Pharmaceutical Sciences and Drug Design
ISSN: 3062-4428
2025, Volume 5, Page No: 217-224

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Clinical Significance of Sustained Nintedanib Treatment in Idiopathic Pulmonary Fibrosis: A 12-Month Real-World Evaluation

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Received: 29 May 2025; **Revised:** 16 October 2025; **Accepted:** 21 October 2025

ABSTRACT

Evidence from clinical trials such as INPULSIS-ON indicates that extended use of nintedanib is generally safe for patients with idiopathic pulmonary fibrosis (IPF). Nevertheless, real-world data on long-term therapy are scarce. This study examined how effective and tolerable prolonged nintedanib treatment is when used in everyday clinical care. This retrospective review included 104 individuals diagnosed with IPF who received nintedanib. Patients were divided into two cohorts: those who maintained therapy for more than 12 months (P group, n=51) and those who discontinued before reaching 12 months (I group, n=53). Clinical outcomes and treatment tolerance were evaluated across both groups. In the I group, 29 patients halted treatment because of adverse reactions—most commonly diarrhea and nausea or poor appetite. Another 19 discontinued due to disease progression, and 4 because their performance status (PS) worsened. One patient died unexpectedly during therapy. Nausea/anorexia occurred almost twice as often in the I group compared with the P group (49.06% vs 25.49%). Patients who continued therapy beyond 12 months lived significantly longer (median 35 vs 12 months) and showed a markedly smaller annual reduction in forced vital capacity (10 mL/year vs 165 mL/year). A poor PS at treatment start was the only factor strongly associated with failing to maintain therapy beyond 12 months. Patients with better initial PS also demonstrated superior survival (27 vs 13 months). Reduced baseline PS markedly increases the likelihood of discontinuing nintedanib within the first year. Maintaining long-term therapy appears to offer a survival advantage for individuals with IPF.

Keywords: Idiopathic pulmonary fibrosis, Nintedanib, Real-world evidence, Performance status, Gastrointestinal intolerance.

How to Cite This Article: Adams G, Hayes W. Clinical Significance of Sustained Nintedanib Treatment in Idiopathic Pulmonary Fibrosis: A 12-Month Real-World Evaluation. Pharm Sci Drug Des. 2025;5:217-24. https://doi.org/10.51847/iE5dkK27c3

Introduction

Nintedanib is an approved antifibrotic therapy for idiopathic pulmonary fibrosis (IPF). Findings from the INPULSIS trials showed that it slows annual forced vital capacity (FVC) decline, reduces the frequency of acute exacerbations, and delays the onset of the first exacerbation episode [1–4]. Additional evidence from the INPULSIS-ON extension and the TOMORROW phase 2 follow-up further supported the long-term safety and tolerability of this medication [1, 5–7].

Although the INPULSIS program compared outcomes between participants who continued nintedanib and those who switched from placebo, it did not examine survival or treatment outcomes based on whether patients were actually able to maintain therapy beyond a year. More recently, tolerability and prolonged use of both nintedanib and pirfenidone have been reported.8 However, these antifibrotic agents differ in their mechanisms and side-effect profiles [2, 8–10].

Existing real-world studies have mainly focused on the first year of nintedanib therapy, including its safety, tolerability, and predictors of early discontinuation [11, 12]. To date, however, no real-world investigations have specifically assessed outcomes associated with continuing versus discontinuing nintedanib after the first year. Therefore, this study aimed to evaluate the long-term clinical performance of nintedanib, with a particular focus

on patients able to remain on therapy for over 12 months. We describe the characteristics of patients who successfully maintained treatment beyond a year, the clinical impact of extended therapy, and factors associated with early discontinuation.

Materials and Methods

Study population

We retrospectively reviewed the records of patients diagnosed with IPF who began nintedanib therapy at Juntendo University Hospital or Juntendo University Urayasu Hospital from April 2015 to December 2018. IPF was diagnosed using the 2011 international guidelines.14 Patients who continued nintedanib for at least 12 months were placed in the continuation group (P group), while those who discontinued earlier formed the non-continuation group (I group). The study protocol was approved by the institutional ethics committee (approval number 18–056), which waived the requirement for informed consent due to the retrospective design.

Clinical evaluation

Baseline data recorded at the start of nintedanib therapy included age, sex, smoking status, height, weight, body mass index (BMI), body surface area (BSA), performance status (PS), and dyspnea evaluated by the modified Medical Research Council (mMRC) scale.15 General condition was assessed using the Eastern Cooperative Oncology Group/World Health Organization PS scale, with PS > 2 considered poor.16 BMI was calculated as weight divided by height squared, and BSA was determined using the Du Bois formula [13].

Disease severity was assessed using the GAP index, derived from age, sex, FVC, and diffusing capacity; scores >6 indicated advanced IPF.18 FVC measurements were reassessed 12 ± 3 months after treatment initiation. Adverse events were monitored every six months according to CTCAE v4.0.

Statistical analysis

Between-group comparisons of baseline characteristics, tolerability, and treatment outcomes were performed using Fisher's exact test, chi-square test, or the Wilcoxon two-sample test. Parametric and non-parametric variables were compared using Student's t-test and Mann–Whitney U-test, respectively. Median survival differences were evaluated using the log-rank test. Factors associated with treatment continuation were analyzed by multivariate methods, including Cox proportional hazards modeling and logistic regression. A p-value < 0.05 was considered statistically significant. Statistical analyses were completed using SPSS version 26.0 (Chicago, IL, USA).

Results and Discussion

Patient characteristics

A total of 104 patients with IPF were included; 51 remained on nintedanib for more than 12 months (P group), while 53 discontinued before 12 months (I group**) (Figure 1)**. In the I group, 29 patients stopped therapy because of adverse events—primarily diarrhea and nausea or loss of appetite. Another 18 discontinued due to disease progression, and 4 because their PS deteriorated. One patient died suddenly during treatment.

Baseline characteristics are shown in **Table 1**. The median age was 73 years (range 62–85), and most participants were male (86.54%) and had a history of smoking (87.50%). Poor PS was observed in 24 patients (23.08%). Median BMI and BSA were 22.8 kg/m² and 1.68 m², respectively. Median FVC was 2.23 L, %FVC was 66.9%, DLco was 7.19 mL/min/mmHg, and %DLco was 29.81%.

Pulmonary function tests were not completed in 11 patients due to prior pneumothorax/mediastinal emphysema or severe cough. Of those who completed testing, 12 were unable to undergo DLco assessment because of cough or hypoxemia. Nintedanib was initiated at a reduced dose (200 mg/day) in 39 patients due to age or compromised PS. Twenty-seven patients had previously received low-dose corticosteroids, with 19 taking prednisolone in response to worsening interstitial pneumonia prior to nintedanib initiation. In most of these cases, nintedanib was started more than a year earlier.

Here is the paraphrased and neatly reformatted table:

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (n = 104)	P Group (n = 51)	I Group (n = 53)	p-value
Age (years), median (range)	73 (46–87)	70 (46–87)	74 (51–87)	0.056
Sex, male	90 (86.5%)	46 (90.2%)	44 (83.0%)	0.391
Smoking history, ever	91 (87.5%)	44 (86.3%)	47 (88.7%)	0.773
Performance status (ECOG), 0/1/2/3/4	31/49/17/6/1	23/25/2/1/0	8/24/15/5/1	0.0003
BMI (kg/m²), median (range)	22.8 (13.6–34.1)	23.3 (15.1–29.7)	22.6 (13.6–34.1)	0.232
Body surface area (m²), median (range)	1.68 (1.21–2.03)	1.71 (1.23–1.93)	1.63 (1.21–2.03)	0.126
GAP index				0.412
• Stage I (0–5) / Stage II–III (6–9)	50/43 (n = 93)	29/21 (n = 50)	21/22 (n = 43)	
Modified MRC dyspnea scale (mMRC)				0.345
• Grade 1/2/3/4	57/28/12/7	31/15/4/1	26/13/8/6	
Nintedanib starting dose				0.648
• 300 mg/day / 200 mg/day	65/39	33/18	32/21	
Prior prednisolone treatment, yes	27 (26.0%)	16 (31.4%)	11 (20.8%)	0.269
Pulmonary function tests				
FVC (L), median (range)	2.23 (0.72–3.82) (n = 93)	2.28 (0.98–3.31) (n = 50)	2.18 (0.72–3.82) (n = 43)	0.437
% predicted FVC, median (range)	66.9 (20.6–109.7) (n = 93)	68.5 (37.5–109.7) (n = 50)	65.3 (20.6–97.2) (n = 43)	0.337
DLco (mL/min/mmHg), median (range)	7.19 (1.99–16.64) (n = 81)	7.39 (2.96–14.02) (n = 44)	6.26 (1.99–16.64) (n = 37)	0.488
% predicted DLco, median (range)	29.8 (8.5–63.5) (n = 81)	30.9 (12.8–57.6) (n = 44)	33.7 (8.5–63.5) (n = 37)	0.779

Abbreviations: P, patients who were able to receive nintedanib for more than 12 months; I, patients who were not able to receive nintedanib for more than 12 months; BMI, body mass index; BSA, body surface area; mMRC, modified Medical Research Council Dyspnea; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide; PSL, prednisolone.

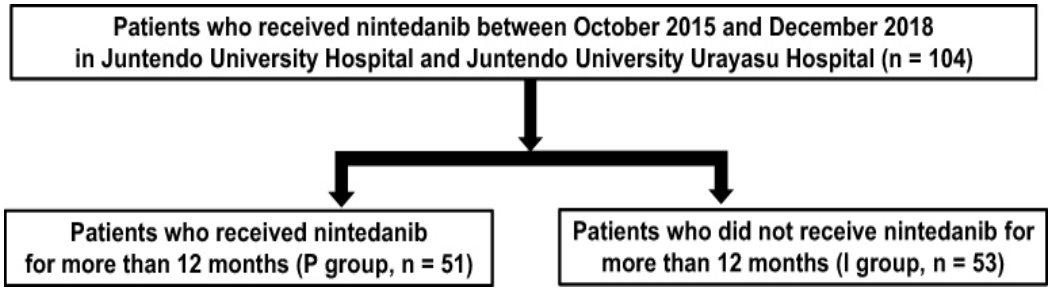


Figure 1. Flowchart of Patient Selection and Group Assignment

Among the 19 patients who had initiated corticosteroid therapy, eight received steroids because their interstitial pneumonia displayed autoimmune-like features. Despite these findings, none met the diagnostic criteria for a defined autoimmune disorder, so clinicians classified their condition as idiopathic interstitial pneumonia—most likely IPF—and subsequently started nintedanib.

The remaining 11 patients had been given low-dose corticosteroids well before publication of the international IPF treatment guidelines.

Of the other eight patients not included above, corticosteroids were prescribed for five individuals to treat drug-induced lung injury occurring on top of IPF. The final three patients received prednisolone for conditions unrelated to lung disease.

Sixteen patients who initially began therapy with the full nintedanib dose later required dose reductions to 200 mg/day. Four patients previously treated with pirfenidone were switched to nintedanib, while three transitioned from nintedanib to pirfenidone because of drug intolerance. Overall, treatment patterns were comparable between the two groups, with no meaningful differences.

Performance status (PS) was significantly better in the P group than in the I group ($p = 0.0003$). Age also trended higher in the P group, although not significantly ($p = 0.056$). Other baseline parameters—including GAP stage, mMRC dyspnea scale, pulmonary function values, corticosteroid exposure, and starting nintedanib dose—did not differ significantly between the groups.

Adverse effects associated with sustained nintedanib Use (>12 Months)

Key adverse events related to prolonged nintedanib therapy are summarized in **Table 2**. Across the entire cohort, diarrhea occurred in 42.31% of patients, nausea in 37.50%, weight loss in 24.04%, and liver dysfunction in 10.58%.

Nausea was observed significantly more frequently in the I group compared to the P group (49.06% vs 25.49%, $p = 0.012$). Similarly, pneumothorax was more common in the I group (13.21% vs 1.96%, $p = 0.031$). Rates of other side effects did not show significant differences between the two groups.

Table 2. Major Adverse Effects of Long-Term Nintedanib Treatment

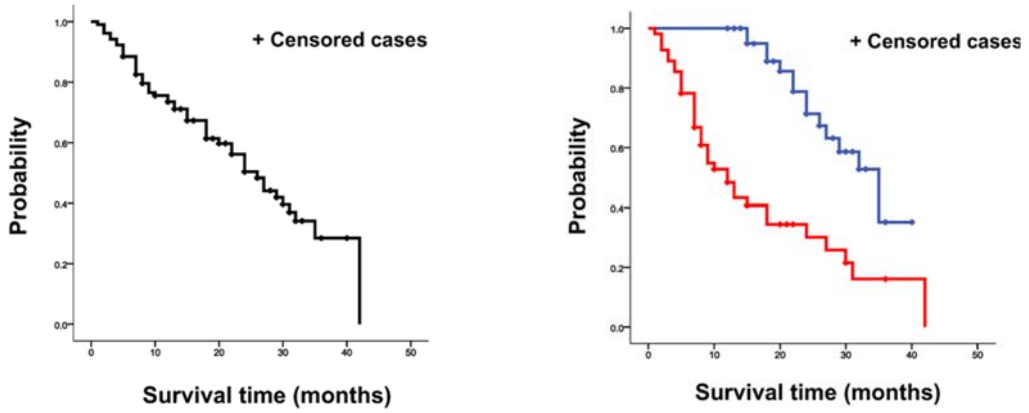
Adverse Effects	All Patients N = 104	P Group n = 51	I Group n = 53	*p*-value
Diarrhea	44 (42.31%)	20 (39.22%)	24 (45.28%)	0.557
Diarrhea > Grade 3	18 (17.31%)	8 (15.69%)	10 (18.87%)	0.667
Nausea/anorexia	39 (37.50%)	13 (25.49%)	26 (49.06%)	0.012
Nausea/anorexia > Grade 3	13 (12.50%)	2 (3.92%)	11 (20.75%)	0.009
Weight loss	25 (24.04%)	13 (25.49%)	12 (22.64%)	0.820
Weight loss > Grade 3	5 (4.81%)	2 (3.92%)	3 (5.66%)	0.782
Liver dysfunction	11 (10.58%)	6 (11.76%)	5 (9.43%)	0.699
Liver dysfunction > Grade 3	6 (5.77%)	3 (5.88%)	3 (5.66%)	0.926
Pneumothorax	8 (7.69%)	1 (1.96%)	7 (13.21%)	0.031
Pneumothorax > Grade 3	6 (5.77%)	1 (1.96%)	5 (9.43%)	0.039
Bleeding	9 (8.65%)	4 (7.84%)	5 (9.43%)	0.773
Bleeding > Grade 3	3 (2.88%)	0 (0.00%)	3 (5.66%)	0.076

Abbreviations: P, patients who were able to receive nintedanib for more than 12 months; I, patients who were not able to receive nintedanib for more than 12 months.

Impact of nintedanib on survival, lung function decline, and acute exacerbations

To determine how patients fared after beginning nintedanib therapy, we analyzed overall survival as well as the drug's influence on acute exacerbation development. As displayed in **Figure 2a**, the entire study population had a median post-treatment survival of 26 months (95% CI: 21.101–30.899).

A clear separation emerged when comparing those who maintained therapy with those who did not **(Figure 2b)**. Individuals who discontinued nintedanib within the first year experienced substantially poorer outcomes, surviving a median of only 12 months (95% CI: 8.097–15.903). In contrast, patients who remained on treatment for more than 12 months achieved a median survival of 35 months (95% CI: 27.031–42.969). This difference was pronounced and statistically significant (hazard ratio: 26.148; $p = 0.001$).

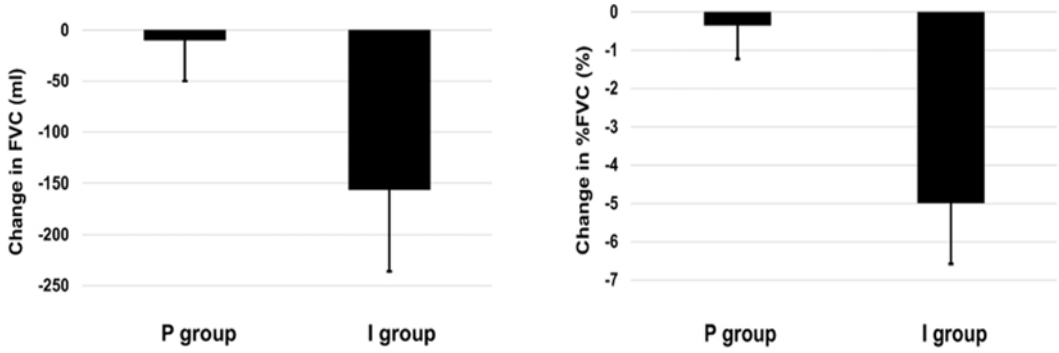


a) b)

Figure 2. The time from the initiation to the end of nintedanib treatment. (a) All patients. (b) Patients who were (P group: blue line) and those who were not (I group: red line) able to receive nintedanib for more than 12 months. The p-value was calculated using the Log rank test.

Figure 2 shows how long patients remained on nintedanib therapy. Panel A depicts the overall distribution of treatment duration, while Panel B contrasts two subsets: individuals who continued the drug for over 12 months (P group, blue) and those who discontinued earlier (I group, red). A Log-rank test was applied to compare the curves.

We subsequently assessed how lung function changed over one year in each group. The I group demonstrated a far more pronounced loss of FVC across the year, with a median drop of 165 mL (n = 16), whereas the P group showed only a minor reduction of 10 mL (n = 37) (p = 0.028) **(Figure 3a)**. A similar pattern appeared when evaluating percent predicted FVC, where the I group again exhibited a sharper decline (4.99%/year) compared with the P group (0.35%/year) (p = 0.012) **(Figure 3b).**



a) b)

Figure 3. The annual change in forced vital capacity (FVC). The difference in the annual change in (a) FVC volume (mL) and (b) %FVC between the I and the P groups. The p-value was calculated using the Log rank test.

Figure 3 depicts the annual changes in forced vital capacity (FVC). Panel A shows the yearly decline in absolute FVC (mL), while Panel B illustrates the change in %FVC for the two groups. Statistical comparisons were made using the Log-rank test.

We next examined the occurrence of acute exacerbations of IPF in both groups. Although not statistically significant, the I group experienced a higher rate of exacerbations compared with the P group (16.98% vs 5.88%; p = 0.076).

Risk factors for early nintedanib discontinuation

To identify factors associated with stopping nintedanib within the first year, a multivariate analysis was conducted using age, baseline performance status (PS), and the occurrence of nausea or pneumothorax as candidate variables. Among these, poor PS at treatment initiation emerged as the only independent predictor of discontinuation within 12 months **(Table 3).**

Table 3. Risk Factors for Discontinuing Nintedanib Treatment After 12 Months

Variables	OR	95% CI	*p*-value
Age	0.452	0.042–4.329	0.485
Performance status	0.014	0.002–0.167	0.007
Nausea/anorexia	2.210	0.885–5.664	0.096
Pneumothorax	5.802	0.847–115.806	0.083

Abbreviations: OR, odds ratio; CI, confidence interval.

Finally, we compared overall survival between patients with good versus poor baseline performance status (PS). Patients with better PS had a significantly longer median survival of 27 months (95% CI: 21.034–32.966) compared with 13 months (95% CI: 5.098–20.902) in those with poor PS. This difference was statistically significant (hazard ratio: 5.834; p = 0.016) as shown in **Figure 4**.

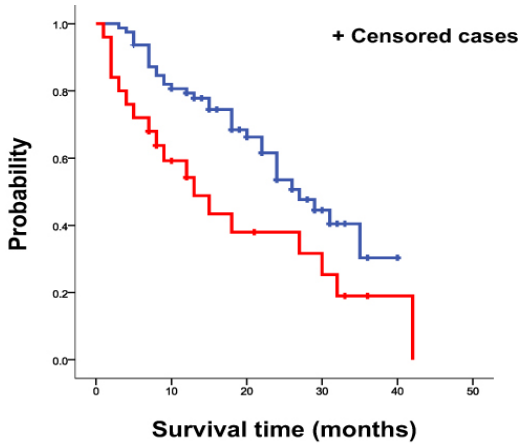


Figure 4. The difference in survival probability since the initiation of nintedanib therapy in patients with poor PS (red line) and good PS (blue line).

To the best of our knowledge, this is the first study to assess both the tolerability and efficacy of nintedanib in a real-world clinical setting. Our findings can be summarized in five key points: (1) the rate of nintedanib discontinuation within 12 months was higher among patients with poor performance status (PS), nausea/anorexia, or pneumothorax compared with those with good PS or without these adverse effects; (2) poor PS emerged as the only independent predictor of early treatment discontinuation; (3) early discontinuation was associated with a greater annual decline in forced vital capacity (FVC); (4) survival was significantly shorter in patients who could not continue therapy beyond 12 months; and (5) patients with good PS demonstrated longer survival compared with those with poor PS.

Previous studies have highlighted PS as an important determinant of adverse effects associated with nintedanib, particularly diarrhea and nausea [12]. Although PS has been widely applied in oncology to evaluate patient general condition, it has not been routinely used for antifibrotic therapy assessment. Nintedanib, having been originally developed as an anti-cancer agent, may warrant PS evaluation when used as an antifibrotic. Supporting this, Oishi *et al*. reported that poor PS predicts early discontinuation of both nintedanib and pirfenidone [14]. While nintedanib and pirfenidone differ mechanistically—nintedanib inhibits multiple tyrosine kinase receptors including VEGFR, PDGFR, and FGFR [15–18], whereas pirfenidone's anti-inflammatory mechanism remains unclear—their antifibrotic effects are comparable, but toxicity profiles differ. Future studies should also examine pirfenidone in this context.

In the present study, poor PS was confirmed as the main risk factor for discontinuing nintedanib after 12 months, consistent with previous reports [14]. These results emphasize the importance of baseline PS assessment for planning prolonged therapy, as it appears crucial for sustaining treatment and optimizing outcomes. Although the use of PS has been limited in interstitial pneumonia, evidence suggests that it correlates with overall patient condition and may therefore serve as a useful clinical metric in real-world practice.

Nausea and anorexia are well-documented adverse effects of nintedanib. In our prior work, patients who experienced nausea had significantly shorter survival, although the mechanism remained unclear [12]. In the current study, while nausea and anorexia were not independent predictors of early discontinuation, their incidence was higher among patients unable to continue therapy beyond 12 months. Moreover, the I group experienced a more pronounced annual FVC decline, suggesting a potential interplay between adverse events, treatment discontinuation, and survival.

Among the cohort, 27 patients had received corticosteroids prior to nintedanib initiation, with prednisolone doses kept below 15 mg/day. This aligns with clinical trials permitting low-dose corticosteroid use in combination with nintedanib [2], indicating that corticosteroid co-administration is unlikely to have significantly influenced our findings.

Pulmonary function testing was feasible in only 16 patients within the I group due to severe respiratory symptoms or poor general condition. In those assessed, FVC decline was greater than in patients who could not undergo testing, suggesting that discontinuation of nintedanib is associated with accelerated lung function deterioration. Thus, continued nintedanib treatment for more than 12 months may help slow pulmonary function decline.

Analyses excluding patients who died within 12 months did not materially change the findings, including baseline characteristics, risk factors for early discontinuation, or survival outcomes, supporting the robustness of the results.

This study has several limitations. First, its retrospective design and relatively small sample size resulted in patient heterogeneity, particularly in baseline pulmonary function, which may bias efficacy assessments. Second, as a real-world study, patients had poorer general condition and baseline lung function compared with controlled trials, such as INPULSIS, which may limit comparability. Third, adverse events were collected every six months, which could have led to underreporting. Larger prospective studies are warranted to validate these findings.

Conclusion

Our results indicate that poor baseline PS is the only significant predictor of nintedanib discontinuation within 12 months. Early discontinuation reduces therapeutic benefit, as evidenced by a greater FVC decline in patients unable to maintain therapy. Given the association between poor PS and gastrointestinal adverse events, including diarrhea and nausea, nintedanib should ideally be initiated before PS deteriorates—that is, early in the course of IPF—to maximize both tolerability and efficacy.

Acknowledgments: We would like to thank Editage for English language editing.

Conflict of Interest: None

Financial Support: None

Ethics Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study protocol was approved by Juntendo University's ethics committee (number 18-056). The ethics committee waived the requirement for informed consent by the retrospective study.

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