Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD

Gerald Schulman,* Tomas Berl,† Gerald J. Beck,‡ Giuseppe Remuzzi,§ Eberhard Ritz,¶ Kiyoshi Arita,¶ Akira Kato,** and Miho Shimizu¶

*Vanderbilt University School of Medicine, Nashville, Tennessee; †University of Colorado Health Sciences Center, Denver, Colorado; ‡Cleveland Clinic Foundation, Cleveland, Ohio; §Mario Negri Institute for Pharmacological Research, Bergamo, Italy; †University of Heidelberg, Heidelberg, Germany; ¶Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; and **Kureha Corporation, Tokyo, Japan

ABSTRACT

Reduced GFR in patients with CKD causes systemic accumulation of uremic toxins, which has been correlated with disease progression and increased morbidity. The orally administered spherical carbon adsorbent AST-120 reduces systemic toxin absorption through gastrointestinal sequestration, which may slow disease progression in these patients. The multinational, randomized, double-blind, placebo-controlled Evaluating Prevention of Progression in CKD (EPPIC)-1 and EPPIC-2 trials evaluated the effects of AST-120 on the progression of CKD when added to standard therapy. We randomly assigned 2035 adults with moderate to severe disease (serum creatinine at screening, 2.0–5.0 mg/dl for men and 1.5–5.0 mg/dl for women) to receive either placebo or AST-120 (9 g/d). The primary end point was a composite of dialysis initiation, kidney transplantation, and serum creatinine doubling. Each trial continued until accrual of 291 primary end points. The time to primary end point was similar between the AST-120 and the placebo groups in both trials (EPPIC-1: hazard ratio, 1.03; 95% confidence interval, 0.84 to 1.27; \( P = 0.78 \)) (EPPIC-2: hazard ratio, 0.91; 95% confidence interval, 0.74 to 1.12; \( P = 0.37 \)); a pooled analysis of both trials showed similar results. The estimated median time to primary end points for the placebo groups was 124 weeks for power calculations, but actual times were 189.0 and 170.3 weeks for EPPIC-1 and EPPIC-2, respectively. Thus, disease progression was more gradual than expected in the trial populations. In conclusion, the benefit of adding AST-120 to standard therapy in patients with moderate to severe CKD is not supported by these data.


CKD, defined as kidney damage or a GFR<60 ml/min per 1.73 m² for ≥3 months,¹ is associated with increased risk for cardiovascular events, hospitalization, and death² and is a global public health problem. A meta-analysis of population-based studies from 40 countries and regions reported a 6.3% overall prevalence of CKD stages 3–5 (<60 ml/min per 1.73 m²).³ Furthermore, approximately 1870 cases of ESRD per million population were reported in 2010 compared with 1355 per million in 2000,⁴ underscoring the need for treatments to slow or prevent the progression of CKD.

Early management of CKD is recommended to reduce cardiovascular events and additional complications of decreased GFR, improve quality of life, and prolong survival.⁵ Current guidelines focus on managing factors that can hasten CKD progression, such as hypertension and diabetes.⁶–⁸ Although angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) slow the progression of CKD, especially in patients

Received January 10, 2014. Accepted September 14, 2014.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Gerald Schulman, Vanderbilt University School of Medicine, 1211 21st Avenue, Nashville, TN 37212. Email: gerald.schulman@vanderbilt.edu

Copyright © 2015 by the American Society of Nephrology
with marked albuminuria,9–14 many patients still require dialysis or transplantation.

Decreased GFR in CKD is correlated with increased levels of uremic toxins such as indoxyl sulfate and p-cresyl sulfate.15 Recently, several groups demonstrated in patients with chronic renal disease a direct association between levels of indoxyl sulfate and p-cresyl sulfate on one hand and overall mortality and cardiovascular disease on the other hand.16–19 The accumulation of uremic toxins appears to accelerate disease progression by causing functional renal impairment, fibrosis, inflammation, and oxidative stress.20 AST-120 was effective in slowing the progression of renal disease and improving uremic symptoms.21 AST-120 was also shown to delay the progression of CKD in relatively small clinical trials22–24 and to inhibit the hepatic synthesis of indoxyl sulfate by blocking the gastrointestinal absorption of its biochemical precursor indole,25 and it may reduce glomerulosclerosis and tubulointerstitial injury in patients with CKD.26 Results from a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial in the United States indicated that AST-120 (2.7 g/d, 6.3 g/d, or 9 g/d) was associated with dose-dependent reductions in malaise and serum indoxyl sulfate levels in patients with CKD.27 After reviewing the phase 2 data, it was decided to conduct two identical confirmatory trials rather than one larger confirmatory trial with significance set to a lower, more conservative P value. We conducted two large, multinational, randomized, double-blind, safety and efficacy trials—Evaluating Prevention of Progression in Chronic Kidney Disease (EPPIC-1 and EPPIC-2; ClinicalTrials.gov NCT00500682 and NCT00501046)—to determine whether the addition of AST-120 (9 g/d) to standard therapy in patients with moderate to severe CKD can slow the progression of renal disease, defined as initiation of dialysis, kidney transplantation, or doubling of serum creatinine (sCr) level.

RESULTS

Study Population

In total, 3815 patients were screened and 2035 were randomly assigned (1020 in EPPIC-1 and 1015 in EPPIC-2) (Figure 2). Demographic and baseline clinical characteristics were similar between the AST-120 and the placebo groups in each trial and in the pooled analysis from both trials (Table 1). Across treatment groups in both EPPIC trials, most patients were white, male, and had stage 4 CKD. Compliance with study drug was similar when analyzed for the intent to treat (ITT) and the safety populations. For the safety population, compliance was high. Median durations of treatment were 102.1 and 96.3 weeks in the AST-120 group and 103.3 and 91.6 weeks in the placebo group for EPPIC-1 and EPPIC-2, respectively (Table 2).

Efficacy

Results of the primary and secondary end point analyses are shown in Table 3. The 95% confidence intervals (95% CIs) for all hazard ratios (HRs) included 1.0. As shown in Figure 3A (top), there was no significant difference in time from randomization to occurrence of a primary end point event between the AST-120 and the placebo groups in either EPPIC-1 (HR, 1.03; 95% CI, 0.84 to 1.27; \( P=0.78 \)) or EPPIC-2 (HR, 0.91; 95% CI, 0.74 to 1.12; \( P=0.37 \)). Pooled analysis of both trials (Figure 3B, top) also demonstrated no significant difference between the two treatment groups (HR, 0.97; 95% CI, 0.83 to 1.12; \( P=0.64 \)). Furthermore, a disparity was observed between projected and actual disease progression rates in placebo-treated patients in the pooled analysis of both EPPIC trials (Figure 3B, top). Although differences in change from baseline in eGFR were not significant between the AST-120 and the placebo groups in EPPIC-1 (\( P=0.93 \); Figure 3A, bottom left), a significant difference was observed in EPPIC-2 (\( P=0.004 \); Figure 3A, bottom right) and in the pooled analysis of both trials (\( P=0.04 \); Figure 3B, bottom). Although we estimated the median time to the primary end point event for the placebo group to be 124 weeks, the actual time was 189.0 and 170.3 weeks for EPPIC-1 and EPPIC-2, respectively.

Prespecified subgroup analyses revealed covariate-based differences in the effects of AST-120 on the time from randomization...
to the occurrence of a primary end point event in EPPIC-2 but not in EPPIC-1 (Figure 4A). In EPPIC-2, significant covariate-based differences were seen in patients with a urinary total protein to urinary creatinine ratio (UP/UCr) < 2.0 (HR, 0.67; 95% CI, 0.49 to 0.93; P=0.02), patients aged ≥65 years (HR, 0.63; 95% CI, 0.42 to 0.95; P=0.03), patients enrolled from the United States (HR, 0.67; 95% CI, 0.46 to 0.99; P=0.04), and patients without anemia (HR, 0.5; 95% CI, 0.30 to 0.84; P=0.01). When the data for both trials were pooled, no significant covariate-based differences in the time to the occurrence of the primary end point were identified (Figure 4B).

AST-120 did not alter BP or 24-hour urinary protein excretion levels. During the course of the study, the changes from baseline in systolic BP, diastolic BP, and 24-hour urinary protein excretion were not significantly different between AST-120 and placebo in both the EPPIC-1 and the EPPIC-2 trials (data not shown).

Change from baseline in the Kidney Disease Quality of Life Short Form 36 (KDQOL-36) score, assessed only for EPPIC-2, did not show a trend across increasing 12-week intervals in favor of either AST-120 or placebo. When the mixed-effects model was applied to change from baseline in the KDQOL-36 score, no statistically significant difference was observed between treatment groups for the SF-12 Physical Health Composite or the SF-12 Mental Health Composite.

Baseline Characteristics Predicting Renal Disease Progression

Pooled analysis of the placebo ITT population from both EPPIC trials was conducted to identify baseline characteristics that could be useful predictors of renal disease progression (i.e., the primary end point). Poor correlation was observed between renal disease progression and baseline renal disease severity; therefore, similar proportions of patients in the pooled placebo ITT population were identified as having a rate of eGFR decline that was below (i.e., fast) or above (i.e., slow) the median (−3.51 ml/min per 1.73 m² per year; Figure 5A). The likelihood of reaching the primary end point was significantly greater in patients with a fast eGFR decline than in patients with a slow eGFR decline (HR, 5.89; 95% CI, 4.57 to 7.60; P<0.001; Figure 5B). Further analysis of baseline factors indicated that the UP/UCr and the prevalence of hematuria were significantly higher in patients with fast eGFR decline than in patients with slow eGFR decline (both P<0.001; Table 4). Age was also significantly associated with eGFR decline (P<0.001; Table 4) but showed an opposite trend in the event rate (data not shown).

Strong associations were seen among UP/UCr, cumulative event-free rates, and mean eGFR decline in the pooled placebo ITT population (Figure 6, A and B, left). An association between hematuria status and mean eGFR decline was seen, and cumulative event-free rates were higher in hematuria-negative
than in hematuria-positive (trace, 1+, 2+, or 3+) patients (Figure 6, A and B, right); however, no clear trend was seen between hematuria-positive (trace, 1+, 2+, or 3+) status and cumulative event-free rates because of the small number of patients with hematuria-positive (trace, 1+, 2+, or 3+) status. Cumulative event-free rates in the pooled placebo ITT population were highest in hematuria-negative patients with UP/UCr $<0.5$ and lowest in hematuria-positive patients with UP/UCr $>1.0$ at baseline (Figure 6C).

### Safety

Adverse events (AEs) in the safety population are summarized in Table 5. At least one severe treatment-emergent AE affected 105 (20.7%) and 104 (20.5%) patients in the AST-120 group and 94 (18.5%) and 110 (21.8%) patients in the placebo group in EPPIC-1 and EPPIC-2, respectively; similar rates were also seen when data for the two trials were pooled (Table 5). There was virtually no difference in the rate of mild or moderate treatment-emergent AEs in the AST-120 or placebo groups in either trial or in the pooled analysis. The most commonly reported treatment-related AEs in the AST-120 groups occurred in the gastrointestinal disorder system organ class (constipation, nausea, diarrhea), which affected similar proportions of patients in the placebo groups. Other treatment-related AEs were uncommon in this class and in other system organ classes and included decreased appetite and pruritus. Sixty-nine (13.6%) and 43 (8.5%) patients in the AST-120 group and 52 (10.2%) and 61 (12.1%) patients in the placebo group discontinued treatment with study drug in EPPIC-1 and EPPIC-2, respectively, because of treatment-emergent AEs (Table 5).

### Table 1. Demographic and baseline clinical characteristics of the ITT population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EPPIC-1 (n=1002)</th>
<th>EPPIC-2 (n=997)</th>
<th>Pooled (n=1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST-120</td>
<td>Placebo</td>
<td>AST-120</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56.3±14.9</td>
<td>55.6±14.9</td>
<td>54.4±15.5</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>61.8</td>
<td>64.9</td>
<td>54.6</td>
</tr>
<tr>
<td>Race, %a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78.6</td>
<td>79.9</td>
<td>82.8</td>
</tr>
<tr>
<td>Black or African American</td>
<td>8.4</td>
<td>8.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Asian</td>
<td>5.2</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Other</td>
<td>7.8</td>
<td>8.0</td>
<td>8.2</td>
</tr>
<tr>
<td>CKD cause, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>41.8</td>
<td>42.4</td>
<td>39.0</td>
</tr>
<tr>
<td>Nondiabetic nephropathy</td>
<td>58.2</td>
<td>57.6</td>
<td>61.0</td>
</tr>
<tr>
<td>GN</td>
<td>25.6</td>
<td>28.7</td>
<td>24.8</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>14.8</td>
<td>13.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Other</td>
<td>17.8</td>
<td>14.9</td>
<td>17.4</td>
</tr>
<tr>
<td>Use of ACEI or ARB, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84.4</td>
<td>85.5</td>
<td>84.4</td>
</tr>
<tr>
<td>Baseline sCr, mg/dl±SD</td>
<td>3.09±0.88</td>
<td>3.10±0.84</td>
<td>3.06±0.87</td>
</tr>
<tr>
<td>Baseline eGFR, ml/min per 1.73 m²±SD</td>
<td>22.72±8.00</td>
<td>22.54±7.25</td>
<td>22.61±7.87</td>
</tr>
<tr>
<td>Baseline UP/UCr ratio n±SD</td>
<td>499</td>
<td>501</td>
<td>499</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.94±1.33</td>
<td>1.99±1.33</td>
<td>1.99±1.32</td>
</tr>
<tr>
<td>CKD stage, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>1.0</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>3b</td>
<td>18.8</td>
<td>15.3</td>
<td>16.6</td>
</tr>
<tr>
<td>4</td>
<td>62.0</td>
<td>69.3</td>
<td>66.2</td>
</tr>
<tr>
<td>5</td>
<td>18.2</td>
<td>15.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Baseline anemia status, %c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>69.7</td>
<td>70.3</td>
<td>70.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²±sd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>500</td>
<td>502</td>
<td>498</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>29.4±6.1</td>
<td>29.2±7.1</td>
<td>28.9±6.8</td>
</tr>
</tbody>
</table>

Data are presented as the mean±SD, n, or %, as indicated. There were no significant differences between the two treatment groups except for baseline sCr ($P=0.03$), baseline eGFR ($P=0.03$), and CKD stage ($P=0.04$) for EPPIC-2.

*aRace was self-reported.

*bTo convert sCr from mg/dl to μmol/L, multiply by 88.4.

*cAnemia was defined as a hemoglobin level $<13.5$ g/dl (men) or $<12.0$ g/dl (women).

*dBody mass index is the weight in kilograms divided by the square of the height in meters.
DISCUSSION

These trials were not able to demonstrate a beneficial effect of AST-120 on progression of CKD. Although the efficacy of AST-120 in preventing progression may be questioned by these trials, the fact that the rate of progression of the placebo group was underestimated mitigates this conclusion. This finding differs from the results of previous AST-120 trials conducted in Japan in patients with CKD.22–24,28

First, this discrepancy could be attributed to the difference between actual and estimated placebo event curves. We based the estimated curve on an assumed 1/sCr slope of —0.01 dl/mg per month, which yielded an expected median time of 124 weeks until a primary end point event consistent with renal disease progression occurred. However, the actual mean 1/sCr slope for both trials was —0.006 dl/mg per month, and the actual median time for progression in EPPIC-1 and EPPIC-2 was 189.0 and 170.3 weeks, respectively, suggesting a failure to select patients with progressive CKD. It is possible that the inclusion criterion of UP/U Cr = 0.5 was insufficient to enrich the population with patients with progressive disease.

Second, regional differences in the initiation of dialysis could have contributed to the results observed in the EPPIC trials. Initiation of dialysis in Russia and Ukraine, countries with high enrollment, was markedly different from that in North America and Europe (Table 6). Because of this difference, the median time to event for the placebo group could not be calculated for patients in Russia or Ukraine within the follow-up period, whereas it was 135.6 and 150.0 weeks for EPPIC-1 and EPPIC-2, respectively, in the United States.

Third, covariate imbalances may explain the trial results. No correlation between renal disease progression and indicators of disease severity, such as baseline sCr level, eGFR, or diabetes, was observed in the EPPIC data. Randomization was stratified by enrollment country or center, CKD cause, and

Table 2. Study drug exposure and compliance (safety population)

<table>
<thead>
<tr>
<th>Drug Compliance</th>
<th>EPPIC-1 (n=1016)</th>
<th>EPPIC-2 (n=1012)</th>
<th>Pooled (n=2028)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST-120 (n=507)</td>
<td>Placebo (n=509)</td>
<td>AST-120 (n=507)</td>
</tr>
<tr>
<td>Compliance, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>503</td>
<td>502</td>
<td>505</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>91.4±13.9</td>
<td>90.5±15.0</td>
<td>90.3±14.4</td>
</tr>
<tr>
<td>Median</td>
<td>96.1</td>
<td>96.1</td>
<td>95.4</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>10.0, 120.0</td>
<td>6.2, 114.9</td>
<td>7.8, 119.3</td>
</tr>
<tr>
<td>Categorical summary, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33%</td>
<td>4 (0.8)</td>
<td>4 (0.8)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>≥33% to &lt;50%</td>
<td>9 (1.8)</td>
<td>14 (2.8)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>≥50% to &lt;67%</td>
<td>20 (4.0)</td>
<td>29 (5.8)</td>
<td>24 (4.8)</td>
</tr>
<tr>
<td>≥67% to &lt;83%</td>
<td>41 (8.2)</td>
<td>40 (8.0)</td>
<td>49 (9.7)</td>
</tr>
<tr>
<td>≥83% to &lt;100%</td>
<td>356 (70.8)</td>
<td>349 (69.5)</td>
<td>366 (72.5)</td>
</tr>
<tr>
<td>≥100% to &lt;110%</td>
<td>71 (14.1)</td>
<td>65 (12.9)</td>
<td>47 (9.3)</td>
</tr>
<tr>
<td>≥110%</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>503</td>
<td>502</td>
<td>505</td>
</tr>
</tbody>
</table>

Duration of treatment, wk

| n               | 507            | 509            | 507            | 505            | 1014           | 1014           |
| Mean±SD        | 91.0±50.3      | 92.6±52.6      | 94.1±49.9      | 87.8±50.6      | 92.5±50.1      | 90.2±51.6      |
| Median         | 102.1          | 103.3          | 96.3           | 91.6           | 98.0           | 95.86          |
| Minimum, maximum | 0.1, 206.9    | 0.3, 207.3     | 0.4, 210.4     | 0.0, 206.0     | 0.1, 210.4     | 0.0, 207.3     |

Categorical summary, wk, n (%) |

| <24            | 65 (12.8)      | 71 (13.9)      | 57 (11.2)      | 72 (14.3)      | 122 (12.0)     | 143 (14.1)     |
| ≥24 to <48     | 68 (13.4)      | 63 (12.4)      | 56 (11.0)      | 55 (10.9)      | 124 (12.2)     | 118 (11.6)     |
| ≥48 to <72     | 50 (9.9)       | 51 (10.0)      | 48 (9.5)       | 70 (13.9)      | 98 (9.7)       | 121 (11.9)     |
| ≥72 to <96     | 48 (9.5)       | 45 (8.8)       | 91 (17.9)      | 81 (16.0)      | 139 (13.7)     | 126 (12.4)     |
| ≥96 to <120    | 117 (23.1)     | 104 (20.4)     | 93 (18.3)      | 82 (16.2)      | 210 (20.7)     | 186 (18.3)     |
| ≥120 to <144   | 84 (16.6)      | 89 (17.5)      | 74 (14.6)      | 70 (13.9)      | 158 (15.6)     | 159 (15.7)     |
| ≥144 to <168   | 48 (9.5)       | 52 (10.2)      | 49 (9.7)       | 42 (8.3)       | 97 (9.6)       | 94 (9.3)       |
| ≥168           | 27 (5.3)       | 34 (6.7)       | 39 (7.7)       | 33 (6.5)       | 66 (6.5)       | 67 (6.6)       |
| Total          | 507            | 509            | 507            | 505            | 1014           | 1014           |

Patients received a study medication kit every 3 months that consisted of 94 bottles of study medication (30 capsules of study medication per bottle). To evaluate study medication compliance, patients were asked to return all bottles (used and unused). Site personnel counted the remaining capsules to calculate the compliance rate. Results were similar in the ITT population.

*Total dose taken/total dose required)×100.

b[(Date of last dose)–(date of first dose)+1]/7.
Table 3. Primary and secondary efficacy end points from the EPPIC trials

<table>
<thead>
<tr>
<th>End Point</th>
<th>AST-120</th>
<th>Placebo</th>
<th>AST-120 versus Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
<td>N</td>
</tr>
<tr>
<td>EPPIC-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>500</td>
<td>178 (35.6)</td>
<td>502</td>
</tr>
<tr>
<td>ITT (censored at last sCr)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>500</td>
<td>159 (31.8)</td>
<td>502</td>
</tr>
<tr>
<td>ITT (90 d lagging censoring)</td>
<td>500</td>
<td>153 (30.6)</td>
<td>502</td>
</tr>
<tr>
<td>ITT (14 d lagging censoring)</td>
<td>500</td>
<td>135 (27.0)</td>
<td>502</td>
</tr>
<tr>
<td>PP (censored at last contact)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>451</td>
<td>156 (34.6)</td>
<td>445</td>
</tr>
<tr>
<td>Secondary end point&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>500</td>
<td>213 (42.6)</td>
<td>502</td>
</tr>
<tr>
<td>PP (censored at last contact)</td>
<td>451</td>
<td>189 (41.9)</td>
<td>445</td>
</tr>
<tr>
<td>Individual end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>500</td>
<td>161 (32.2)</td>
<td>502</td>
</tr>
<tr>
<td>Doubling of sCr</td>
<td>500</td>
<td>36 (7.2)</td>
<td>502</td>
</tr>
<tr>
<td>Death</td>
<td>500</td>
<td>49 (9.8)</td>
<td>502</td>
</tr>
<tr>
<td>EPPIC-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>500</td>
<td>172 (34.4)</td>
<td>497</td>
</tr>
<tr>
<td>ITT (censored at last sCr)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>500</td>
<td>156 (31.2)</td>
<td>497</td>
</tr>
<tr>
<td>ITT (90 d lagging censoring)</td>
<td>500</td>
<td>152 (30.4)</td>
<td>497</td>
</tr>
<tr>
<td>ITT (14 d lagging censoring)</td>
<td>500</td>
<td>124 (24.8)</td>
<td>497</td>
</tr>
<tr>
<td>PP (censored at last contact)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>447</td>
<td>155 (34.7)</td>
<td>437</td>
</tr>
<tr>
<td>Secondary end point&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>500</td>
<td>204 (40.8)</td>
<td>497</td>
</tr>
<tr>
<td>PP (censored at last contact)</td>
<td>447</td>
<td>180 (40.3)</td>
<td>437</td>
</tr>
<tr>
<td>Individual end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>500</td>
<td>146 (29.2)</td>
<td>497</td>
</tr>
<tr>
<td>Doubling of sCr</td>
<td>500</td>
<td>57 (11.4)</td>
<td>497</td>
</tr>
<tr>
<td>Death</td>
<td>500</td>
<td>49 (9.8)</td>
<td>497</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>1000</td>
<td>350 (35.0)</td>
<td>999</td>
</tr>
<tr>
<td>ITT (censored at last sCr)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1000</td>
<td>315 (31.5)</td>
<td>999</td>
</tr>
<tr>
<td>ITT (90 d lagging censoring)</td>
<td>1000</td>
<td>305 (30.5)</td>
<td>999</td>
</tr>
<tr>
<td>ITT (14 d lagging censoring)</td>
<td>1000</td>
<td>259 (25.9)</td>
<td>999</td>
</tr>
<tr>
<td>PP (censored at last contact)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>898</td>
<td>311 (34.6)</td>
<td>882</td>
</tr>
<tr>
<td>Secondary end point&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT (censored at last contact)</td>
<td>1000</td>
<td>417 (41.7)</td>
<td>999</td>
</tr>
<tr>
<td>PP (censored at last contact)</td>
<td>898</td>
<td>369 (41.1)</td>
<td>882</td>
</tr>
<tr>
<td>Individual end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>1000</td>
<td>307 (30.7)</td>
<td>999</td>
</tr>
<tr>
<td>Doubling of sCr</td>
<td>1000</td>
<td>93 (9.3)</td>
<td>999</td>
</tr>
<tr>
<td>Death</td>
<td>1000</td>
<td>98 (9.8)</td>
<td>999</td>
</tr>
</tbody>
</table>

N, number of patients in the respective population; PP, per protocol.

<sup>a</sup>Primary end point was time to onset of renal disease progression calculated as the time from randomization to the date when the first component of a triple composite end point (initiation of dialysis, kidney transplantation, or doubling of sCr) occurred; the primary analysis was conducted on the ITT (censored at last contact) population. Other analyses on the primary end point were performed to evaluate the robustness of results to censoring patterns.

<sup>b</sup>First occurrence of dialysis, kidney transplantation, or doubling of sCr through 84 days after last sCr assessment or last dose. Patients who did not have an event in this period were censored at last sCr assessment.

<sup>c</sup>PP included all patients in the ITT population who had no major protocol violations or deviations. Blinded data review was conducted before database lock and trial unblinding using detailed criteria, including minimum compliance rate. During the blinded data review, the two major protocol violations that excluded a patient from the PP population were any treatment other than that randomly assigned and treatment compliance rate, 67% and/or treatment period, 8 weeks.

<sup>d</sup>The secondary end point was time to onset of renal disease progression, calculated as the time from randomization to the date when the first component of a quadruple composite end point (initiation of dialysis, kidney transplantation, doubling of sCr, or death) occurred.
Figure 3. Primary efficacy end point (triple composite end point). (A) EPPIC-1 and EPPIC-2 trials. (B) Pooled analysis of both trials. Kaplan–Meier analysis and eGFR relative change from baseline analyzed using a mixed-effect model for repeated measures and analysis of covariance in the ITT population.
Therefore, any imbalances in baseline characteristics would have been observed by country or by site, rather than overall. It is possible that the stratification factors did not effectively balance the distribution of patients with progressive disease.

Fourth, compliance might have been a limitation because AST-120 is associated with a high pill burden given the need for 30 capsules per day. This might have caused a higher early termination rate than initially anticipated, resulting in an insufficient treatment course in part of the population. Compliance rates were based upon pill counts from all returned patient bottles. Although the data from the EPPIC trials show high compliance rates and support the tolerability of AST-120 9 g/d for long-term use, we cannot confirm whether patients actually took all required pills. Certainly, the measurement of uremic toxin (i.e., indoxyl sulfate and p-cresyl sulfate) levels in at least a subset of participants will provide a better index of compliance in future studies.

Finally, pooled analysis of the baseline characteristics in the placebo ITT population from both EPPIC trials identified a subgroup of patients who experienced rapid decline in eGFR and who were at increased risk for renal disease progression compared with those who experienced slow decline in eGFR; a significantly higher UP/UCr and a higher prevalence of hematuria were also seen in these patients at high risk. In a Japanese trial that showed significant efficacy of AST-120, a 24-week observation period was incorporated to identify patients experiencing rapid disease progression (data on file). However, this type of observation period was not baseline sCr level. Therefore, any imbalances in baseline characteristics would have been observed by country or by site, rather than overall. It is possible that the stratification factors did not effectively balance the distribution of patients with progressive disease.

Fourth, compliance might have been a limitation because AST-120 is associated with a high pill burden given the need for 30 capsules per day. This might have caused a higher early termination rate than initially anticipated, resulting in an insufficient treatment course in part of the population. Compliance rates were based upon pill counts from all returned patient bottles. Although the data from the EPPIC trials show high compliance rates and support the tolerability of AST-120 9 g/d for long-term use, we cannot confirm whether patients actually took all required pills. Certainly, the measurement of uremic toxin (i.e., indoxyl sulfate and p-cresyl sulfate) levels in at least a subset of participants will provide a better index of compliance in future studies.

Finally, pooled analysis of the baseline characteristics in the placebo ITT population from both EPPIC trials identified a subgroup of patients who experienced rapid decline in eGFR and who were at increased risk for renal disease progression compared with those who experienced slow decline in eGFR; a significantly higher UP/UCr and a higher prevalence of hematuria were also seen in these patients at high risk. In a Japanese trial that showed significant efficacy of AST-120, a 24-week observation period was incorporated to identify patients experiencing rapid disease progression (data on file). However, this type of observation period was not baseline sCr level. Therefore, any imbalances in baseline characteristics would have been observed by country or by site, rather than overall. It is possible that the stratification factors did not effectively balance the distribution of patients with progressive disease.

Fourth, compliance might have been a limitation because AST-120 is associated with a high pill burden given the need for 30 capsules per day. This might have caused a higher early termination rate than initially anticipated, resulting in an insufficient treatment course in part of the population. Compliance rates were based upon pill counts from all returned patient bottles. Although the data from the EPPIC trials show high compliance rates and support the tolerability of AST-120 9 g/d for long-term use, we cannot confirm whether patients actually took all required pills. Certainly, the measurement of uremic toxin (i.e., indoxyl sulfate and p-cresyl sulfate) levels in at least a subset of participants will provide a better index of compliance in future studies.

Finally, pooled analysis of the baseline characteristics in the placebo ITT population from both EPPIC trials identified a subgroup of patients who experienced rapid decline in eGFR and who were at increased risk for renal disease progression compared with those who experienced slow decline in eGFR; a significantly higher UP/UCr and a higher prevalence of hematuria were also seen in these patients at high risk. In a Japanese trial that showed significant efficacy of AST-120, a 24-week observation period was incorporated to identify patients experiencing rapid disease progression (data on file). However, this type of observation period was not...
feasible for the large trials reported here. Adding these baseline factors (U/P or U/Cre $\geq 1.0$ and hematuria positive) to inclusion criteria may be useful in future studies to enrich recruitment with participants who are more likely to experience rapid CKD progression.

In conclusion, the benefit of adding AST-120 to standard therapy in patients with moderate to severe CKD was not supported by the data from these trials.

CONCISE METHODS

Study Design

EPPIC-1 and EPPIC-2 were randomized, double-blind, placebo-controlled, phase 3 trials conducted between July 2007 and February 2012, at 239 sites in Argentina, Brazil, Canada, Czech Republic, France, Germany, Italy, Mexico, Poland, Russia, Spain, Ukraine, and the United States. The trials were identical in design except that EPPIC-2 included quality-of-life assessments. In addition, the investigation sites for EPPIC-1 and EPPIC-2 did not overlap.

After a 2-week screening period, patients were randomly assigned in a 1:1 ratio to receive placebo or AST-120 (9 g/d). During randomization, treatment groups were stratified using the Pocock and Simon minimization method based on enrollment center or country, CKD cause (diabetic or nondiabetic nephropathy), and baseline sCr level ($\leq 3.0$ or $>3.0$ mg/dl). The AST-120 dose was selected based on results from a dose-ranging phase 2 study. Both AST-120 and placebo were administered in 300-mg capsules. Patients were to take 10 capsules three times daily (a total of 30 capsules daily) with meals and 1 hour after other medications except phosphate binders, which could be taken simultaneously because no interactions between AST-120 and phosphate binders have been demonstrated (data on file, Kureha Corporation). We performed follow-up clinical and laboratory assessments at weeks 2, 6, 12, 24, 36, and 48 and every 12 weeks thereafter until the trial ended.

Patients

Eligible patients were aged $\geq 18$ years, had moderate to severe CKD (defined as sCr at screening of 2.0–5.0 mg/dl for men or 1.5–5.0 mg/dl for women), and proteinuria (defined as U/P or U/Cre $\geq 0.5$ at screening) or progressive decline of renal function (defined as a $>10\%$ increase in sCr within 3 months after screening). Patients were expected not to require dialysis or kidney transplantation within 6 months of trial entry and to survive for 1 year or longer. In addition, BP must have been stable, defined as sitting BP of $\leq 160/90$ mmHg at screening and at baseline. Patients with hypertension must have had stable BP, defined as no more than one measurement of $>160/90$ mmHg in the 3 months before screening. If a patient was receiving antihypertensive therapy, treatment must have been stable (defined as no change in medication or dose in the 3 months before baseline) and must have included either an ACEI or an ARB unless contraindicated.

Exclusion criteria included uncontrolled hypertension, obstructive or reversible kidney disease, nephrotic syndrome (UP/UCr $>6.0$), adult polycystic kidney disease, uncontrolled arrhythmia or severe cardiovascular disease (New York Heart Association Class III–IV), immunosuppressive therapy within 3 months or accelerated or malignant hypertension within 6 months, and history of any of the following: kidney transplantation, malabsorption, inflammatory bowel disease, hiatal hernia, active peptic ulcer, and severe gastrointestinal dysmotility not attributable to the use of a phosphate binder.

Assessments and Outcomes

The primary end point was a triple composite of time from the date of randomization to the date of kidney disease progression, as indicated by initiation of dialysis, kidney transplantation, or doubling of sCr
level, whichever occurred first. Because an earlier study of AST-120 found no significant differences between AST-120–treated and placebo-treated patients in 24-hour urinary creatinine excretion and sCr, indicating that inconsequential or no amounts of creatinine were adsorbed by AST-120 in the gut, sCr was determined to be a valid measure of renal function in patients treated with AST-120, and an increase in sCr was selected as a component of the composite end point. The secondary end point was a quadruple composite of the primary end point and death. In addition, EPPIC-2 included KDQOL-36 assessments. The trials continued until accrual of the target number of end point outcomes. Patients in both trials underwent treatment until the end of the trial or dropout, initiation of dialysis, or kidney transplantation. Safety was evaluated by assessing the incidence and severity of AEs and by laboratory assessments, 12-lead electrocardiograms, and vital sign and physical examinations.

### Statistical Analysis

Assuming a 30% dropout rate, 291 primary end point events from 980 patients (490 in each treatment group) were needed to detect a 28% decrease in risk for development of the triple composite end point in the AST-120 group compared with the placebo group using a two-sided log-rank test at the 0.05 significance level and 80% power. The risk reduction was defined as $100 - \frac{3}{HR}$. To estimate sample size requirements, we assumed that the median time to the primary end point event in the placebo group was 124 weeks, which corresponded to a 55% event rate at 3 years based on event rate data from the Reduction in Endpoints with the Angiotensin Antagonist Losartan study. HRs were estimated for a study population with an assumed mean sCr value of 3.0 mg/dl and an assumed mean UP/UCr ratio of 2.0 and then were multiplied. The resultant combined HR was reduced considering the EPPIC population would potentially be composed of 50% patients without diabetes and because the sCr level and the UP/UCr ratio are not totally independent risk factors.

Descriptive statistics were used to summarize demographic and baseline clinical characteristics for each treatment group; these groups were compared using chi-squared tests for categorical data and two-sample t tests for continuous data. For efficacy analyses, we compared time to onset of renal disease progression (defined by the primary end point) between the treatment groups by using maximum partial likelihood methods based on the stratified Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Table 4. Baseline characteristics associated with CKD progression (pooled placebo ITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>eGFR Decline Fast Group (n=499;10.22±0.43)</td>
</tr>
<tr>
<td>CKD cause</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Nondiabetic nephropathy</td>
</tr>
<tr>
<td>CKD stage</td>
</tr>
<tr>
<td>3a</td>
</tr>
<tr>
<td>3b</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>sCr, mg/dl</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
</tr>
<tr>
<td>UP/UCr</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
<tr>
<td>Positive (+)</td>
</tr>
<tr>
<td>Negative (-)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black or African American</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Use of ACEI or ARB</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Baseline anemia status</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. Median eGFR decline is 3.51 ml/min per 1.73 m² per year (~0.292 ml/min per 1.73 m² per month). Fast, median; slow, 2 median. Hematuria (+): trace, 1+, 2+, or 3+. *Anemia was defined as a hemoglobin level <13.5 g/dl (men) or <12.0 g/dl (women). **Body mass index is weight in kilograms divided by square of the height in meters.
Figure 6. Effect of UP/UCr and hematuria status on renal disease progression. (A) Event rate based on baseline UP/UCr level or hematuria status (pooled placebo ITT population). (B) Mean eGFR decline based on baseline UP/UCr level or hematuria status (pooled placebo ITT population). (C) Event rate based on combined baseline UP/UCr level and hematuria status (pooled placebo ITT population). K-M, Kaplan–Meier.
Table 5. Summary of AEs (safety population)

<table>
<thead>
<tr>
<th>Description of AE</th>
<th>EPPIC-1 (n=1016)</th>
<th>EPPIC-2 (n=1012)</th>
<th>Pooled (n=1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST-120 (n=507)</td>
<td>Placebo (n=509)</td>
<td>AST-120 (n=507)</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>Patients</td>
<td>Events</td>
</tr>
<tr>
<td>Treatment-emergent AE</td>
<td>2483</td>
<td>436 (86.0)</td>
<td>2589</td>
</tr>
<tr>
<td>Severe</td>
<td>193</td>
<td>105 (20.7)</td>
<td>185</td>
</tr>
<tr>
<td>Moderate</td>
<td>854</td>
<td>210 (41.4)</td>
<td>925</td>
</tr>
<tr>
<td>Mild</td>
<td>1435</td>
<td>121 (23.9)</td>
<td>1476</td>
</tr>
<tr>
<td>Unknown*</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>142</td>
<td>93 (18.3)</td>
<td>147</td>
</tr>
</tbody>
</table>

Treatment-related AEs occurring in ≥1% of patients in either treatment group

| Gastrointestinal disorders | 103 | 72 (14.2) | 101 | 72 (14.1) | 146 | 89 (17.6) | 142 | 89 (17.6) | 249 | 161 (15.9) | 243 | 161 (15.9) |
| Constipation | 25 | 25 (4.9) | 22 | 21 (4.1) | 29 | 25 (4.9) | 21 | 19 (3.8) | 54 | 50 (4.9) | 43 | 40 (3.9) |
| Nausea | 14 | 13 (2.6) | 13 | 13 (2.6) | 19 | 18 (3.6) | 12 | 12 (2.4) | 33 | 31 (3.1) | 25 | 25 (2.5) |
| Diarrhea | 13 | 12 (2.4) | 11 | 9 (1.8) | 22 | 17 (3.4) | 22 | 18 (3.6) | 35 | 29 (2.9) | 33 | 27 (2.7) |
| Abdominal distention | 10 | 10 (2.0) | 10 | 8 (1.6) | 14 | 14 (2.8) | 12 | 12 (2.4) | 24 | 24 (2.4) | 22 | 20 (2.0) |
| Flatulence | 7 | 7 (1.4) | 12 | 12 (2.4) | 10 | 10 (2.0) | 15 | 14 (2.8) | 17 | 17 (1.7) | 27 | 26 (2.6) |
| Vomiting | 3 | 3 (0.6) | 4 | 3 (0.6) | 10 | 8 (1.6) | 9 | 8 (1.6) | 13 | 11 (1.1) | 13 | 11 (1.1) |
| Abdominal pain | 7 | 6 (1.2) | 6 | 5 (1.0) | 10 | 6 (1.2) | 5 | 5 (1.0) | 17 | 12 (1.2) | 11 | 10 (1.0) |
| Abdominal discomfort | 3 | 3 (0.6) | 0 | 0 | 7 | 7 (1.4) | 0 | 0 | 10 | 10 (1.0) | 0 | 0 |
| Dyspepsia | 5 | 5 (1.0) | 5 | 5 (1.0) | 2 | 2 (0.4) | 9 | 8 (1.6) | 7 | 7 (0.7) | 14 | 13 (1.3) |
| Stool discolored | 1 | 1 (0.2) | 4 | 4 (0.8) | 3 | 3 (0.6) | 10 | 10 (2.0) | 4 | 4 (0.4) | 14 | 14 (1.4) |
| Gastritis | 0 | 0 | 1 | 1 (0.2) | 3 | 3 (0.6) | 13 | 10 (2.0) | 3 | 3 (0.3) | 14 | 11 (1.1) |
| Metabolism and nutrition disorders | 7 | 7 (1.4) | 10 | 10 (2.0) | 5 | 4 (0.8) | 10 | 10 (2.0) | 12 | 11 (1.1) | 20 | 20 (2.0) |
| Decreased appetite | 1 | 1 (0.2) | 5 | 5 (1.0) | 3 | 2 (0.4) | 6 | 6 (1.2) | 4 | 3 (0.3) | 11 | 11 (1.1) |
| Skin and subcutaneous tissue disorders | 8 | 8 (1.6) | 5 | 4 (0.8) | 13 | 11 (2.2) | 11 | 10 (2.0) | 21 | 19 (1.9) | 16 | 14 (1.4) |
| Pruritus | 1 | 1 (0.2) | 2 | 2 (0.4) | 8 | 6 (1.2) | 6 | 6 (1.2) | 9 | 7 (0.7) | 8 | 8 (0.8) |
| Treatment-emergent SAE | 370 | 195 (38.5) | 375 | 184 (36.1) | 343 | 156 (30.8) | 363 | 178 (35.2) | 713 | 351 (34.6) | 738 | 362 (35.7) |
| Treatment-related SAE | 6 | 5 (1.0) | 3 | 3 (0.6) | 8 | 4 (0.8) | 8 | 5 (1.0) | 14 | 9 (0.9) | 11 | 8 (0.8) |
| Treatment-emergent AE leading to discontinuation of study drug | 93 | 69 (13.6) | 64 | 52 (10.2) | 60 | 43 (8.5) | 92 | 61 (12.1) | 153 | 112 (11.0) | 156 | 113 (11.1) |
| Treatment-related AE leading to discontinuation of study drug | 20 | 13 (2.6) | 17 | 15 (2.9) | 15 | 11 (2.2) | 19 | 16 (3.2) | 35 | 24 (2.4) | 36 | 31 (3.1) |
| Death due to treatment-emergent AE | 28 | 23 (4.5) | 17 | 15 (2.9) | 31 | 27 (5.3) | 44 | 37 (7.3) | 59 | 50 (4.9) | 61 | 52 (5.1) |

Data are presented as n or n (%). Treatment-emergent AE/SAEs are AEs/SAEs with onset dates on or after the start of study drug. Treatment-related AE/SAEs are any treatment-emergent AE/SAE in which the relationship to drug was possible, probable, or definite. The safety population included all randomly assigned patients who received ≥1 dose of study drug. SAE, serious adverse event.

*Each patient who experienced a treatment-emergent AE of unknown status experienced multiple treatment-emergent AEs of another status (severe, moderate, or mild).
regression model with 95% CIs. We adjusted for the randomization stratification covariates including enrollment center or country, CKD cause, and baseline sCr level. The Kaplan–Meier method was used to plot the cumulative probability of remaining free of renal disease progression. The Kaplan–Meier method and stratified Cox regression analysis were also used to analyze time from date of randomization to date of first occurrence of the secondary (quadruple composite) end point, but death was considered an event rather than a censored observation as in the primary end point analysis.

We performed prespecified subgroup analyses with unstratified Cox regression analysis and the Kaplan–Meier estimation procedure. Subgroups were based on CKD cause (diabetic or nondiabetic nephropathy), baseline sCr level (≤3.0 or >3.0 mg/dl), CKD stage as determined by eGFR level (stage 3 [3a and 3b combined], 4, or 5), C-reactive protein level (<1.0, 1.0–3.0, or >3.0 mg/L), anemia status, age (aged <65 years or ≥65 years), race (white, black or African American, Asian, or other), sex, country and region of residence (North America, Latin America, or Europe, including Russia and Ukraine), baseline ACEI or ARB therapy, and baseline UP/UCr (<2.0 or ≥2.0).

The difference between treatment groups in the relative mean change from baseline in eGFR over the first 96 weeks of the study was assessed using a mixed-effect model for repeated measures.

Data from the pooled placebo population of the EPPIC trials were analyzed to identify patients with rapidly progressing renal disease. Patterns of eGFR decline during the first 96 weeks of treatment were examined to elucidate the distribution and degree of renal disease progression. The pooled placebo group was divided into two groups (based on eGFR decline [fast or slow]) using the median eGFR slope as the cutoff. Baseline characteristics were compared between these two groups to identify factors that influenced renal disease progression using chi-squared tests for categorical data and two-sample t tests for continuous data. The mean change rate and the SEM in eGFR from baseline to week 96 were calculated and analyzed using repeated measures and analysis of covariance with covariates (treatment, visit, interaction terms between treatment group and visit, region, baseline sCr [continuous data], and CKD cause).

The safety population included all randomly assigned patients who received ≥1 doses of study drug. The ITT population included all randomly assigned patients who received ≥1 doses of study drug and had ≥1 postbaseline sCr measurements. Patients who did not reach the primary end point were censored at the date of last contact. Sensitivity analyses of the primary efficacy end point were performed to evaluate the robustness of the results to censoring patterns.

Full materials and methods for the EPPIC-1 and EPPIC-2 studies are published online in the Supplemental Material for this article.

ACKNOWLEDGMENTS

The EPPIC trials were sponsored by Mitsubishi Tanabe Pharma Corporation and Kureha Corporation. Medical writing and editorial support provided by ApotheCom (Yardley, PA) was funded by Mitsubishi Tanabe Pharma America.

Baseline characteristics of patients enrolled in the EPPIC trials were presented at the National Kidney Foundation 2012 Spring Clinical Meeting, held May 9–13, 2012, in Washington, DC. Results from the EPPIC trials were presented at the 2012 Annual Meeting of the American Society of Nephrology, held October 30–November 4, 2012, in San Diego, California.

The following individuals comprise the EPICC Steering Committee: G. Schulman (Chair, United States), T. Berl (United States), G.J. Beck (United States), G. Remuzzi (Italy), and E. Ritz (Germany). Members of the EPICC Data Monitoring Committee are as follows: A. Cheung...
DISCLOSURES

G.S. reports having received consulting fees or honoraria, payment for lectures including service on speakers bureaus, and support for travel to meetings for the study or other purposes from Kureha Corporation and Mitsubishi Tanabe Pharma Corporation. T.B. reports having received fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like from Kureha Corporation and Mitsubishi Tanabe Pharma Corporation; consultancy fees from Sanofi; fees for expert testimony from AstraZeneca; and payment for lectures including service on speakers bureaus from Otsuka. G.J.B. reports having received consulting fees from Kureha Corporation and Mitsubishi Tanabe Pharma Corporation as a steering committee member for EPPIC-1 and EPPIC-2 and consulting fees or honoraria for participation in other review activities such as data and safety monitoring boards. G.R. reports having received consulting fees or honoraria from Kureha Corporation and Mitsubishi Tanabe Pharma Corporation, and his institution has received payment for consultancy work from Alexion Pharmaceuticals, AstraZeneca, Pharmatek, and Reata Pharmaceuticals. E.R. reports receiving payment for lectures including service on speakers bureaus from AbbVie, Amgen, Daiichi Sankyo, and Medice and receiving consulting fees from Kureha Corporation and Mitsubishi Tanabe Pharma Corporation as a steering committee member for EPPIC-1 and EPPIC-2. K.A. and M.S. report employment with Mitsubishi Tanabe Pharma Corporation. A.K. reports employment with Kureha Corporation.

REFERENCES

9. Tishler CC, Toto RD, Wright JT Jr, Xu S: African American Study of Kidney Disease and


This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2014010042/-/DCSupplemental.
Supplementary Appendix

Study Oversight

Members of the Steering Committee, Data Monitoring Committee, and Endpoint Adjudication Committee (see Acknowledgments for full listings of committee members) collaborated with the sponsors to develop the protocol and to monitor the trial. The protocols for the EPPIC trials were approved by local ethics committees, and the trials were conducted in accordance with Good Clinical Practice Guidelines of the International Conference on Harmonisation, the Declaration of Helsinki, and the European Union Clinical Trials Directive 2001/20/EC. All patients provided written informed consent. The Steering Committee, blinded to treatment assignments, oversaw the conduct of the trials and advised investigators on implementation. The Data Monitoring Committee reviewed unblinded safety data periodically throughout the trials. Verification of date and occurrence of end points was performed by the Endpoint Adjudication Committee, which reviewed blinded records from all patients who either reached a component of the primary end point or died.

Data were collected by the investigators and were analyzed by the sponsors. Confidentiality agreements were in place between the investigators and the sponsors. The manuscript was prepared by the first author and sponsor representatives with assistance from sponsor-funded medical writers. All authors critically reviewed the manuscript and agreed to submit for publication. All authors assume responsibility for the accuracy and completeness of the reported analyses and attest that the trial was conducted and reported consistently with the protocols.
Supplementary Materials and Methods (EPPIC-1)

Trial Title

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of AST-120 for Prevention of Chronic Kidney Disease Progression in Patients With Moderate to Severe Chronic Kidney Disease (EPPIC-1)

Study Objectives

The primary objectives of this study were:

• To demonstrate that AST-120, added to standard-of-care therapy in moderate to severe chronic kidney disease (CKD), reduced the risk for progression of CKD as assessed by the development of a component of a triple composite end point (initiation of dialysis, kidney transplantation, or doubling of serum creatinine [sCr]) compared with placebo

• To demonstrate the general safety and tolerability of long-term AST-120 therapy in CKD patients

The secondary objectives of this study were:

• To demonstrate the efficacy of AST-120 in reducing the risk for developing a component of a quadruple composite end point (initiation of dialysis, kidney transplantation, doubling of sCr, or death) compared with placebo

• To evaluate the effects of AST-120 versus placebo on other measures of renal function

• To assess the effects of AST-120 versus placebo on fat-soluble vitamin levels (A, D, E, and K), vitamin B-12, and folate levels
Study Population

Inclusion Criteria

Patients who met all the following inclusion criteria could be enrolled in the study:

1. Age 18 years or older

2. Moderate to severe CKD (in men: sCr $\geq 2.0$ mg/dL [$\geq 177$ $\mu$mol/L] and $\leq 5.0$ mg/dL [$\leq 442$ $\mu$mol/L]; in women: sCr $\geq 1.5$ mg/dL [$\geq 133$ $\mu$mol/L] and $\leq 5.0$ mg/dL [$\leq 442$ $\mu$mol/L]), not anticipated to require dialysis or renal transplantation in the next 6 months

3. Patient survival expected to be no less than 1 year

4. Serum creatinine in men $\geq 2.0$ mg/dL ($\geq 177$ $\mu$mol/L) and $\leq 5.0$ mg/dL ($\leq 442$ $\mu$mol/L) and in women $\geq 1.5$ mg/dL ($\geq 133$ $\mu$mol/L) and $\leq 5.0$ mg/dL ($\leq 442$ $\mu$mol/L) at the initial screening visit

5. Proteinuria/progressive deterioration in renal function

   • Urinary total protein to urinary total creatinine ratio (both values measured as mg/dL or other like units) must be $\geq 0.5$ on a spot void obtained at the screening visit

   OR

   • If the urinary total protein to urinary total creatinine ratio was $<0.5$, then the patient could return for a second screening visit 3 months later. If the sCr value at the second screening visit was $>10\%$ higher than the first screening visit but not $>5.0$ mg/dL [$\leq 442$ $\mu$mol/L] or if the urinary total protein to urinary total creatinine ratio was $\geq 0.5$, then the patient could be enrolled

6. Sitting blood pressure $\leq 160/90$ mm Hg at both screening and baseline visits. In addition, blood pressure, if measured, had to have been stable in hypertensive patients over the 3 months before screening, with no more than 1 blood pressure reading $>160/90$ mm Hg
7. Patients who were treated for hypertension had to have been on a stable antihypertensive regimen, defined as no changes in antihypertensive medications or doses in the last 3 months before the baseline visit and had to include a stable dose of either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-II-receptor blocker (ARB) unless contraindicated

8. Stable nutritional status

9. Willingness to comply with the study and to provide written informed consent

**Exclusion Criteria**

Patients who met any of the following exclusion criteria were not enrolled in the study:

1. Obstructive or reversible cause of kidney disease

2. Nephrotic syndrome, defined as a ratio of urinary total protein to urinary creatinine (both components measured as mg/dL or other like units) of >6.0 as measured on a spot void

3. Adult polycystic kidney disease

4. History of previous kidney transplantation

5. History of alcohol or drug abuse in the past 12 months

6. Known human immunodeficiency virus (HIV) infection

7. Received immunosuppressive therapy (including systemic corticosteroids for more than 5 days at a daily dose in excess of 0.1 mg/kg, prednisone equivalent) in the past 3 months or anticipated to require such treatment during the study course

8. History of recent (past 6 months) accelerated or malignant hypertension

9. Likely to require changes in ACEI or ARB regimens during the course of this study
10. Uncontrolled arrhythmia or severe cardiac disease (New York Heart Association Class III-IV), including myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, cerebrovascular accident, or transient ischemic attack in the past 6 months
11. History of malabsorption, inflammatory bowel disease, hiatal hernia, active peptic ulcer, or severe GI dysmotility not attributable to the use of a phosphate binder
12. History of cancer in the past 5 years (cervical carcinoma in situ, low-grade cutaneous malignancy, and other low-grade malignancy were exemptions)
13. Alanine transaminase (ALT) or aspartate transaminase (AST) values >2.5 times the upper limit of normal (ULN)
14. Received any investigational agent or participated in a clinical study in the past 3 months
15. Presence of any significant medical condition that might create an undue risk with study participation or that might significantly confound the collection of safety and efficacy data in this study
16. For women of childbearing potential, positive pregnancy test result of serum beta human chorionic gonadotropin (βHCG), unwillingness to use approved single barrier or oral contraception, or unwillingness to be sexually abstinent

Sample Size
A total of 291 primary events (composite end point with three components) were considered sufficient to provide 80% power to detect a 28% risk reduction for the AST-120 group compared with the placebo group, with a two-sided log-rank test at the 5% significance level. The risk reduction (%) was defined as 100 × (1-hazard ratio). To estimate sample size requirements, it was assumed that the median time to first event in the placebo group would be 31 months,
corresponding to an event rate of 55% at 3 years (if the hazard rate was constant). It was further assumed that patients would be enrolled over a 24-month period and treated for at least 18 months. To achieve the required number of events and to allow for a 30% dropout rate, it was anticipated that a total of approximately 980 patients would be required (490 patients per treatment group). A Steering Committee (SC), blinded to treatment assignments, monitored the overall event rate and adjusted enrollment or follow-up duration, as needed, to maintain the original power specifications.

**Visit Schedule Summary**

This was an event-driven study, consisting of a 2-week prerandomization screening period, followed by a treatment period lasting until accrual of 291 primary renal end point outcomes. The study was anticipated to take a total of approximately 42 months to complete (24 months for enrollment and 18 months for treatment).

Following randomization at the baseline visit, patients were scheduled to return for follow-up evaluations during the treatment period at weeks 2, 6, 12, 24, 36, and 48 and every 12 weeks thereafter until the conclusion of the study.

**Study Governance**

The following committees were established.

**Steering Committee:** G. Schulman (Chair, USA), T. Berl (USA), G.J. Beck (USA), G. Remuzzi (Italy), E. Ritz (Germany)
The SC consisted of five experts in nephrology and statistics who were responsible for reviewing the protocol, for reviewing and approving the Charters for the other study committees, for recommending upward adjustments to sample size based on blinded review of the number of primary end points achieved over time, for reviewing recommendations from the Data Monitoring Committee (DMC) and the Endpoint Adjudication Committee (EAC), and for providing advice to the sponsor with regard to other aspects of study implementation. Any adjustments to sample size were performed only to validate the event rate assumed when the initial sample size was calculated. Monitoring the total number of events in this manner, without access to the observed effect, size, or other unblinded information, did not require an adjustment to the final significance level for the study. All SC responsibilities were documented in a separate charter.

**Data Monitoring Committee:** A. Cheung (Chair, USA), E. Lakatos (USA), J. Daugirdas (USA)

The DMC consisted of at least three experts in nephrology and statistics. This committee reviewed accumulating safety data periodically throughout the study. The DMC made recommendations to the SC to terminate or continue the study, depending on safety concerns. The DMC’s specific duties and procedures were described in a DMC charter that was subject to approval by the SC.

**Endpoint Adjudication Committee:** D. Sica (Chair, USA), M. Rocco (USA), L. Szczech (USA)
The EAC consisted of three medical experts who reviewed and verified renal outcome end points. The EAC (1) reviewed blinded records from all patients who reached an end point or who died, (2) verified that an end point was attained, and (3) verified the date the end point was attained. The EAC interpreted patient records according to criteria specified in their charter, as approved by the SC.

**End Point Visit**

**Initiation of Dialysis or Transplantation**

Patients scheduled for dialysis or kidney transplantation completed a "Discontinuation Visit" 1 to 2 weeks before the intervention. Patients continued on their assigned study drug until dialysis or transplantation actually occurred. Once a patient underwent dialysis or transplantation, an Endpoint Achievement Report (EAR) was completed. The date of the end point event was the date on which dialysis began or transplantation occurred. A posttreatment visit was then completed 2 weeks later. Thereafter, each patient was contacted annually by telephone to assess survival until the last patient in the study reached study completion.

**Doubling of Serum Creatinine**

Patients who returned for their regularly scheduled visits and had sCr levels that increased twofold or more (ie, doubled) over baseline were asked to stop taking the study drug and to return to the clinic approximately 1 week later (5-10 days) for a Creatinine Endpoint Achievement (CEA) visit. At this visit, a second sCr sample was collected, and the patient was asked to resume taking study medication.
A third sCr sample was drawn 4 to 6 weeks after the initial doubled sCr result was obtained. This 4- to 6-week sample served as the confirmatory measurement. Patients with confirmed doubling of sCr at this point continued their regular visit schedule and study drug administration until they achieved another component of the composite end point, or they were terminated early, or the study was concluded. Any patient who refused to continue study drug after achieving the confirmed end point of sCr doubling was followed up every 12 weeks for sCr levels and every 24 weeks for 24-hour urine measurement of creatinine and protein. A patient who refused these visits or who began dialysis or underwent kidney transplantation was contacted annually to determine survival status unless the patient withdrew consent to be contacted.

If either follow-up sCr sample did not demonstrate a doubling of sCr, the patient continued in the study and returned for his or her next regularly scheduled visit. If a subsequent sCr result showed a doubling over the baseline value, the procedures outlined above were to be repeated.

If a clinical outcome (dialysis or renal transplantation) occurred during the process of confirming a doubling of sCr, this event was considered the primary end point event and sCr levels were no longer required.

**Completion of the Study**

When 291 renal outcome events occurred and met the criteria for an adjudicated study event, the study was considered completed. Because of inherent delays in the data collection and event
adjudication processes, it was likely that more than 291 events would occur before finalization of the database. All available data and events were included in the final analysis.

Analysis Population

All-Randomized Population

The All-Randomized population included all randomly assigned patients.

Intent-to-Treat (ITT) Population

The ITT population included all randomly assigned patients who received at least one dose of study medication and had at least one postbaseline evaluation of serum creatinine.

Per-Protocol (PP) Population

The PP population included all patients in the ITT population who had no major protocol violations or deviations. Detailed criteria, including minimum compliance rate, used to define this population were specified based on blinded data review before database lock and study unblinding.

Safety (SAF) Population

The SAF population included all patients who were randomly assigned and received study medication. Patients in the SAF population were allocated into groups "as treated" in the event that randomized treatment was incorrectly dispensed at the start of the study. If medication was dispensed incorrectly during the course of treatment, patients in the AST-120 group who
received placebo in error were retained in the AST-120 group; however, patients in the placebo group exposed to AST-120 for more than 10% of doses were allocated to the AST-120 group.
Efficacy End Point

Renal Disease Progression

Renal disease progression was defined by the development of a component of the triple composite end point (initiation of dialysis, kidney transplantation, or doubling of sCr).

Primary Efficacy End Point

The primary efficacy end point was time to onset of renal disease progression. Time to onset of renal disease progression was calculated as the time from randomization to the date when the first of the component events occurred. The date used to define doubling of sCr was the date on which sCr was first observed to have increased twofold or more over the baseline value, as verified approximately 1 week (5-10 days) after drug was stopped, and then was confirmed 4 to 6 weeks later.

Secondary Efficacy End Points

The first secondary efficacy end point was defined as follows:

- Time from randomization to first reaching the quadruple composite end point (initiation of dialysis, kidney transplantation, doubling of sCr, or death)

The primary efficacy end point and the first secondary efficacy end point were analyzed in fixed sequence to control alpha at the 5% level.

The following secondary efficacy end points were also evaluated:
• Time from randomization to development of end-stage renal disease (ESRD), defined as initiation of dialysis or kidney transplantation
• Time from randomization to doubling of sCr
• Time from randomization to death
• sCr
• Creatinine clearance
• 24-Hour urinary protein excretion
• Urinary excretion of creatinine
• 1/sCr slope (slope of reciprocal serum creatinine over time)
• Estimated glomerular filtration rate (eGFR)

General Statistical Methodology
For continuous variables, descriptive statistics included number of patients used in the calculation (n), mean, standard deviation (SD) or standard error (SE), and median, minimum, and maximum values. Frequencies and percentages were displayed for categorical data. All meaningful patient data collected in the case report form (CRF) and laboratory data were listed. Listings were sorted by patient within center/site and treatment group.

All statistical comparisons were performed using two-sided tests at the $\alpha=5\%$ significance level, unless specifically stated otherwise. All null hypotheses were defined as no treatment difference.

All summaries, analyses, and data listings were generated with SAS version 9 or higher.
The underlying assumptions of the planned analysis methods for the efficacy variables were investigated. If the assumptions were not met, suitable transformation or alternative nonparametric methods were used.

**Efficacy Analyses**

*Primary Efficacy End Point*

The primary efficacy variable was the time to onset of renal disease progression, calculated as the time from the date of randomization to the date when the patient first developed a component of the triple composite end point (initiation of dialysis, kidney transplantation, or doubling of sCr), as verified and adjudicated by the EAC. The date of onset was determined by the EAC in accordance with the protocol and the EAC charter. The date used to define a doubling of sCr was the date on which the sCr was first observed to have increased twofold or more over the baseline value, as verified approximately 1 week (5-10 days) after drug had been stopped, and then was confirmed 4 to 6 weeks later. Patients who did not reach this triple composite end point were censored on the date of last contact. The date of last contact was defined as the date of the patient’s last assessment for any study-related purpose, as recorded in the CRF; for instance, the date of last contact was the latest date among the following: last visit date, termination visit date, date of last dose, last laboratory test date, or date of last telephone contact. In the event the patient died, the date of death was used for the censoring date.

Definitions of events and censored observations are summarized in Table S4 below.

**Table S4. Primary Analysis (progression based on EAC assessment)**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Outcome</th>
<th>Outcome Date</th>
</tr>
</thead>
</table>

14
Progression observed on or before the date of last contact | Event | Date of progression
--- | --- | ---
Death before documented progression | Censored | Date of death
No progression on or before the date of last contact | Censored | Date of last contact

*Earliest of the following events: doubling of sCr (as confirmed 4-6 weeks later), renal transplantation, or start of renal dialysis.

**Primary Analysis**

The primary efficacy analysis was based on the ITT population using the primary efficacy end point.

The stratified Cox proportional hazards regression model was used to compare time to onset of renal disease progression (defined by the primary efficacy end point) between the AST-120 and the placebo groups with the following stratification factors: region (North America, Central/Latin America, or Europe), baseline sCr level (above/below 3.0 mg/dL), and diabetic nephropathy status (yes/no). The hazard ratio (AST-120 relative to placebo), estimated by maximum partial likelihood methods based on the stratified Cox proportional hazards regression model, and a 95% confidence interval were used to characterize the difference in progression rates between the two treatment groups. In addition, risk reduction was computed using the following formula:

\[
\text{Risk reduction} \, (\%) = (1 - \text{hazard ratio}) \times 100
\]

Median time from randomization to onset of renal disease progression was estimated based on the Kaplan-Meier method for the primary end point.
Cumulative probability of remaining free of renal disease progression (as defined by the primary end point) was estimated and plotted graphically using the Kaplan-Meier method.

**Supportive Analyses of the Primary Efficacy End Point**

The secondary and supportive statistical analyses described below were performed for the primary efficacy end point.

The stratified Cox regression analysis and Kaplan-Meier estimation procedure were repeated for the All-Randomized (if any patients were excluded from the ITT population) and the PP populations. Stratification factors and censoring rules were the same as those used for the primary efficacy analysis.

Stratified log-rank test: As a secondary analysis, the stratified log-rank test was used to evaluate the treatment effect for the ITT population, with the same stratification factors and censoring rules as those used in the primary analysis.

Other covariate adjustment: The stratified Cox regression model, with strata defined above, was used to adjust for the effect of other prognostic factors as an exploratory analysis. The model included strata defined previously for the primary efficacy analysis, along with covariates for age group (<65 or ≥65 years), race (White/Black or African American/Asian/Other), sex, use of ACEI or ARB at baseline (yes/no), and urinary protein to urinary creatinine ratio at baseline (<2.0 or ≥2.0). Interactions between treatment and each covariate were evaluated at the 0.10 significance level; if not significant, they were removed from the model. This multivariate
analysis was based on the ITT population and used the same censoring rules as those used for the primary analysis.

Sensitivity Analyses of the Primary Efficacy End Point

Alternative censoring rules were applied to the primary efficacy variable as sensitivity analyses to ensure that results were robust to the effects of censoring patterns.

The primary method of analysis (stratified Cox model) was used in each case, and the following censoring rules applied: Hazard ratio, risk reduction (%), and their confidence intervals were computed as described above for the primary end point. These analyses were conducted for both the ITT and the PP populations.

Censoring at Last sCr assessment Date

1. All adjudicated events (confirmed doubling of sCr, dialysis, or transplantation) were included in the analysis, but patients without an adjudicated event were censored on the last sCr assessment date

2. All adjudicated events (confirmed doubling of sCr, dialysis, or transplantation) were included in the analysis if they occurred within 12 weeks (84 days) after the last dose of study medication or within 12 weeks (84 days) after the last posttreatment sCr assessment. Patients without an adjudicated event observed up to either time point were censored on the last sCr assessment date

Censoring Based on Last Dose of Study Treatment
Analyses of the primary efficacy end point (triple composite end point) were performed and included all adjudicated events up to 14 days and 3 months (90 days) after the last dose of study medication. That is, patients without an event on or before 14 days or 90 days after the last dose were censored at this date.

**Secondary Efficacy End Points**

*Quadruple Composite End Point (the first secondary efficacy end point)*

Time from randomization to the first occurrence of the quadruple composite end point (initiation of dialysis, kidney transplantation, doubling of sCr, or death using event dates established by the EAC) was analyzed using the Kaplan-Meier method and the stratified Cox regression model as described above for the primary analysis. Deaths were considered events rather than censored observations. Patients not reaching any component of the quadruple composite end point were censored on the date of last contact. The same rules used for the primary analysis of the triple composite end point were applied. Hazard ratio, risk reduction (%), and their 95% confidence intervals were computed as described above for the primary end point. Median time from randomization to the first occurrence of the quadruple composite end point was estimated based on the Kaplan-Meier method. The cumulative probability of remaining free of the quadruple composite end point was estimated and plotted graphically using the Kaplan-Meier method. These analyses were conducted for both the ITT and the PP populations.

**Components of the Composite End Points**

Time to each of the components of the composite end points (ESRD, doubling of sCr, and death) were analyzed using the Kaplan-Meier method and the unstratified Cox regression model with
three covariates: region (North America, Central/Latin America, or Europe), sCr level (above/below 3.0 mg/dL), and diabetic nephropathy status (yes/no). Hazard ratios and risk reductions were calculated along with their 95% confidence intervals. The median time from randomization to the event was estimated based on the Kaplan-Meier method. The cumulative probability of remaining free of each event was estimated and plotted graphically using the Kaplan-Meier method. For each of these three end points, analyses were conducted for the ITT population with censoring on the date of last sCr assessment for doubling of sCr and on the date of last contact for the other two components.

**eGFR**

eGFR was measured at baseline, week 6, and every 12 weeks during the treatment period and at early termination/discontinuation. The following formula was used to estimate eGFR:

\[
eGFR(\text{mL/min/1.73m}^2) = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})
\]

Change in eGFR from baseline to week 96 was analyzed using the mixed-effect model for repeated measures and analysis of covariance (ANCOVA).
Supplementary Materials and Methods (EPPIC-2)

Title
A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of AST-120 for Prevention of Chronic Kidney Disease Progression in Patients With Moderate to Severe Chronic Kidney Disease, Including Assessment of Quality of Life (EPPIC-2)

Study Objectives
The objectives were the same as those for EPPIC-1, with the exception of the exploratory objective of Kidney Disease Quality of Life (KDQOL) assessment.

All other procedures and methods of the study were the same as those for EPPIC-1. The following were conducted for the exploratory analysis of KDQOL:

KDQOL-36
The KDQOL-36 comprises 36 questions concerning the patient’s health, kidney disease, and effects of kidney disease on daily life. KDQOL-36 was administered to all patients at the baseline visit, week 12, and every 24 weeks from the baseline visit to end of the study.

Scoring and Coding for the KDQOL-36
Twelve questions concern physical and mental health from the SF-12, four questions concern burden of kidney disease, 12 questions concern symptoms/problems of kidney disease, and eight questions concern effects of kidney disease. However, one question for dialysis patients was
excluded because only pre-dialysis patients were enrolled in this study. All negatively framed questions were reversed so that higher scores reflected better quality of life.

**Summary and Analysis of the KDQOL-36**

Results from the KDQOL-36 were summarized and analyzed as follows: Descriptive statistics were used to summarize the scores for SF-12 physical health composite, SF-12 mental health composite, burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease domains.

For the KDQOL questionnaire, items left blank (missing data) were not used to calculate scale scores. That is, scores were calculated based on the average of all nonmissing items in the scale. However, patients with missing values for any items in the SF-12 physical and mental health composite scores were not included in the analysis of these scales.

Differences between treatment groups in change from baseline scores were assessed by a mixed-effects model for repeated measures up to week 96. The model included fixed effects for treatment, visit, treatment by visit interaction, region (North America, Central/Latin America, or Europe), diabetic nephropathy status (yes/no), and baseline sCr (above/below 3.0 mg/dL), with baseline score as a covariate and a random effect for patients. Treatment differences in least-squares means (LS means) and associated 95% confidence intervals were estimated for each visit and across visits.
An ANCOVA model was used as a secondary analysis to assess the effect of treatment on the change from baseline to the last observation up to week 48 or 96 in scores of KDQOL for SF-12 physical health composite, SF-12 mental health composite, burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease. Patients who prematurely terminated the study drug or who had incomplete data were included in the analysis using the last observation carried forward (LOCF) procedure up to week 48 or 96. The model included treatment, region (North America, Central/Latin America, or Europe), serum creatinine level (above/below 3.0 mg/dL), diabetic nephropathy status (yes/no), and baseline score as covariates. Within-treatment changes from baseline were evaluated using the same ANCOVA model.

These analyses were conducted for the ITT population.

All questionnaire responses and composite scores were listed for each patient.