INTRODUCTION

Benign prostatic hyperplasia (BPH), characterised by lower urinary tract symptoms (LUTS), is highly prevalent among ageing men, with more than one-third of those aged 50 years or over experiencing moderate-to-severe LUTS. The symptoms of BPH are known to substantially impair the quality of life for patients. Importantly, patients who visit their clinician because of LUTS may already have...
moderate-to-severe symptoms\textsuperscript{4} and, as such, are at an increased risk of further disease progression.\textsuperscript{5,7}

In patients with BPH and moderate-to-severe LUTS who are at an increased risk of disease progression, the recommended first-line treatment is combination therapy with a 5-alpha reductase inhibitor (5ARI) and alpha-1 blockers (a1Bs).\textsuperscript{5,7} This evidence-based recommendation is consistent across international treatment guidelines for BPH.\textsuperscript{5,7} Additionally, evidence for the use of combined 5ARI and phosphodiesterase-5 inhibitor (PDE-5i) treatment in these patients is emerging.\textsuperscript{6,7} The rationale behind the use of combination therapy relates to the complementary mechanism of action of a1B/PDE-5i and 5ARI drugs. a1Bs (eg tamsulosin) and PDE-5i (eg tadalafil) cause relaxation of prostatic urethra smooth muscle by blocking alpha-1 adrenergic receptor stimulation and inhibiting PDE-5, respectively, providing rapid relief from LUTS secondary to prostate enlargement.\textsuperscript{6,7} 5ARIs (eg dutasteride) provide inhibition of 5AR isoenzymes,\textsuperscript{7} which can reduce prostate volume (PV), improve symptoms, prevent the progression of BPH and reduce the relative risk of acute urinary retention (AUR) or BPH-related surgery.\textsuperscript{8,10}

Previous literature has supported the use of combination therapy in patients with BPH at risk of disease progression.\textsuperscript{10-13} The 4-year Combination of Avodart and Tamsulosin (CombAT) study\textsuperscript{10,12} found that dutasteride 0.5 mg/tamsulosin 0.4 mg combination therapy reduced the relative risk of clinical progression compared with monotherapy.\textsuperscript{10,12} A higher incidence of AUR or BPH-related surgery was reported in patients treated with monotherapy compared with those treated with combination therapy.\textsuperscript{10,12} Furthermore, a recent study assessing the effectiveness of dutasteride 0.5 mg/tamsulosin 0.2 mg combination therapy compared with tamsulosin 0.2 mg monotherapy in patients from China, Japan, South Korea and Taiwan reported significant improvements in International Prostate Symptom Score (IPSS) in patients treated with combination therapy compared with monotherapy at 2 years.\textsuperscript{14} Patients in the combination therapy group also showed significant improvements in peak urinary flow rate and PV, as well as a significantly reduced risk of AUR or BPH-related surgery at 2 years.\textsuperscript{14}

Evidence also indicates that early intervention with 5ARI therapy (ie within 30 days of initiation of a1B therapy) has a positive impact on men with BPH who are at risk of disease progression.\textsuperscript{15,16} Analyses of data from US claims databases showed that early intervention improved outcomes and reduced BPH-related costs compared with delayed intervention.\textsuperscript{15-18} Delayed initiation of treatment with a 5ARI (ie >30 days but <6 months after initiation of a1B therapy) resulted in patients being significantly more likely to experience AUR and disease progression, as well as require surgery.\textsuperscript{15,16} A previous study conducted in a Japanese population reported beneficial effects of early initiation of dutasteride plus a1B therapy.\textsuperscript{19} This small study found that over half of patients (n = 39/74) showed symptom improvement 1 week after drug administration.\textsuperscript{19} Furthermore, a recent study using computerised clinical trial simulations showed that immediate initiation of dutasteride 0.5 mg/tamsulosin 0.4 mg combination therapy in patients with LUTS/BPH at risk of progression resulted in a significantly greater responder rate and symptomatic improvement in IPSS compared with switching from tamsulosin monotherapy after >6 months.\textsuperscript{20} Delaying the initiation of combination therapy also resulted in a decrease in clinical response.\textsuperscript{20}

Despite clinical guidelines and preliminary findings highlighting the benefit of early initiation of dutasteride, such clinical practice is not widely adopted in Japan. This may be because of the current lack of clinical trial data and real-world evidence to support the benefit of early initiation. Furthermore, the optimal timing for dutasteride initiation in male patients with moderate-to-severe BPH is as yet unclear. The aim of this study was to evaluate the effects of initiating add-on dutasteride therapy at different time points in Japanese patients with moderate-to-severe BPH.

What's known

- Previous literature has supported the use of 5-alpha reductase inhibitor (5ARI)/alpha-1-blocker (a1B) combination therapy in patients with benign prostatic hyperplasia (BPH) at risk of disease progression.
- Evidence indicates that early intervention with 5ARI therapy (within 30 days of initiation of a1B therapy) has a positive impact on these patients.
- However, early 5ARI (dutasteride) initiation is not widely adopted in Japanese clinical practice because of a lack of evidence demonstrating its benefits.

What’s new

- In the Japanese real-world clinical setting, early initiation of dutasteride (within 6 months of starting BPH medical treatment) was superior to late initiation (2 years after starting BPH medical treatment) in reducing the risk of first acute urinary retention over a 4-year period.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a multicentre, observational, retrospective chart review study using anonymised data from medical records in Japan. Eligible patients were categorised into three groups based on when dutasteride was added to their existing BPH therapy: early initiation, patients initiated on dutasteride ≤6 months from baseline; intermediate initiation, patients initiated on dutasteride between >6 months and 2 years from baseline and late initiation, patients initiated on dutasteride >2 years after baseline. Baseline was defined as the initiation date of any medical treatment for BPH (eg a1B and/or PDE-5i). Patients were followed from baseline until first episode of AUR or BPH-related surgery. In the absence of these events, patients were followed for 4 years.
A total of 34 clinical sites were involved in the study. The protocol, amendments and other relevant documents were reviewed and approved by institutional review boards/independent ethics committees for 13 of the study sites or a central review board for 21 of the study sites. The study was performed according to local regulation and consensus ethical principles derived from international guidelines including the Declaration of Helsinki 2008. Patients were able to opt out of the study by responding to a notice posted at each study site location and website.

2.2 | Data source

Institutions were selected based on the availability of baseline information from medical records and the frequency of dutasteride prescriptions. Medical records were transcribed and anonymised by principal investigators, clinical site staff and/or the site coordinator at the study sites, using the anonymisation application “Secure Tokumei-kun” (Medical Data Vision Ltd. [MDV], Tokyo, Japan). The coordinators supported the entry and anonymisation of data for only 13 of the study sites. The anonymised data were collected and converted for analysis by MDV and the dataset was provided to IQVIA for statistical analysis. The enrolment period spanned from October to December 2018.

2.3 | Patient population

2.3.1 | Inclusion criteria

Male patients with moderate-to-severe BPH, aged ≥50 years, with a history of a dutasteride prescription following initial BPH diagnosis were eligible for inclusion. In addition, patients had to have a PV ≥ 30 mL and an IPSS score ≥ 12 points at baseline, and both the date of dutasteride initiation and initiation of any medical treatment for BPH had to be specified. Patients were also required to have either a medical record for 4 years from baseline (to be used as an observational period in the instance of no clinical events [ie first AUR or BPH-related surgery]), or until the date of first AUR or BPH-related surgery.

2.3.2 | Exclusion criteria

Patients were excluded from the study if they had urinary symptoms or changes in voiding function that were unrelated to BPH, prostate cancer or history of treatment for prostate cancer, history of any medical treatment or AUR or BPH-related surgery before baseline, or postvoiding residual >250 mL at baseline. Patients were also excluded if they had previously participated in other Japanese clinical studies for BPH or had initiated dutasteride therapy as a preoperative treatment for BPH.

2.4 | Objectives and assessments

2.4.1 | Primary objective

The primary objective of this study was to evaluate the cumulative incidence over 4 years of the first episode of AUR or BPH-related surgery in the early vs late initiation groups.

2.4.2 | Secondary objectives

Secondary objectives of this study were to evaluate the cumulative incidence over 4 years of the first episode of AUR alone or BPH-related surgery alone in the early vs late and early vs intermediate initiation groups, and time to first episode of AUR alone and BPH-related surgery alone in the early vs late and early vs intermediate initiation groups. Time to the first AUR or BPH-related surgery after dutasteride initiation in the early vs late and early vs intermediate initiation groups was also evaluated.

2.4.3 | Exploratory analysis

An exploratory analysis of the incidence of first AUR or BPH-related surgery, first AUR alone and BPH surgery alone was conducted according to the site at which patients had first AUR or BPH-related surgery. As a total of 193 events in 1206 patients were observed in the overall analysis population (including 13 events observed after the 4-year follow-up period), a cut-off of 16% (193/1206) was selected to differentiate patients who had first AUR or surgery at a high incidence site (>16% of total events) and those whose surgery was conducted at a low incidence site (≤16% of total events).

2.5 | Statistical analysis

All patients who met the inclusion/exclusion criteria were included in the analysis population. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), with a two-sided significance level of \( P < .05 \). Demographics and baseline characteristics were reported descriptively.

The propensity score (PS) was generated using a logistic regression model: dutasteride initiation group as response variable with the independent variables being study site and baseline characteristics (including age, PV and IPSS). Comparison of the incidence of first episode of AUR and/or BPH-related surgery was carried out using a Cox proportional hazard model with the PS as a covariate and the timing (early vs late and early vs intermediate) of dutasteride initiation as an independent variable. Comparison of the proportion of subjects with first episode of AUR and/or BPH-related surgery was performed using a logistic regression model. A sensitivity analysis was conducted using a Cox proportional hazard model taking into account the inverse probability of treatment weight (IPTW) based on the PS and PS matching of early vs late groups.

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

3 | RESULTS

3.1 | Baseline demographics and clinical characteristics

Clinical data for 1438 patients were entered in the anonymisation tool; 232 (16%) of these patients were excluded (Figure 1). The
remaining 1206 patients were divided into three groups: early initiation (n = 793), intermediate initiation (n = 233) and late initiation (n = 180). Demographics and baseline characteristics were similar across initiation groups; the majority of patients were ≥65 years of age, with PV ≥40 mL and IPSS ≥16 (Table 1).

3.2 Incidence of first AUR and/or BPH-related surgery from baseline

The cumulative incidence of first AUR or BPH-related surgery at 4 years from baseline was 14%, 17% and 15% in the early, intermediate and late dutasteride initiation groups, respectively. Early initiation was not superior to either late or intermediate initiation in reducing the risk of these events (early vs late: hazard ratio [HR] 0.733, 95% confidence interval [CI] 0.468-1.150; early vs intermediate: HR 0.789, 95% CI 0.534-1.167; Figure 2A).

However, the incidences of first AUR alone and BPH-related surgery alone showed different trends. The cumulative incidence of first AUR at 4 years from baseline was 3%, 6% and 11% in the early, intermediate and late dutasteride initiation groups, respectively. Although early initiation was not significantly superior to intermediate initiation in reducing the risk of the first AUR (HR 1.724; 95% CI 0.826-3.599), early initiation was superior to late initiation in reducing that risk (HR 3.449; 95% CI 1.796-6.623; Figure 2B).

Paradoxically, early initiation was inferior to late initiation in reducing the risk of BPH-related surgery. The cumulative incidence of BPH-related surgery at 4 years from baseline was 12%, 12% and 4% in the early, intermediate and late dutasteride initiation groups, respectively. Nominally, the HR of BPH surgery was 0.235 (95% CI 0.112-0.495) when comparing early and late initiation groups. The difference in the risk of BPH-related surgery between early and intermediate initiation groups was minimal (HR 0.610; 95% CI 0.389-0.955; Figure 2C). Results from the IPTW sensitivity analysis and PS matching analysis showed a similar trend (Table S1).

3.3 Incidence of AUR and/or BPH-related surgery from dutasteride initiation

Regarding the time to first AUR or BPH-related surgery from dutasteride initiation, there was no significant difference in the Kaplan-Meier curves amongst the three study groups (Log-rank test: P = .8406) (Figure 3A). However, the cumulative incidence of first AUR alone in the late initiation group increased rapidly compared with the early and intermediate initiation groups, and there was a significant difference between the Kaplan-Meier curves (Log-rank test: P = .0024) (Figure 3B). The time to BPH-related surgery alone after dutasteride initiation was similar amongst all study groups without a significant difference (Log-rank test: P = .3033) (Figure 3C).

3.4 Subgroup analysis

To investigate a possible explanation for the increased risk of BPH-related surgery in the early initiation group compared with the late initiation group, we examined the incidence of BPH-related surgery in each participating institution. Interestingly, we noticed that incidence varied greatly amongst the participating clinical sites and hypothesised that inclusion of sites whose treatment preference was surgery may have introduced study bias. To investigate this possibility, a subgroup analysis was conducted in patients who had a first AUR or BPH-related surgery event at low (≤16% of events; n = 729) or high (>16% of events; n = 477) incidence sites. Age at baseline was similar in both low and high incidence site subgroups;

FIGURE 1 Patient disposition.

| Number of patients excluded n = 232† |
|---------------------------------|
| Incorrectly formatted, missing or outlier date (n = 8) |
| Initiation date of dutasteride prior to baseline (n = 4) |
| Date of AUR and/or BPH-related surgery prior to baseline (n = 3) |
| PV <30 mL at baseline (n = 2) |
| PV not measured between −30 d to +30 d from baseline (n = 57) |
| IPSS at baseline <12 (n = 26) |
| IPSS not measured between −30 d to baseline (n = 108) |
| Treatment medicine is not identified (n = 12) |
| Treatment period (last date of dutasteride administration date – baseline) <1277 d (4–0.5 y) (n = 50) |
| Date of surgery and/or AUR are not consistent with other dates (n = 3) |
| Add-on after the observation period (n = 17)‡ |

†Patients may have been excluded for multiple reasons. ‡Dutasteride initiation >1642 d (4 plus 0.5 y) from baseline (n = 4 of these patients were also included in the numbers of patients with other protocol deviations). Abbreviations: AUR, acute urinary retention; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PV, prostate volume; PVR, postvoid residual.
however, a trend was observed in high incidence compared with low incidence sites towards higher median PV (high: 50 mL; low: 43 mL), IPSS (high: 19; low: 16), and postvoid residual (PVR) (high: 47 cc; low: 30 cc) at baseline. In the high incidence site subgroup, the incidences of first AUR or BPH-related surgery and BPH-related surgery alone were significantly higher in the early vs late dutasteride initiation groups (first AUR or BPH-related surgery: HR 0.339 [95% CI 0.190-0.605]; BPH-related surgery alone: HR 0.107 [95% CI 0.039-0.294]). However, the incidence of first AUR alone was lower in the early vs late groups (HR 2.438; 95% CI 1.030-5.769) and increased rapidly in the late initiation subgroup at around 1.5-2 years after dutasteride initiation (Figure 4; upper panel). The incidences of first AUR or BPH-related surgery and BPH-related surgery alone were also significantly higher in the early vs intermediate dutasteride initiation groups (first AUR or BPH-related surgery: HR 0.039 [95% CI 0.039-0.094]; BPH-related surgery alone: HR 0.049 [95% CI 0.040-0.091]). The Kaplan–Meier curve of BPH-related surgery showed similar trends to the overall population (Figure 4; upper panel). Conversely, in the low incidence site subgroup, the incidence of first AUR or BPH-related surgery and first AUR alone was significantly lower in the early vs late dutasteride initiation groups (first AUR or BPH-related surgery: HR 4.833 [95% CI 2.156-10.832]; first AUR alone: HR 5.263 [95% CI 2.005-13.814]) (Figure 4; lower panel). The incidence of BPH-related surgery alone was not significantly different in those two study groups (HR 3.839 [95% CI 0.890-16.570]) (Figure 4; lower panel). When comparing early vs intermediate initiation groups in the low incidence site subgroup, there were no statistical differences in the cumulative incidences in all three objectives (first AUR or BPH-related surgery: HR 1.556 [95% CI 0.574-4.222]; first AUR alone: HR 2.133 [95% CI 0.657-6.926]; BPH-related surgery alone: HR 1.490 [95% CI 0.320-6.941]) (Figure 4; lower panel).

4 | DISCUSSION

Randomised controlled trials have shown that treatment with dutasteride reduces AUR and BPH-related surgery in patients with BPH at risk of disease progression, and database studies.
**FIGURE 2** Cumulative incidence of A) first AUR or BPH-related surgery, B) first AUR alone and C) BPH-related surgery alone from baseline (start of initial therapy) (analysis population). Abbreviations: AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio.
SHIMA et al. indicate that earlier initiation of dutasteride prevents disease progression to a greater extent than later initiation. However, the appropriate timing of dutasteride initiation in Japanese patients with BPH has not yet been determined. This retrospective chart review study evaluated the effect of early, intermediate or late dutasteride initiation in a real-world setting in Japanese patients.
with moderate-to-severe BPH and PV ≥30 mL at risk of disease progression.

This study found that early initiation of dutasteride (within 6 months after the start of any medical treatment for BPH) did not reduce the risk of first AUR or BPH-related surgery from baseline compared with intermediate or late dutasteride initiation. However, when first AUR and BPH-related surgery were evaluated separately, significant differences between the early and late initiation groups were observed. The incidence of first AUR was higher in the late initiation group compared with the early initiation group, in line with previous reports; this difference was also observed if only patients after dutasteride initiation were taken into account, and may be related to a higher PV because of disease progression. The incidence of first AUR was 11% in the late initiation group in this study compared with an incidence of 6.8% in the tamsulosin-only group in the CombAT trial; possibly because of our study population including patients of older age and more comorbidities than patients in CombAT. Limited data on disease progression rate (including rate of worsening in PV, PVR and IPSS from baseline) were collected in this study; therefore, it was not possible to directly evaluate the impact of disease progression (such as increased PV) on the decision to initiate an intervention such as BPH surgery. However, it is possible that the BPH-related surgery findings observed in the late dutasteride initiation group may be related to a higher PV at the time dutasteride therapy was initiated compared with baseline.

Conversely, the risk of BPH-related surgery was higher in the early vs late initiation group, which appears paradoxical based on the reduced risk of BPH surgery with dutasteride and α1B combination treatment demonstrated in previous studies. This may be because of selection bias in the study design, which was difficult to foresee. The prevalence of BPH-related surgery in the early initiation group may have been underestimated because of inclusion of data from clinical institutions at which BPH-related surgery is performed proactively. An exploratory subgroup analysis was conducted according to the site at which patients had a first AUR and/or BPH-related surgery event, with patients divided into low (≤16% of events) and high (>16% of events) incidence site subgroups. This analysis revealed that the incidence of BPH-related surgery in patients who had surgery at high incidence sites was similar to that seen in the overall population. Therefore, the incidence of BPH-related surgery shown in this study may reflect the incidences seen in the high incidence site subgroup, and suggests that the high incidence sites may be more likely to prescribe surgery as a treatment for patients with BPH than low incidence sites. Given that the indication for surgery varies between different hospitals and clinics, the incidence of BPH-related surgery may have been influenced by

FIGURE 4 Cumulative incidence of first AUR and/or BPH-related surgery from baseline by site of BPH-related surgery (high >16% and low ≤16% incidence site) (analysis population). Abbreviations: AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CI, confidence interval; int, intermediate; OR, odds ratio.
patients’ baseline disease severity and/or individual hospital practice. Analysis of baseline data revealed a trend towards more severe BPH (higher PV, IPSS and PVR) in patients receiving treatment in high incidence sites compared with low incidence sites; therefore, earlier and more frequent surgery in high incidence sites may have been driven by baseline disease status. Additionally, in the early initiation group, although high incidence sites contributed a lower proportion of patients, they contributed a higher proportion of surgery events than low incidence sites. In the intermediate initiation group, although the proportion of patients was similar across both low and high incidence sites, high incidence sites contributed a higher proportion of surgery events compared with low incidence sites.

The higher proportion of surgery events observed in high incidence sites compared with low incidence sites cannot be fully explained by differences in patient demographics alone; it may partly reflect local variation in hospital practice regarding BPH surgery indication. The timing for BPH-related surgery may depend on disease progression as well as the surgery schedule and/or policy of each individual site; therefore, additional and unassessed reasons for site-level bias in BPH-related surgery may exist. Conversely, the cumulative incidence of first AUR observed in this study shows a similar profile across high and low incidence sites. Additionally, when comparing early, intermediate and late initiation of dutasteride treatment, different profiles of BPH-related surgery events were observed. In summary, although there were unexpected observations in this study, the exploratory analyses suggest that primary end-point findings (time to first AUR and BPH-related surgery) may be driven by the incidence of BPH-related surgery in high incidence sites, and that this may reflect slightly higher BPH severity at baseline. It is also possible that the incidence of BPH-related surgery may have been influenced by site-level differences in clinical practice regarding the timing and indication of BPH-related surgery.

In addition, patients who had BPH-related surgery without dutasteride administration were not eligible for the study; therefore, the incidence of surgery is more likely to be underestimated in the intermediate and late groups, in which the period of non-dutasteride drug therapy was longer. Kaplan–Meier analysis of the time to BPH-related surgery after dutasteride initiation showed little difference between groups, which may partially explain this site selection bias.

This study had a number of limitations. The study population size was smaller than initially planned, largely because of the strict inclusion criteria that limited the number of eligible patients, particularly in a real-world setting. The population was further reduced as the inclusion/exclusion criteria were set at baseline to avoid sampling bias, but many patients did not have records of PV, PVR or IPSS at baseline, which were necessary for inclusion. These parameters are measured prior to dutasteride initiation but not always at initiation of other BPH therapy; as such, patient numbers were lower in the intermediate and later initiation groups as the values may not have been measured until dutasteride was prescribed. Also, the number of patients with first AUR or BPH-related surgery available in the real-world setting may have been overestimated, as sample size estimates were based on a prospective study.12 Although our sample size was lower than planned, the significant difference in incidence of first AUR between the early and late initiation groups indicates that the sample size used was sufficient to assess differences between groups.

Further limitations include possible confounding from a number of clinical measurements that were not collected as part of the study, including intravesical prostatic protrusion and bladder function. Also, the study collected data from patients at selected institutions, which may limit the generalisability of the results; source document verification was not implemented; adherence to dutasteride therapy was not confirmed and some patients may have had unrecorded prior BPH history in a non-study institute. Finally, patients with prior dutasteride treatment were not eligible for the study but may be able to provide important data in an additional analysis.

In this retrospective chart review study, a beneficial effect of early vs late dutasteride initiation on the cumulative frequency of first AUR or BPH-related surgery over 4 years in real-world setting was not demonstrated. However, an important observation is that early initiation of dutasteride following initiation of BPH treatment reduces the risk of first AUR compared with intermediate and late initiation of dutasteride; this finding has previously been shown only in database studies with a lack of demographic adjustment.15-18 A nominally higher risk of BPH-related surgery was observed in the early initiation group compared with the intermediate and late initiation groups. Exploratory analyses suggest that this observation may have been influenced by BPH-related surgery event numbers observed in the high incidence site subgroup, potentially because of differential baseline disease severity and site-level variation in surgery indication practices. A randomised controlled trial is warranted to further evaluate the benefit of early dutasteride initiation on BPH-related surgery and disease progression in this population.

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DISCLOSURES
YS, YK, AK, JMP-M and MY are all employees of GlaxoSmithKline (GSK). JMP-M holds stocks/shares in GSK. NM, TY and HT have previously served in a consultant role for GSK. NM has received lecture fees from Kissey and research grants from Astellas. TY has received grants from Pfizer, Astellas and Daiichi-Sankyo.

AUTHOR CONTRIBUTIONS
YS, YK, AK, JMP-M, MY and NM contributed to the concept/design of the study. NM served as an external medical expert for the study. TY and HT have served as site principal investigators in the study. All authors were involved in the analysis/interpretation of the data and drafting the article or revising it critically for important intellectual content.

DATA STATEMENT
Anonymised data collection and data analysis was supported by MDV and IQVIA, respectively. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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