Efficacy and safety of a once-daily single-tablet regimen of tenofovir, lamivudine, and efavirenz assessed at 144 weeks among antiretroviral-naïve and experienced HIV-1-infected Thai adults

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\textsuperscript{**} Clinical trial number NCT01160120.

\textsuperscript{***} Data from this study were presented in part at the Eleventh International Congress on HIV and Drug Therapy in HIV Infection, Glasgow, UK, held on November 11–15, 2012 (Poster #P312; Safety and efficacy of once daily single generic fixed dose combination tablet of tenofovir, lamivudine and efavirenz among HIV-infected Thais).

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integrate inhibitor, recent World Health Organization (WHO) guidelines from 2016 continue to recommend TDF/FTC or TDF + lamivudine (3TC) + efavirenz (EFV) once daily as the preferred first-line regimen for resource-limited settings (WHO, 2017; European AIDS Clinical Society (EACS), 2017; Department of Health and Human Services (DHHS), 2017; Gunthard et al., 2016). A previous study showed that a once-daily regimen of TDF, 3TC, and EFV (administered as individual agents) was superior to once-daily EFV in combination with 3TC/AZT (Arribazabalaga et al., 2007; Bartlett et al., 2007; Matthews et al., 2008), 3TC/stavudine (d4T) (Gallant et al., 2004), or 3TC/abacavir administered twice daily (Condoluci et al., 2008). The successful long-term treatment of HIV/AIDS requires exceptionally high levels of adherence to prevent the emergence of drug-resistant HIV variants, which can result in treatment failure and the risk for AIDS progression. To achieve plasma HIV RNA of <50 copies/ml, the most convenient regimen with the lowest number of pills taken once daily is preferred.

The availability of cheap antiretroviral (ARV) drugs is essential for treatment scale-up and to maintain the sustainability of national HIV programs in resource-limited settings that have been hard hit by the HIV/AIDS epidemic, such as Thailand. Generic ARV drugs are generally 3–10 times cheaper than branded products and are therefore increasingly used in resource-limited settings. The generic single-tablet regimen (STR) is a significant innovation, as it reduces the number of pills taken each day. In addition, fixed-dose combinations (FDCs) are easier to manage for both patients and healthcare workers. Therefore, a generic STR of d4T (or zidovudine), 3TC, and nevirapine (NVP) has been used widely in the developing world. However, in 2010, the WHO recommended that countries phase out the use of d4T due to its serious side effects.

In 2009, Mylan Laboratories in India filed an application for a new drug approval with the US Food and Drug Administration for a generic STR of TDF/3TC/EFV at 600/300/300 mg. Based on a bioequivalence study in India, this generic FDC yielded comparable bioequivalence data to the branded individual EFV, 3TC, and TDF (unpublished data). However, there are no efficacy and safety data in HIV-infected subjects. This generic STR will give patients the opportunity to access a ‘ease-of-use’ product not currently available on the market, as well as help improve their quality of life and adherence. In addition, there are limited data on the use of the generic TDF/3TC/EFV worldwide. Therefore, this study was performed to assess the long-term safety and efficacy of a STR of TDF/3TC/EFV over a period of 144 weeks. Mid-level concentrations of TDF, 3TC, and EFV were evaluated to ensure that this generic STR was identical to separate tablets of branded TDF and EFV.

**Materials and methods**

This open-label, phase II trial was conducted at HIV-NAT, Thai Red Cross AIDS Research Centre (TRC-ARC), Bangkok, Thailand, from May 2010 to June 2015 (registered at clinicaltrials.gov, NCT01160120). Treatment-experienced and treatment-naïve patients older than 18 years of age with no concurrent AIDS-defining illness or history of drug resistance, with an estimated glomerular filtration rate (eGFR) of >60 ml/min/1.73 m², and with no history of drug abuse or of taking CYP450 inhibitors or inducers within 14 days of the study were recruited. Additional inclusion criteria for treatment-experienced patients were (1) currently using individual TDF, 3TC, and EFV (as separate tablets) as their first-line regimen, and (2) an HIV RNA of <50 copies/ml for the last 6 months. The treatment-experienced group took branded TDF, branded EFV, and generic 3TC (from the Government Pharmaceutical Organization (GPO)) up until the baseline visit.

This study was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University. All patients provided their consent.

**Pharmacokinetic analysis**

Blood from treatment-experienced and treatment-naïve patients was collected 11–13 h after the last drug administration on the fourth week of the study to assess the mid-dose (C₁₂) levels

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Figure 1. Study flow diagram.
of tenofovir, 3TC, and EFV. For the treatment-experienced patients, blood was also taken at baseline (when the patients were on individual branded TDF and EFV as separate tablets) 11–13 h after the last drug administration for comparison with the drug levels of the generic single FDC at week 4. Plasma concentrations of individual medications were determined using a previously developed and validated reverse-phase high-performance liquid chromatography (HPLC) assay (Droste et al., 2005; Fletcher and Bushman, 2003). The 3TC plasma levels were tested at the Program for Health: Prevention and Treatment (PHPT) Research Unit, Chiang Mai. The tenofovir and EFV plasma levels were tested at the HIV–NAT Research Laboratory, TRC-ARC, Thailand. Plasma levels of tenofovir, 3TC, and EFV were linear over the range of 0.015–1.5 mg/l, 0.028–10.9 mg/l, and 0.2–20.0 mg/l, respectively. The PHPT Research Unit and HIV–NAT Laboratory participate in the International Quality Control and Quality Assessment Program and have been cross-validated with other PK laboratories (Droste et al., 2003).

All other laboratory tests were done at the HIV–NAT Laboratory, Chulalongkorn University Hospital. HIV–RNA viral load, CD4 cell counts, and various other safety parameters including complete blood count, blood chemistry, and liver and renal function, were performed at baseline and at weeks 4, 12, 24, 48, 96, and 144. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula for the Thai population (eGFR = $175 \times C_{\text{Cr}} \times (\text{Age})^{-0.203} \times 0.742$ (if female) $\times 1.129$) (Praditpornsilpa et al., 2011).

The primary outcome of the study was the comparison of drug levels between formulations and bioequivalence of each composite drug with a 90% confidence interval (CI) within 0.80–1.25. The secondary endpoints were the percentages of patients with undetectable HIV–RNA (<50 copies/ml) and CD4 changes at weeks 48, 96, and 144.

### Statistical analysis

In general, all subjects enrolled in the trial were included in the statistical evaluation for safety and efficacy. Of all subjects included, one was excluded from the statistical analysis for pharmacokinetics because baseline data were not obtained due to problems in collecting blood. Demographic, clinical, and laboratory parameters were recorded for the patients. Continuous variables are expressed as the median with interquartile range (IQR). Differences in continuous and categorical variables between the experienced and naïve groups were assessed using the Wilcoxon rank sum test and Chi-square test, respectively. All p-values reported are two-sided. Statistical significance was defined as $p < 0.05$. Stata version 13.1 (Stata Corp., College Station, TX, USA) was used for the analysis.

### Results

The study scheme is presented in Figure 1. Of the total 100 patients enrolled, 30% were female and the median age was 34 (IQR 28–38) years. Fifty-one patients were treatment-naïve. The median baseline CD4 cell count was 512 (IQR 395–620) cells/µl for treatment-experienced patients and 230 (IQR 156–284) cells/µl for treatment-naïve patients. The median baseline log$_{10}$ HIV-1 RNA for treatment-naïve subjects was 4.9 (IQR 4.2–5.3) copies/ml. Nineteen percent of the subjects were also co-infected with hepatitis B virus and 3% were co-infected with hepatitis C virus. The baseline characteristics of the treatment-experienced and treatment-naïve patients are summarized in Table 1.

### Virological and immunological response

At baseline, there were 27 treatment-naïve patients with a CD4 count <250 cells/µl (range 10–244 cells/µl). Of these 27 patients, 10 continued to have a CD4 <250 cells/µl at week 24 and six continued to have a CD4 <250 cells/µl at week 48. The median CD4 count for the treatment-naïve patients at weeks 24 and 48 were 364 (IQR 262–452) and 400 (IQR 325–505) cells/µl, respectively. Changes in the absolute CD4 cell count and CD4 percentage are summarized in Figure 2A and Table 2.

From the intention-to-treat (ITT) analysis, the proportion of cases with HIV RNA <50 copies/ml at week 48, 96, and 144 was 96%, 94%, and 94%, respectively, for ARV-experienced patients and 88%, 90%, and 80%, respectively, for ARV-naïve patients. From the per-protocol (PP) analysis, the proportion of cases with HIV RNA <50 copies/ml at week 48, 96, and 144 was 98%, 100% and 100%, respectively, for ARV-experienced patients and 88%, 94%, and 91%, respectively, for ARV-naïve patients (Figure 2B). One naïve patient had virological failure at week 12 with baseline primary drug resistance of K70R, T69D, V75L.

### Pharmacokinetic data (Figure 3)

At week 4 (n = 100), the median $C_{\text{ss}}$ for tenofovir, 3TC, and EFV was 0.084 (IQR 0.066–0.1) mg/l, 0.224 (IQR 0.17–0.3) mg/l, and 1.88 (IQR 1.44–2.73) mg/l, respectively. Therapeutic cut-off levels for 3TC, TDF, and EFV of >0.05 mg/l, >0.05 mg/l, and >1.0 mg/l, respectively, were used.

Among the treatment-experienced patients, the geometric mean ratio (GMR) of the tenofovir plasma concentration at week 4 (single generic FDC) over baseline (branded TDF) was 0.98 (95% CI 0.94–1.04). There was only one patient outlier (1.52). At week 4, this patient had a tenofovir (generic) level of 0.102 mg/l. The GMR of 3TC levels at week 4 over baseline (generic 3TC) was 1.14 (95% CI 1.02–1.28). With regard to the EFV levels, the GMR at week 4 of

### Table 1

Baseline characteristics of the 100 study patients.$^a$

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=100)</th>
<th>Treatment-experienced patients (n=49)</th>
<th>Treatment-naïve patients (n=51)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.5 (28.5–39)</td>
<td>38 (35–43)</td>
<td>30 (25–35)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex: male</td>
<td>70 (70)</td>
<td>27 (55.1)</td>
<td>43 (84.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV transmission risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>43 (43)</td>
<td>31 (63.3)</td>
<td>12 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>56 (56)</td>
<td>17 (34.7)</td>
<td>39 (76.5)</td>
<td></td>
</tr>
<tr>
<td>HBV co-infection</td>
<td>19 (19)</td>
<td>16 (32.7)</td>
<td>3 (5.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HCV co-infection</td>
<td>3 (3)</td>
<td>2 (41)</td>
<td>1 (2)</td>
<td>0.61</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>21.9 (20.1–23.8)</td>
<td>22.6 (20.9–24.5)</td>
<td>21 (19.4–21.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration on ARV for the group</td>
<td>-</td>
<td>8.9 (6.3–13.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, cells/µl</td>
<td></td>
<td>512 (395–620)</td>
<td>230 (156–284)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA log$_{10}$ copies/ml</td>
<td>-</td>
<td>&lt;50</td>
<td>49 (4.2–5.3)</td>
<td></td>
</tr>
</tbody>
</table>

*HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; ARV, antiretroviral.

$^a$ Data represent the number (%) or median (interquartile range).
generic EFV over branded EFV was 0.86 (95% CI 0.79–0.93). All drug concentrations for the generic STR were within 80–120% of the branded separate tablets and thus interpreted as bioequivalent.

Safety profile (Figure 4)

There were no significant changes in the eGFR between the baseline visit and follow-up visits (Figure 4A). However, one treatment-experienced patient had subclinical deterioration of the eGFR which was <60 ml/min/1.73 m² at weeks 24 and 48 (58 and 50 ml/min/1.73 m², respectively). Also, there were no significant differences in the lipid profile between the baseline visit and follow-up visits (Figure 4B). High cholesterol and triglyceride were observed in 30–50%.

Three serious adverse events were reported during the study period: tension headache, cervical dysplasia, and infective endocarditis. The tension headache occurred 1.5 months after taking generic TDF/3TC/EFV and resolved spontaneously within 1 month. The case of cervical dysplasia was reported when the affected patient was hospitalized for a hysterectomy, which was performed 6 months after the baseline visit. The case of infective endocarditis (Enterococcus faecalis) was diagnosed 6 months after the baseline visit; this patient was treated in the hospital for 6 weeks and made a full recovery.

Seventy-seven possible study drug-related adverse events were reported. The most common adverse events were central nervous system (CNS) toxicity (dizziness (28%) and short-term memory loss (4%)) and skin rash (10%). The majority of the CNS adverse events occurred during the first few days of treatment and resolved spontaneously after 1–4 weeks. However, three patients discontinued the study drug due to EFV intolerance. Another three cases were pregnant. They had healthy newborns without congenital anomalies.

Discussion

In order to achieve the 90–90–90 target by 2030, ART scale-up is essential. However, this will be difficult because treatment for HIV-infected patients is life-long. Therefore, it is crucial to make the drugs accessible, affordable, efficacious, and easy to take, which is the case for generic STRs. In the present study, the plasma drug concentrations and efficacy over a period of 144 weeks of a generic STR including TDF/3TC/EFV (one tablet a day) was investigated. The pharmacokinetic data confirm that this generic FDC has comparable plasma concentrations to the separate tablets. Drug concentrations below the target cut-off values at the time of generic STR use were found in only four patients for TDF, two patients for 3TC, and three patients for EFV. However, all of them had HIV RNA <50 copies/ml over the 144 weeks. Excellent virological efficacy over the 144 weeks was also found for both ARV treatment-naïve patients with high baseline viral loads and treatment-experienced patients with undetectable viral loads, especially in patients with high levels of adherence and no primary drug resistance.

This one tablet a day regimen was associated with high levels of adherence and with minimal treatment-limiting toxicity. None of these patients developed grade 3/4 renal toxicity, in contrast to the findings of a study from West India (Pujari et al., 2008). Pujari et al. found that 2.8% of their HIV-infected patients from West India developed grade 3/4 renal toxicity when taking a generic STR of TDF/3TC/EFV. The present study patients were younger (mean age 32 years compared to 40 years) and none of them had comorbidities, so the TDF-related nephrotoxicity was relatively low in this study population.

Table 2

Virological success and median CD4 cell counts during the study (by on-treatment analysis).

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Experienced</th>
<th>Naive</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 (cells/µL), median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>433 (331–564)</td>
<td>563 (420–750)</td>
<td>364 (262–452)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 48</td>
<td>475 (351–598)</td>
<td>550 (434–739)</td>
<td>400 (325–505)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 72</td>
<td>502 (378–637)</td>
<td>590 (473–774)</td>
<td>431 (336–548)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 96</td>
<td>510 (403–641)</td>
<td>527 (451–736)</td>
<td>495 (363–586)</td>
<td>0.02</td>
</tr>
<tr>
<td>Week 120</td>
<td>486 (408–656)</td>
<td>564 (416–702)</td>
<td>461 (396–532)</td>
<td>0.02</td>
</tr>
<tr>
<td>Week 144</td>
<td>526 (432–650)</td>
<td>582 (459–744)</td>
<td>489 (371–603)</td>
<td>0.01</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>92/99 (92.9)</td>
<td>48/48 (100)</td>
<td>44/51 (86.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Week 48</td>
<td>92/99 (92.9)</td>
<td>47/48 (97.9)</td>
<td>45/51 (88.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Week 72</td>
<td>93/97 (95.9)</td>
<td>46/46 (100)</td>
<td>47/51 (92.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Week 96</td>
<td>92/96 (95.8)</td>
<td>46/47 (97.9)</td>
<td>46/49 (93.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>Week 120</td>
<td>83/88 (94.3)</td>
<td>45/45 (100)</td>
<td>38/43 (88.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Week 144</td>
<td>87/91 (95.6)</td>
<td>46/46 (100)</td>
<td>41/45 (91.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
The high efficacy of the generic STR of TDF/3TC/EFV at week 144 in this study (94% of ARV-experienced patients and 80% of ARV-naive patients) is comparable to the data reported for the branded FDC of EFV, FTC, and TDF as the first-line or switched highly active ART regimen among patients with similar baseline HIV disease status in developed countries (Dejesus et al., 2009; Gallant et al., 2006; Omeje and Okwundu, 2012). Furthermore, the virological efficacy recorded in this study is far superior to that reported in other ARV studies conducted in Thailand in which a STR of d4T or zidovudine (AZT)/3TC/NVP was used (Anekthananon et al., 2004; Manosuthi et al., 2007; van Leth et al., 2004). Although the generic STR of d4T or AZT with 3TC and NVP is effective in achieving virological, immunological, and clinical success in the developing world (Anekthananon et al., 2004; Kiertiburanakul et al., 2007; Laurent et al., 2007; Laurent et al., 2004; Pujari et al., 2004), the serious side effects of d4T are of concern. Therefore, the use of a non-thymidine analog such as TDF is preferred instead. Furthermore, in 2010, the WHO recommended that countries phase out the use of d4T due to its serious side effects.

There are several advantages to starting with TDF-based ART for the treatment of HIV infection. In randomized clinical trials, a combination of TDF/3TC (FTC)/EFV was superior to AZT or d4T/3TC/EFV, with better virological and immunological outcomes and less treatment-limiting toxicity in the TDF group (Gallant et al., 2004; Pozniak et al., 2006). In addition, a systematic review of clinical trials demonstrated that TDF/FTC or TDF/3TC combined with EFV achieves a greater virological response than other nucleoside backbones (Bartlett et al., 2007). In the present study, the patients showed a robust immunological and virological response, with >90% of them having a viral load <50 copies/ml over the 144 weeks.

This generic STR of TDF/3TC/EFV has numerous advantages, such as a low pill burden (only one tablet a day), being cheaper than the generic STR of TDF/FTC/EFV or separate drugs, fewer prescription errors, simplified HIV program management, and improved effectiveness in treating concomitant chronic hepatitis B virus infection. Chronic hepatitis B virus co-infection in the Asia region is relatively high due to perinatal transmission; 19% of the patients in this study were found to have a concomitant chronic hepatitis B virus infection. However, its disadvantage is the difficulty in adjusting the dose in cases with a low eGFR or TDF-related renal toxicity.

Generic ART will play a critical role in HIV treatment scale-up in many resource-limited settings, especially during and after international funding donors phase out their programs. In the near future, more HIV-infected patients in resource-poor settings will engage in HIV treatment programs, because early ART is recommended in the international guidelines (WHO, 2017; European AIDS Clinical Society (EACS), 2017; Department of Health and Human Services (DHHS), 2017; Gunthard et al., 2016). Furthermore, treatment as a prevention strategy is also recommended, especially in special populations such as men who have sex with men. Therefore, generic drugs may be a good alternative option in resource-limited settings, particularly generic STRs.
which carry a lower cost, have high efficacy, little toxicity, and the least number of pills taken once daily to improve adherence. Hence one tablet of the generic STR TDF/3TC/EFV would be a good choice for the successful long-term treatment of HIV/AIDS worldwide. It will help delay the need for second-line therapy, which is more expensive, as well as make the ART program more feasible and sustainable in the long run.

Presently, integrase inhibitor-based regimens are the preferred ART in many resource-rich countries (European AIDS Clinical Society (EACS), 2017; Department of Health and Human Services (DHHS), 2017; Gunthard et al., 2016). Dolutegravir is of particular interest to resource-limited settings because it is well tolerated, taken once a day, and has a higher barrier to resistance. The result of the SINGLE randomized clinical trial indicated that dolutegravir plus abacavir (ABC)–3TC maintained superiority over TDF/FTC/EFV through 144 weeks in previously untreated HIV-infected patients: 71% on dolutegravir/ABC/3TC vs. 63% on EFV/TDF/FTC had a viral load <50 copies/ml (Walmsley et al., 2015). Additionally, ViiV Healthcare extended their Medicines Patent Pool license agreement for dolutegravir to cover all lower middle-income countries. Unfortunately, Thailand is excluded from this program. The cost of dolutegravir in Thailand is still expensive at 285 USD per month. Therefore, dolutegravir cannot be the preferred first-line ART in the HIV program in Thailand at the present time. It is hoped that the

Figure 4. Change in (A) eGFR, and (B) cholesterol, triglyceride, LDL, and HDL.
generic STR of dolutegravir/3TC (FTC)/TAF will become available soon. This regimen would be a promising first-line ART in resource-limited settings with high levels of hepatitis B virus co-infection. This study has some limitations. First, due to budget constraints, the study had only one arm, which means that it is not as powerful as a double-blind randomized controlled trial. Second, the sample size was relatively small and the duration of follow-up was relatively short. Long-term follow-up of this generic STR is warranted to evaluate the long-term efficacy and toxicity. However, the results of this study will have a major impact on the scale-up of first-line therapy and will result in improved access to therapy nationwide. Third, the separate 3TC tablet used was also a generic drug from the Thai GPO. Branded 3TC could not be used in this study because of its cost. Finally, the low EFV-related CNS toxicity may in part be because 50% of patients already tolerated EFV prior to taking the generic STR used. Additionally, the low TDF renal toxicity is mainly due to younger age and less co-morbidity, and 76% of them were homosexual males. Therefore, the results of this study may not be generalizable to an older and female population.

In conclusion, although this study was not a randomized clinical trial, it does demonstrate that the use of a generic STR of TDF/3TC/EVF is safe and highly effective as a first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen. Comparative randomized controlled trials with a larger sample size and a longer follow-up period of more than 144 weeks are required to show that this generic STR is superior to other regimens. The results from this study support the use of a generic STR of TDF/3TC/EVF as the first-line ART in resource-limited settings, and this generic drug could help us to achieve the UNAIDS goal by 2030.

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Conflict of interest

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Author contributions

AA, WM, SG, VS, WT, NT, JS, DMB, and KR contributed to the conception and the design of the study, acquisition of data, interpretation of data, drafting of the article, critical revision for important intellectual content and final approval of the version to be submitted. NT and DMB worked on the PK part of the study. AA, KR, and JS critically revised the manuscript. JS analyzed the data.

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