A Double-blind Placebo-Controlled Study of Emtricitabine in Chronic Hepatitis B

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**Background:** Emtricitabine is a nucleoside analogue approved for treatment of human immunodeficiency virus 1 with clinical activity against hepatitis B virus (HBV).

**Methods:** To compare the safety and efficacy of emtricitabine with placebo in patients with HBV, we conducted a randomized (2:1), double-blind study at 34 sites in North America, Asia, and Europe that enrolled adults between November 2000 and July 2002 who had chronic HBV infection but had never been exposed to nucleoside or nucleotide treatment. Each patient received either 200 mg of emtricitabine (n=167) or placebo (n=81) once daily for 48 weeks and underwent a pretreatment and end-of-treatment liver biopsy. Histologic improvement was defined as a 2-point reduction in Knodell necroinflammatory score with no worsening in fibrosis.

**Results:** At the end of treatment, 103 (62%) of 167 patients receiving active treatment had improved liver histologic findings vs 20 (25%) of 81 receiving placebo (P<.001), with significance demonstrated in subgroups positive (P<.001) and negative (P=.002) for hepatitis Be (HBe) antigen. Serum HBV DNA readings showed less than 400 copies/mL in 91 (54%) of 167 patients in the emtricitabine group vs 2 (2%) of 81 in the placebo group (P<.001); alanine aminotransferase levels were normal in 63% (109/167) vs 25% (20/81), respectively (P<.001). At week 48, 20 (13%) of 159 patients in the emtricitabine group with HBV DNA measured at the end of treatment had detectable virus with resistance mutations (95% confidence interval, 8%-18%). The rate of seroconversion to anti-HBe (12%) and HBe antigen loss were not different between arms. The safety profile of emtricitabine during treatment was similar to that of placebo. Posttreatment exacerbation of HBV infection developed in 23% of emtricitabine-treated patients.

**Conclusion:** In patients with chronic HBV, both positive and negative for HBe antigen, 48 weeks of emtricitabine treatment resulted in significant histologic, virologic, and biochemical improvement.

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**For editorial comment see page 9**

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**Group Information:** A list of the members of the FTCB-301 Study Group appears on page 55.
The primary objective of this randomized, double-blind, placebo-controlled trial was to compare the safety and efficacy of emtricitabine with placebo over 48 weeks in patients with CHB. The study was conducted at 34 sites in the United States, Canada, Hong Kong, Singapore, Bulgaria, Czech Republic, and Greece in compliance with the Declaration of Helsinki and was approved by ethics committees and appropriate regulatory authorities. Patients were enrolled between November 21, 2000, and July 30, 2002, and all provided written informed consent. An interactive voice response system (ClinPhone Inc, Nottingham, England) was used to centrally randomize (2:1) to emtricitabine (200 mg orally) or identical placebo once daily; placebo was considered a standard comparator at the time the trial was initiated. Patients were stratified by screening HBV DNA to balance arms in terms of HBV DNA replication (≤10 MEq/mL vs >10 MEq/mL; Quantiplex branched DNA technique; Chiron Corporation, Emeryville, Calif) and also by geographic region (North America, Asia, and Europe with a block size of 6).

Assessments included analysis of liver biopsy specimens taken prior to and at the end of treatment (week 48); HBeAg and HB surface antigen evaluation at entry and week 48; adverse events analysis; serum HBV DNA evaluation, determination of alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, alkaline phosphatase, and albumin levels, prothrombin time, blood chemical analysis every 4 weeks (determining levels of creatine kinase, lactate dehydrogenase, creatinine, glucose, amylase, sodium ions [Na⁺], and potassium ions [K⁺]); and a complete blood cell count, including differential determination, every 12 weeks. After week 48, patients could enter a 24-week treatment-free follow-up period or enroll in a rollover protocol.

**METHODS**

The primary efficacy end point was liver histologic findings, with improvement defined as a reduction of at least 2 points in the Knodell necroinflammatory score without worsening of the Ishak fibrosis score. The Ishak system for fibrosis scoring was also used, potentially allowing for greater discrimination. Scoring and ranked assessments of necroinflammation and fibrosis (improved, no change, or worse) were interpreted by a central independent histopathologist who was unaware of treatment assignment and biopsy order.

Secondary parameters included serum HBV DNA, ALT, serologic, and resistance mutations findings. Serologic testing was performed using the DiaSorin Plus assay (DiaSorin Inc, Stillwater, Minn). Status of HBeAg (positive or negative) was determined at baseline for subgroup analysis.

For statistical analysis of the data, serum HBV DNA was measured at baseline and week 48 using a polymerase chain reaction assay, the Cobas Amplicor HBV Monitor test (Roche Molecular Systems, Pleasanton, Calif).

**PATIENTS**

Men and women with CHB aged 18 to 70 years could enroll if they were HBeAg-positive or HBeAg-negative with detectable serum HBV DNA and no prior therapy with a nucleoside or nucleotide analogue. The Chiron Quantiplex HBV DNA assay (limit of detection, 0.7 MEq/mL) was used for rapid assessment of eligibility. Prior interferon alfa therapy was not cause for exclusion if the treatment had ended 6 months before screening and 3 months before the first biopsy. Entry criteria included creatinine clearance of at least 60 mL/min, prothrombin time less than 1.5 times the upper limit of normal (ULN) and at least 60% that of control, total bilirubin level no more than 2 times the ULN, ALT level no more than 10 times the ULN, and no ascites, variceal hemorrhage, or hepatic encephalopathy. Elevated ALT level of 1.3 times the ULN or higher within 3 months of screening was required unless qualifying liver histologic results were already available.

Exclusion criteria included a Knodell necroinflammatory score of 3 or lower, hepatitis C or HIV infection, α-fetoprotein level higher than 50 ng/mL, hemoglobin level lower than 9.2 g/dL for men or 8.8 g/dL for women, neutropenia (<1000 cells/µL), thrombocytopenia (<75 000/µL), pregnancy, or breastfeeding.

**END POINTS**

The primary efficacy end point was liver histologic findings, with improvement defined as a reduction of at least 2 points in the Knodell necroinflammatory score without worsening of the Knodell fibrosis score. The Ishak system for fibrosis scoring was also used, potentially allowing for greater discrimination. Scoring and ranked assessments of necroinflammation and fibrosis (improved, no change, or worse) were interpreted by a central independent histopathologist who was unaware of treatment assignment and biopsy order.

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For statistical analysis of the data, serum HBV DNA was measured at baseline and week 48 using a polymerase chain reaction assay, the Cobas Amplicor HBV Monitor test (Roche Molecular Systems, Pleasanton, Calif).
SAFETY ANALYSIS

The primary safety analysis included all patients who received at least 1 dose of study medication and all events during treatment. The severity of adverse events and laboratory abnormalities (performed at Covance Central Laboratory Services, Indianapolis, Ind) was graded using criteria defined by the Division of AIDS.16 Posttreatment exacerbations of CHB were prospectively defined as either a 10-fold increase in ALT and/or aspartate aminotransferase levels from treatment nadir or an increase to 20 times the ULN.

RESISTANCE SURVEILLANCE AND BASELINE SUBTYPE DETERMINATION

Resistance surveillance was performed on patients with detectable viremia by Cobas monitoring (≥400 copies/mL) at week 48, with the matching baseline sample using di-deoxy sequencing technology (ABI Prism 3100; Applied Biosystems, Foster City, Calif).17 The primers used for amplification allowed for sequence analysis of domains A through E (amino acids rt75-rt255) of the HBV polymerase and also for amino acids 67 through 226 of the surface antigen, which was used for the determination of HBV subtype at baseline for all enrolled patients. Among viremic patients at week 48, sequence analysis, which included an evaluation of all genotypic changes from the consensus sequence, was performed for all baseline and week 48 samples using ClustalAlignment (National Center for Biotechnology Information, Bethesda, Md). The proportion of patients developing mutations associated with resistance to emtricitabine,18-20 specifically rtM204I/V with or without rtL180M and rtV173L, was determined.

STATISTICAL ANALYSIS

The study was designed to enroll 240 patients, 160 given emtricitabine (200 mg once daily) and 80 in the placebo group. Using a .05 2-sided significance test, we had 85% power to detect a 20% difference between arms assuming a placebo group. Using a .05 2-sided significance test, we had 85% power to detect a 20% difference between arms assuming a placebo group.
proportion with serum HBV DNA values below the limit of detection and normal ALT and serologic responses. Differences in categorical end points between the treatment groups were evaluated using the Cochran-Mantel-Haenszel test; in continuous end points, a van Elteren test, in both cases controlling for randomization strata (region and screening HBV DNA value). For change in continuous variables and ranked assessment of histologic findings, paired time points were analyzed with a “missing=excluded” approach. All significance tests were 2-sided using an α level of 0.05, and all data were analyzed prior to breaking the treatment codes.

**RESULTS**

**CHARACTERISTICS OF THE PATIENTS**

Screening, randomization, and disposition of study participants are depicted in Figure 1. Among 248 enrolled patients, 167 were randomized to emtricitabine and 81 to placebo, with the last patient completing the regimen on June 25, 2003. All patients underwent baseline liver biopsies, and 91% of the patients in both groups underwent liver biopsies at week 48 (152 emtricitabine; 74 placebo). A total of 67 patients had prior interferon alfa treatment (29% emtricitabine [n=48]; 24% placebo [n=19]) and 1 patient (emtricitabine group) had prior lamivudine exposure. The emtricitabine and placebo treatment groups were well balanced with respect to demographics and disease status at entry (Table 1). Most patients in both groups had ALT levels exceeding the ULN (152 emtricitabine [91%] and 72 placebo [89%]), and 3 patients had baseline serum HBV DNA values lower than 400 copies/mL (2 emtricitabine [1%], 1 placebo [1%]; all detectable at screening). The emtricitabine and placebo groups included 104 (62%) and 51 (63%) HBeAg-positive patients and 63 (38%) and 30 (37%) HBeAg-negative patients, respectively. Seventeen patients discontinued treatment prior to week 48 (8 emtricitabine [5%] and 6 placebo [7%]) with 3% in the emtricitabine group [n=5] and 2% in the placebo group [n=2] owing to adverse events.

**HISTOLOGIC RESPONSE**

Histologic response using intention-to-treat numbers (missing=failure) was achieved in 103 (62%) of 167 patients in the emtricitabine group vs 20 (25%) of 81 patients receiving placebo (P<.001) (Figure 2). Similar rates of histologic improvement were observed among HBeAg-positive and HBeAg-negative patients receiving emtricitabine (63% and 59%, respectively) vs placebo (25% and 23%, respectively) (Table 2). Significant histologic improvement relative to placebo was observed for all subgroups including screening HBV DNA strata, geographic region, HBV subtype, entry total Knodell score, gender, age, and ethnic origin; the histologic response produced by emtricitabine did not significantly vary by HBV genotype (data not shown).

Treatment with emtricitabine resulted in significant decreases in the Knodell necroinflammatory score, with an overall median decrease from baseline of 3.0 points vs 0.0 points in the placebo group (P<.001) (Table 2). Among HBeAg-positive and HBeAg-negative patients given emtricitabine, a median decline of 2 and 4 points was observed, respectively (P<.001 vs placebo). Using the Ishak system, emtricitabine produced a significant decrease in fibrosis for all comparisons to placebo, overall and for HBeAg-positive and HBeAg-negative subsets (P=.01). The change in Knodell fibrosis score was also significant (P=.01) for all emtricitabine-treated patients and for the HBeAg-positive subgroup (P=.02), but statistical significance was not reached among HBeAg-negative patients (Table 2).

Ranked assessment showed a significant improvement in necroinflammatory activity (77%) with less worsening relative to placebo as illustrated in Figure 3 (P<.001 overall and for HBeAg-positive and HBeAg-negative subsets). Ranked assessment of fibrosis showed significantly more improvement (39% vs 26%) and less worsening (13% vs 26%) with emtricitabine than placebo (P=.01), which was significant among HBeAg-negative patients (P=.04) and showed a strong trend among HBeAg-positive patients (P=.05) (Figure 3).

Although all patients underwent a liver biopsy at study entry, 9% of patients in each arm had no end-of-treatment liver biopsy (n=15 emtricitabine; n=7 placebo). In the emtricitabine arm, 8 patients refused the procedure, 3 discontinued treatment owing to adverse events, 2 were lost to follow-up, 1 requested withdrawal, and 1 discontinued treatment owing to pregnancy. In the placebo group, 3 patients refused biopsy, 3 requested withdrawal, and 1 discontinued treatment owing to an adverse event.

**Virologic Response**

At week 48, serum HBV DNA was suppressed below 400 copies/mL in 54% of patients in the emtricitabine arm (n=91) (39% HBeAg-positive [n=41] and 79% HBeAg-negative [n=50]) vs 2% in the placebo arm [n=2] (2% [n=1] and 3% [n=1], respectively) (P<.001). Serum HBV DNA decreased by a median of 4.5 log_{10} copies/mL in the emtricitabine arm, 4.7 log_{10} copies/mL among HBeAg-
positive patients, and 4.1 log10 copies/mL among HBeAg-negative patients, which was significantly greater than placebo (P < .001) (Table 2). Seroconversion to anti-HBe and HBeAg loss occurred with the same frequency among HBeAg-positive and HBeAg-negative patients, which was significantly greater than placebo, and 4.1 log10 copies/mL among HBeAg-negative patients (Table 2).

**RESISTANCE**

Sixty-four patients in the emtricitabine group had serum HBV DNA values greater than 400 copies/mL at week 48. All were genotyped. Mutations associated with emtricitabine resistance in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase, rtM204V with or without rtL180M and rtV173L, were identified in 19 of these patients. No treatment-emergent rtM204I was detected. An additional single patient had an isolated rtL180M mutation. The 48-week incidence of emtricitabine resistance mutations was 13% (95% CI, 8%-18%). Among the 20 affected patients, 9 (45%) had normal ALT levels at week 48, and 13 (65%) had a histologic response per protocol. Mutations in the YMDD motif were observed in 17 (17%) of 99 HBeAg-positive patients (95% CI, 8%-18%).

**BIOCHEMICAL RESPONSE**

At week 48, 109 (65%) of 167 patients in the emtricitabine group had a normal ALT level compared with 20 (25%) of 81 in the placebo group (P < .001). The median decrease in ALT level was 52 U/L in the emtricitabine group and 25 U/L in the placebo group (P < .001), with similar decreases among HBeAg-positive and HBeAg-negative patients (Table 2).
The incidence of clinical adverse events during treatment was similar in the 2 groups (Table 3). Severe (grade 3 or 4) adverse events were reported in 14 (8%) of 167 emtricitabine-treated patients and 7 of 81 patients given placebo (9%), and serious adverse events occurred in 8% (n = 13) and 9% (n = 7), respectively. Related serious adverse events were rare, 4 (2%) of 167 emtricitabine and 3 (4%) of 81 placebo. During treatment, the incidence of grade 3 or 4 laboratory abnormalities was significantly reduced in the emtricitabine group, 31 (19%) of 167 patients vs 33 (41%) of 81 in the placebo group (P < .001), which was due to the lower incidence of grade 3 or 4 transaminase, ALT (7% emtricitabine [n = 11], 26% placebo [n = 21]) and aspartate aminotransferase (2% emtricitabine [n = 3], 12% placebo [n = 10]) (P ≤ .001) (Table 3).

Posttreatment follow-up safety data were available from 145 patients in the emtricitabine group (median follow-up, 110 days) and 63 patients in the placebo group. Posttreatment exacerbation of CHB developed in 33 patients (23%) who had received emtricitabine and 3 placebo patients (5%) (P = .001), with a median time to onset of 10 weeks following the end of treatment (interquartile range, 8-16 weeks). One patient randomized to emtricitabine with marked bridging fibrosis at entry developed severe icteric posttreatment exacerbation of CHB and required liver transplantation. All other patients recovered without clinical complications (overall, 14 with and 19 without antiviral therapy).

In patients with CHB, 48 weeks of treatment with emtricitabine (200 mg, once daily) resulted in significant histologic improvement in 62% (103/167) of patients and complete viral suppression in 54% (91/167) (39% HBeAg-positive [41/104]; 79% HBeAg-negative [50/63]). The median decrease in levels of serum HBV DNA was 4.5 log10 copies/mL with emtricitabine treatment. These results are similar to those achieved by lamivudine in two 52-week pivotal clinical trials in HBeAg-positive patients and in adefovir dipivoxil clinical trials among HBeAg-positive and HBeAg-negative patients. In the adefovir dipivoxil studies the proportion of patients with undetectable serum HBV DNA was 21% and 51% for HBeAg-positive and -negative patients using a polymerase chain reaction assay (limit of detection, 400 copies/mL), with a median decrease in serum HBV DNA of 3.5 and 3.9 log10 copies/mL, respectively.23,24 The lamivudine arms of 2 recently reported entecavir trials in patients not previously exposed to nucleosides demonstrated a mean 4.5– to 5.4-log10 copies/mL decrease in HBV DNA levels, with 38% of HBeAg-positive and 73% of HBeAg-negative patients showing viral suppression below 400 copies/mL.25,26 The entecavir arms suppressed levels of serum HBV DNA by a mean of 6.9 and 5.0 log10 copies/mL, respectively.

Table 3. Incidence of Clinical Adverse Events (~10% in the Emtricitabine Arm) and All Grade 3 or 4 Laboratory Abnormalities During Treatment*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Emtricitabine (n = 167)</th>
<th>Placebo (n = 81)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 adverse event</td>
<td>140 (84)</td>
<td>64 (79)</td>
<td>.38</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (16)</td>
<td>10 (12)</td>
<td>.57</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>22 (13)</td>
<td>14 (17)</td>
<td>.44</td>
</tr>
<tr>
<td>Influenza</td>
<td>21 (13)</td>
<td>12 (15)</td>
<td>.69</td>
</tr>
<tr>
<td>Post procedural pain</td>
<td>21 (13)</td>
<td>5 (6)</td>
<td>.18</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (11)</td>
<td>11 (14)</td>
<td>.53</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (11)</td>
<td>12 (15)</td>
<td>.41</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 laboratory abnormality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 grade 3 or 4 laboratory abnormality</td>
<td>31 (19)</td>
<td>33 (41)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ALT</td>
<td>11 (7)</td>
<td>21 (26)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>9 (5)</td>
<td>5 (6)</td>
<td>.78</td>
</tr>
<tr>
<td>Amylase</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>.66</td>
</tr>
<tr>
<td>Glucose</td>
<td>3 (2)</td>
<td>5 (6)</td>
<td>.12</td>
</tr>
<tr>
<td>AST</td>
<td>3 (2)</td>
<td>10 (12)</td>
<td>.001</td>
</tr>
<tr>
<td>Lipase</td>
<td>2 (1)</td>
<td>0</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Potassium</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Sodium</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>0</td>
<td>2 (2)</td>
<td>.11</td>
</tr>
<tr>
<td>Urine protein</td>
<td>1 (1)</td>
<td>0</td>
<td>&gt; .99</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, not significant.

*Unless otherwise indicated, data are reported as number (percentage) of patients.
†As described by the following terms: abdominal discomfort, abdominal tenderness, abdominal pain upper and lower, and abdominal pain.
with a seroconversion rate to anti-HBe of 16% and 4%, respectively. Similarly, Dienstag et al\(^8\) observed histologic response in 52% (lamivudine) vs 23% (placebo) and HBe seroconversion in 17% and 6%, respectively. In clinical studies of adefovir dipivoxil (10-mg dose once daily), comparable histologic response was reported at 1 year: 53% for adefovir dipivoxil vs 25% for placebo among HBeAg-positive patients\(^23\) and 64% vs 33% among HBeAg-negative patients.\(^24\) Seroconversion to anti-HBe occurred in 12% of patients given adefovir vs 6% given placebo after 48 weeks of treatment.

Thus for the primary end point in the present study (ie, histologic response), the results of emtricitabine treatment were very similar to published studies of lamivudine and adefovir. The present study is the first large randomized study to report combined results for both HBeAg-positive and -negative CHB collectively. While there are differences between these clinical entities, the data are robust overall and demonstrate efficacy in both HBeAg-positive and HBeAg-negative patients independently.

Emtricitabine treatment selected for resistance mutations in 13% of patients (95% CI, 8%-18%) is at the low end of the incidence historically observed for lamivudine for either HBeAg-positive or HBeAg-negative patients.\(^6\) In contrast, adefovir resistance mutations were not observed at 48 weeks, and the incidence at 2 years of rtN236T and rtA181V mutations was low (3%).\(^9\)

Notably, the seroconversion rate among the lamivudine and adefovir trials collectively ranged from 12% to 17%, similar to that observed herein. However, the placebo rate of seroconversion to anti-HBe was uncharacteristically high, about 2-fold greater in the present study than observed historically (4%-6%). This may have been a random effect due to the small number of HBeAg-positive patients in the placebo arm. Since serologic changes were a secondary end point, statistical calculations for sample size were based on histologic response, and the number HBeAg-positive patients (104 emtricitabine, 51 placebo) provided about 20% to 30% power to detect a treatment difference in seroconversion to anti-HBe.

Emtricitabine demonstrated a safety profile similar to placebo during treatment with a lower incidence of grade 3 or 4 elevation of ALT level. Posttreatment exacerbation of CHB occurred at a frequency consistent with that reported in the current US product label for both lamivudine and adefovir. The clinical risk of exacerbation is related to hepatic reserve, which for patients with bridging fibrosis or cirrhosis may be insufficient to accommodate hepatic cytolysis resulting in decompensation. Fatalities have occurred after discontinuation of famciclovir and lamivudine\(^29\) treatment and incipient liver failure (jaundice and coagulopathy) has been reported in 5% of patients in a small series (n=41) following discontinuation of lamivudine therapy.\(^30\) In the present study, 1 patient required orthotopic liver transplantation.

In summary, emtricitabine has significant efficacy at 48 weeks in patients with CHB and treatment resulted in histologic improvement, suppression of HBV DNA, and a decreased ALT level. Emtricitabine selected for resistance mutations in the YMDD motif, which also confer resistance to lamivudine and other 1-nucleosides, and discontinuation of therapy resulted in posttreatment exacerbation of hepatitis at rates similar to those observed with currently approved therapy for CHB. Emtricitabine is approved for the treatment of HIV infection, and thus these data are particularly pertinent for HIV-infected patients who are given emtricitabine as part of their antiretroviral therapy and who might be coinfected with HBV. Coinfected patients make up a significant minority of the HIV-positive population (8%-11%).\(^31,32\) Combination therapy may particularly benefit coinfected patients if drugs with dual activity against both HIV and HBV are used.\(^33\)

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Author Contributions: Dr Rousseau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES