RJ and Nelson HS, key findings were reviewed from the clinical development program for MFNS, comprising more than 20 clinical trials with more than 6000 patients worldwide, showed that MFNS exhibits strong anti-inflammatory activity in vitro and in vivo, and has a rapid onset of action, affording clinically significant symptom relief in 28% of patients within 12 hours of the first dose. Once-daily MFNS is at least as effective as other intranasal glucocorticoids, including twice-daily beclomethasone dipropionate and once-daily fluticasone propionate and budesonide and was well tolerated. [6] Similar findings were reported in another review done by Onrust SV and Lamb HM. [7]

To our knowledge, there are no studies which compared azelastine nasal spray and mometasone furoate nasal spray (MFNS) head to head, but there are studies which compared other nasal corticosteroids with azelastine nasal spray. In a study conducted by Wang D and Clement P intranasal budesonide showed a strong effect on infiltration and activation of eosinophils during the season and on nasal symptom scores in comparison to intranasal azelastine. [8]

In the metaanalysis done by Weiner ,of 17 randomized clinical trials which compared different intranasal corticosteroids with different antihistamine both sedating and non sedating, for the effect on nasal symptoms and total nasal symptom scores, it was concluded that intranasal corticosteroids produced significantly greater relief than oral antihistamines which are in agreement with our study results.[9]

In our study, mean total nasal symptom scores in group I did not differ significantly from group III ($p>0.05$) at day 14 (Fig no 1). These results are supported by the results in a study conducted by Mc Neely and Wiseman LR, in which intranasal azelastine 1 puff per nostril was shown to be as effective as standard doses of other antihistamines including intranasal levocetirizine, oral cetirizine and ebastine at reducing overall symptoms of rhinitis. [10]

In our study, in all the three treatment groups, comparison of the mean total nasal symptom score between successive periods showed that, there was significant decrease in symptom scores at day14 from day 0 ($p<0.05$) and at wk 6 from day14 ($p<0.05$), there was no significant decrease in symptom scores at wk 18 from wk 6 and at wk 24 from wk 18 ($p>0.05$) and no statistically significant difference was found between treatments at 24 wks. (Fig No 3). These results are similar to the results of a study done by Baena-Cagnani and Patel, in which long term efficacy and safety of mometasone furoate nasal spray in children with perennial allergic rhinitis was evaluated and they found that significantly greater mean changes were seen in MFNS-treated patients when compared to placebo between baseline and day 15. This study comprised of a double-blind, 4-week efficacy and safety period followed by a 6-month, open-label safety period. During the double blind period the subjects were randomized to MFNS or placebo, in the open label period all the subjects received MFNS, during which improvement continued through the open-label period. Subjects treated with MFNS in both periods experienced a 45% further reduction in TSS in this study phase, while those who switched from placebo to MFNS saw a further 49% decrease. [11]

In our study, mean number of recurrent episodes of rhinitis during the follow up period of 6 months (from wk 24 to wk 48) were significantly less in group II when compared to Group I and Group III and were significantly less in Group I when compared to Group III (Table No.3), in this follow up period the patients were not on any medication for allergic rhinitis and we found that the recurrent episodes of rhinitis were less in patients who were treated with mometasone when compared to other groups, this shows that it has some residual effect on nasal pathology which improves the quality of life in these patients for a longer period. The recurrent episodes when occurred in patients, they were treated with the same medication which they received during the treatment period for 5-7 days and stopped.

All the three study medications were tolerated well during the study. Similar findings were seen in the study done by Baena-Cagnani and Patel. [11]

So, in this study we observed that if treatment was continued by down titration of dosages for 24 wks despite significant reduction in symptom scores at day 14, in mometasone treated group, the long term clinical outcome was seen in the form of reduced frequency of recurrent allergic rhinitis episodes when compared to patients treated with azelastine and cetirizine. This favorable long term clinical outcome in the form of reduced number of recurrent episodes translates directly into better quality of life in patients and it was well tolerated however some patients complained of dry cough(6) and headache(4) which resolved with symptomatic treatment for 2-3 days. There are no studies to the best of our knowledge which evaluated number of recurrent episodes of rhinitis after withdrawal of treatment.

**Limitations of the study**

This was done as an open label study, it would be more affirmative if done as a blinded study, however as the symptoms sneezing and nasal discharge are objective in nature, lack of blinding might not have affected the outcome of the study. In our study, we used recommended dosages of the three medications and were gradually tapered and withdrawn. According to the ARIA workshop report, 2001, it is recommended to continue the treatment of patients with controlled persistent rhinitis for some time, guidelines for the duration and cessation of treatment are yet to be developed and tested.[1] Therefore, in this study, due to lack of any guidelines, during the six month treatment period, all the three medications were gradually withdrawn, as corticosteroids need to be gradually tapered and withdrawn, as it is not advisable to continue steroids for long periods at high doses when symptoms have resolved due to uncertainity of side effects.

**Conclusion:**

This study has shown that mometasone furoate nasal spray was more effective, to a clinically relevant degree, than azelastine nasal spray and cetirizine in tablet formulation in causing relief of allergic rhinitis symptoms. There was rapid onset of effect, with significant improvement at 2 wks, which improved over a course of 6 months treatment period and this effect has sustained during the 6-month follow up period as evidenced by less number of recurrent episodes of rhinitis. Though, Azelastine nasal spray had similar efficacy as cetirizine, in control of nasal symptoms, the side effects lethargy and sedation were reported more in cetirizine group and so also more number of recurrent episodes during follow up. So, taking all these into consideration, it is concluded that mometasone nasal spray when used for longer duration despite resolution of symptoms, is effective in prevention of recurrent episodes after treatment cessation, when compared to azelastine nasal spray and oral cetirizine. However, this observation needs to be confirmed in further studies.

**Conflict of Interest**

Authors declare that there is no conflict of interest regarding the publication of this paper.

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