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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.

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CKD, defined as kidney damage or a GFR<60 ml/min per 1.73 m^2 for ≥3 months,[1] is associated with increased risk for cardiovascular events, hospitalization, and death[2] 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 m^2).[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

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

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 (Kureha Corporation, Tokyo, Japan) (Figure 1) is an orally administered spherical carbon adsorbent that can adsorb various small molecule uremic toxins. AST-120 was approved in Japan in 1991, for use in delaying the initiation of dialysis and ameliorating the symptoms of uremia in patients with progressive CKD, as well as in Korea and the Philippines. A postregistration clinical trial in Japan confirmed that 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 trials[22–24] 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.

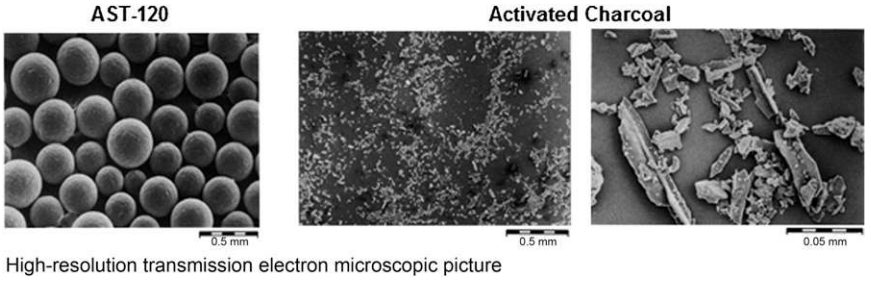

Figure 1. Structural features of AST-120 and activated charcoal (United States Pharmacopeia). High-resolution transmission electron microscopy studies demonstrate that AST-120 differs structurally from activated charcoal (United States Pharmacopeia). AST-120, spherical carbon adsorbent, presents as black, odorless, spherical particles approximately 0.2–0.4 mm in diameter. Composed mainly of carbon (approximately 96%), AST-120 exhibits adsorption ability similar or superior to that of activated charcoal for certain acidic and basic organic compounds known to be increased in renal failure; however, AST-120 has lower adsorption ability than activated charcoal for digestive enzymes.

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

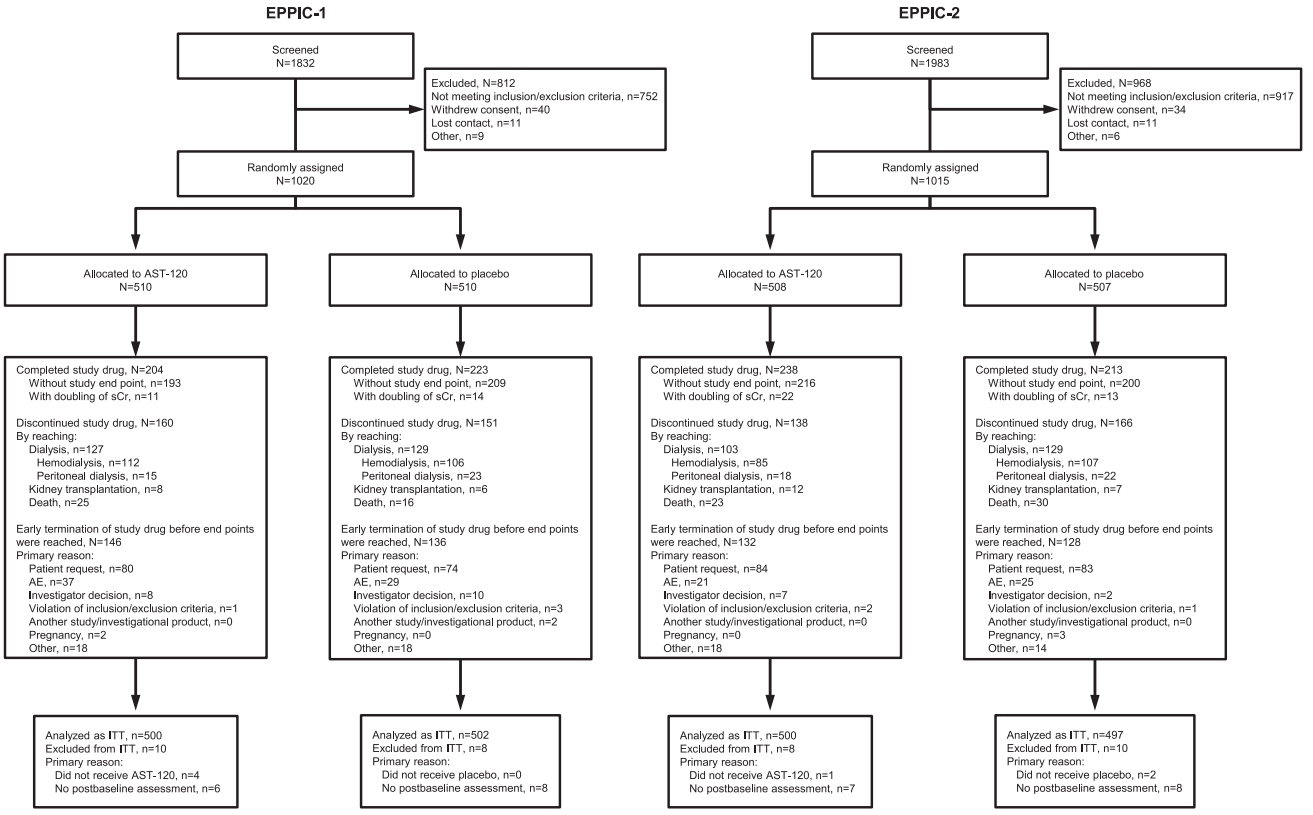

Figure 2. Patient disposition. The ITT population includes all randomly assigned patients who received ≥1 doses of study drug and had ≥1 postbaseline measurements of sCr.

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 m^2 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

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

Characteristic	EPPIC-1 (*n*=1002)		EPPIC-2 (*n*=997)		Pooled (*n*=1999)	
	AST-120 (*n*=500)	Placebo (*n*=502)	AST-120 (*n*=500)	Placebo (*n*=497)	AST-120 (*n*=1000)	Placebo (*n*=999)
Age, yr	56.3±14.9	55.6±14.9	54.4±15.5	55.5±14.6	55.4±15.3	55.6±14.8
Sex, %						
Men	61.8	64.9	54.6	55.5	58.2	60.3
Race, %[a]						
White	78.6	79.9	82.8	77.3	80.7	78.6
Black or African American	8.4	8.0	6.2	9.9	7.3	8.9
Asian	5.2	4.2	2.8	4.2	4.0	4.2
Other	7.8	8.0	8.2	8.6	8.0	8.3
CKD cause, %						
Diabetic nephropathy	41.8	42.4	39.0	38.4	40.4	40.4
Nondiabetic nephropathy	58.2	57.6	61.0	61.6	59.6	59.6
GN	25.6	28.7	24.8	29.2	25.2	28.9
Nephrosclerosis	14.8	13.9	18.8	18.9	16.8	16.4
Other	17.8	14.9	17.4	13.5	17.6	14.2
Use of ACEI or ARB, %						
Yes	84.4	85.5	84.4	82.9	84.4	84.2
Baseline sCr, mg/dl[b]	3.09±0.88	3.10±0.84	3.06±0.87	3.18±0.90	3.07±0.88	3.14±0.87
Baseline eGFR, ml/min per 1.73 m^2	22.72±8.00	22.54±7.25	22.61±7.87	21.55±7.18	22.66±7.93	22.04±7.23
Baseline UP/UCr ratio						
n	499	501	499	494	998	995
Mean±SD	1.94±1.33	1.99±1.33	1.99±1.32	2.02±1.36	1.97±1.33	2.01±1.34
CKD stage, %						
3a	1.0	0.2	0.6	0.4	0.8	0.3
3b	18.8	15.3	16.6	11.7	17.7	13.5
4	62.0	69.3	66.2	69.2	64.1	69.3
5	18.2	15.1	16.6	18.7	17.4	16.9
Baseline anemia status, %[c]						
Yes	69.7	70.3	70.9	72.0	70.3	71.1
Body mass index, kg/m^2[d]						
n	500	502	498	497	998	999
Mean±SD	29.4±6.1	29.2±7.1	28.9±6.8	29.0±7.3	29.1±6.4	29.1±7.2

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.

[a]Race was self-reported.

[b]To convert sCr from mg/dl to μmol/L, multiply by 88.4.

[c]Anemia was defined as a hemoglobin level <13.5 g/dl (men) or <12.0 g/dl (women).

[d]Body mass index is the weight in kilograms divided by the square of the height in meters.

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 to <1.0 at baseline and were 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 2. Study drug exposure and compliance (safety population)

Drug Compliance	EPPIC-1 (*n*=1016)		EPPIC-2 (*n*=1012)		Pooled (*n*=2028)	
	AST-120 (*n*=507)	Placebo (*n*=509)	AST-120 (*n*=507)	Placebo (*n*=505)	AST-120 (*n*=1014)	Placebo (*n*=1014)
Compliance, %[a]						
n	503	502	505	496	1008	998
Mean±SD	91.4±13.9	90.5±15.0	90.3±14.4	90.6±15.5	90.8±14.2	90.6±15.3
Median	96.1	96.1	95.4	96.4	95.8	96.2
Minimum, maximum	10.0, 120.0	6.2, 114.9	7.8, 119.3	3.4, 200.0	7.8, 120.0	3.4, 200.0
Categorical summary, *n* (%)						
<33%	4 (0.8)	4 (0.8)	4 (0.8)	5 (1.0)	8 (0.8)	9 (0.9)
≥33% to <50%	9 (1.8)	14 (2.8)	12 (2.4)	10 (2.0)	21 (2.1)	24 (2.4)
≥50% to <67%	20 (4.0)	29 (5.8)	24 (4.8)	22 (4.4)	44 (4.4)	51 (5.1)
≥67% to <83%	41 (8.2)	40 (8.0)	49 (9.7)	59 (11.9)	90 (8.9)	99 (9.9)
≥83% to <100%	356 (70.8)	349 (69.5)	366 (72.5)	329 (66.3)	722 (71.6)	678 (67.9)
≥100% to <110%	71 (14.1)	65 (12.9)	47 (9.3)	69 (13.9)	118 (11.7)	134 (13.4)
≥110%	2 (0.4)	1 (0.2)	3 (0.6)	2 (0.4)	5 (0.5)	3 (0.3)
Total	503	502	505	496	1008	998
Duration of treatment, wk[b]						
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.

[a](Total dose taken/total dose required)×100.

[b][(Date of last dose)–(date of first dose)+1]/7.

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,[29] 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/UCr≥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 3. Primary and secondary efficacy end points from the EPPIC trials

End Point	AST-120		Placebo		AST-120 versus Placebo	
	N	*n* (%)	N	*n* (%)	HR (95% CI)	*P* Values
EPPIC-1						
Primary end point[a]						
ITT (censored at last contact)	500	178 (35.6)	502	177 (35.3)	1.03 (0.84 to 1.27)	0.78
ITT (censored at last sCr)	500	178 (35.6)	502	177 (35.3)	1.05 (0.86 to 1.30)	0.62
ITT (censored at last sCr)[b]	500	159 (31.8)	502	158 (31.5)	1.04 (0.84 to 1.30)	0.70
ITT (90 d lagging censoring)	500	153 (30.6)	502	156 (31.1)	1.02 (0.81 to 1.27)	0.89
ITT (14 d lagging censoring)	500	135 (27.0)	502	133 (26.5)	1.06 (0.84 to 1.35)	0.61
PP (censored at last contact)[c]	451	156 (34.6)	445	157 (35.3)	1.01 (0.81 to 1.27)	0.91
Secondary end point[d]						
ITT (censored at last contact)	500	213 (42.6)	502	201 (40.0)	1.08 (0.89 to 1.31)	0.42
PP (censored at last contact)	451	189 (41.9)	445	177 (39.8)	1.08 (0.88 to 1.33)	0.44
Individual end point						
ESRD	500	161 (32.2)	502	157 (31.3)	1.05 (0.85 to 1.31)	0.64
Doubling of sCr	500	36 (7.2)	502	48 (9.6)	0.77 (0.50 to 1.19)	0.25
Death	500	49 (9.8)	502	42 (8.4)	1.17 (0.78 to 1.77)	0.45
EPPIC-2						
Primary end point[a]						
ITT (censored at last contact)	500	172 (34.4)	497	183 (36.8)	0.91 (0.74 to 1.12)	0.37
ITT (censored at last sCr)	500	172 (34.4)	497	183 (36.8)	0.93 (0.75 to 1.15)	0.48
ITT (censored at last sCr)[b]	500	156 (31.2)	497	171 (34.4)	0.92 (0.73 to 1.14)	0.43
ITT (90 d lagging censoring)	500	152 (30.4)	497	160 (32.2)	0.96 (0.76 to 1.20)	0.71
ITT (14 d lagging censoring)	500	124 (24.8)	497	140 (28.2)	0.89 (0.70 to 1.14)	0.37
PP (censored at last contact)[c]	447	155 (34.7)	437	160 (36.6)	0.93 (0.74 to 1.17)	0.53
Secondary end point[d]						
ITT (censored at last contact)	500	204 (40.8)	497	217 (43.7)	0.90 (0.74 to 1.09)	0.28
PP (censored at last contact)	447	180 (40.3)	437	190 (43.5)	0.90 (0.73 to 1.11)	0.34
Individual end point						
ESRD	500	146 (29.2)	497	164 (33.0)	0.82 (0.65 to 1.02)	0.08
Doubling of sCr	500	57 (11.4)	497	46 (9.3)	1.18 (0.80 to 1.74)	0.40
Death	500	49 (9.8)	497	61 (12.3)	0.78 (0.53 to 1.13)	0.19
Pooled						
Primary end point[a]						
ITT (censored at last contact)	1000	350 (35.0)	999	360 (36.0)	0.97 (0.83 to 1.12)	0.64
ITT (censored at last sCr)	1000	350 (35.0)	999	360 (36.0)	0.98 (0.85 to 1.14)	0.79
ITT (censored at last sCr)[b]	1000	315 (31.5)	999	329 (32.9)	0.97 (0.83 to 1.13)	0.68
ITT (90 d lagging censoring)	1000	305 (30.5)	999	316 (31.6)	0.97 (0.83 to 1.14)	0.71
ITT (14 d lagging censoring)	1000	259 (25.9)	999	273 (27.3)	0.96 (0.81 to 1.14)	0.62
PP (censored at last contact)[c]	898	311 (34.6)	882	317 (35.9)	0.97 (0.83 to 1.14)	0.70
Secondary end point[d]						
ITT (censored at last contact)	1000	417 (41.7)	999	418 (41.8)	0.99 (0.86 to 1.13)	0.86
PP (censored at last contact)	898	369 (41.1)	882	367 (41.6)	0.99 (0.86 to 1.15)	0.92
Individual end point						
ESRD	1000	307 (30.7)	999	321 (32.1)	0.93 (0.80 to 1.09)	0.37
Doubling of sCr	1000	93 (9.3)	999	94 (9.4)	0.98 (0.73 to 1.30)	0.87
Death	1000	98 (9.8)	999	103 (10.3)	0.94 (0.71 to 1.24)	0.65

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

[a]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.

[b]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.

[c]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.

[d]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.

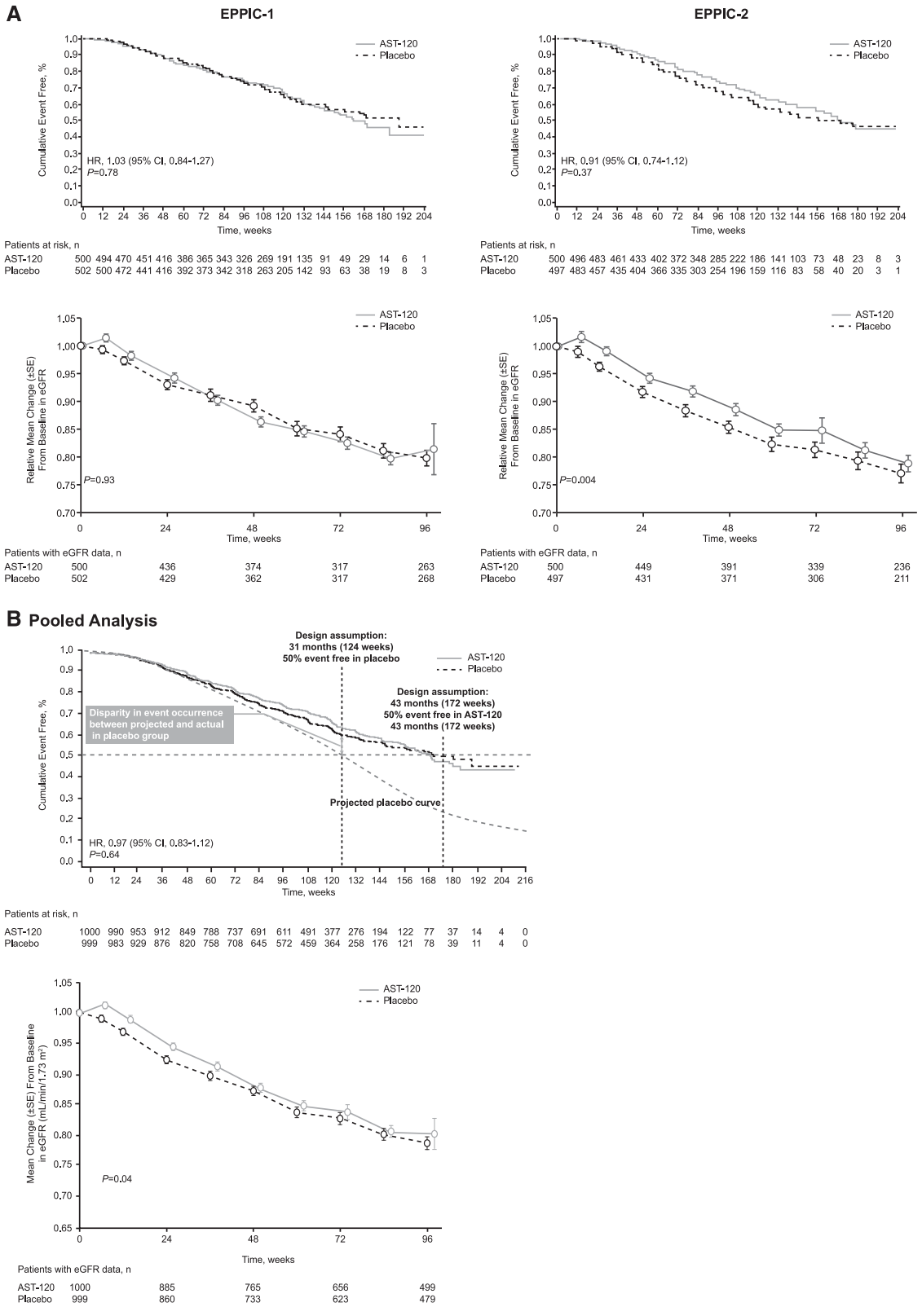

Figure 3. Primary efficacy end point (triple composite end point). (A) EPPIC-1 and EPPIC-2 trials. (B) Pooled analysis of both trials. Kaplan–Meier analysis and eGFR relative change from baseline analyzed using a mixed-effect model for repeated measures and analysis of covariance in the ITT population.

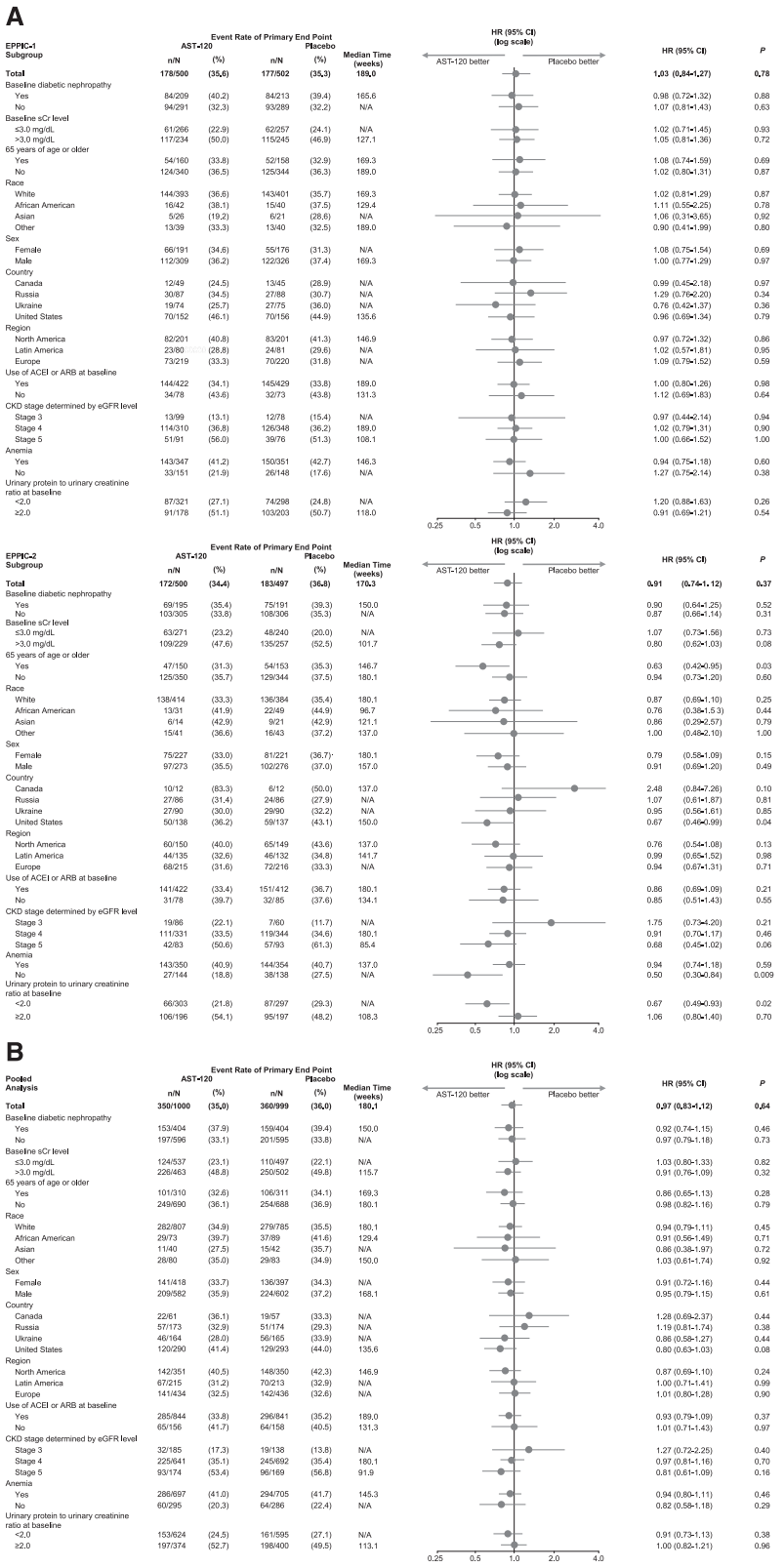

Figure 4. Subgroup analysis by Cox proportional hazards regression in the ITT population. (A) EPPIC-1 and EPPIC-2 trials. (B) Pooled analysis of both trials. Men with hemoglobin levels<13.5 g/dl and women with hemoglobin levels<12.0 g/dl are considered to have anemia. North America includes the United States and Canada; Latin America includes Argentina, Brazil, and Mexico; and Europe includes the Czech Republic, France, Spain, Italy, Germany, Poland, Russia, and Ukraine. (Note: Cox regression model with treatment group, region, baseline sCr level [≤3.0 or >3.0 mg/dl], and CKD cause [diabetic or nondiabetic nephropathy] status as covariates.) Patients not reaching the primary end point are censored at the time of their last contact. N, number of patients in the respective population; n, number of patients who had an event; N/A, not applicable.

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

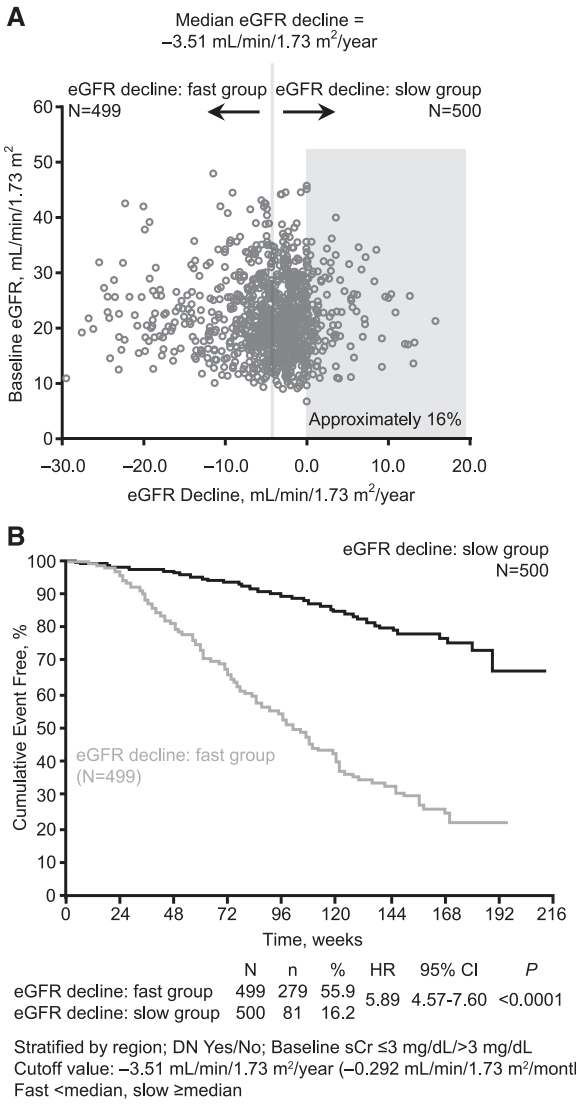

Figure 5. CKD progression. (A) Evaluation of eGFR decline distribution based on baseline eGFR (pooled placebo ITT population). (B) Event rate based on eGFR decline (pooled placebo ITT population). The cumulative probability of remaining free of renal disease progression (as defined by the primary end point) is estimated and plotted graphically with the Kaplan–Meier method for two groups (eGFR slow decline and eGFR fast decline, respectively) divided in the pooled placebo group. Stratified Cox proportional hazards regression is used to compare time to onset of renal disease progression between the slow and fast decline placebo groups. DN, diabetic nephropathy.

feasible for the large trials reported here. Adding these baseline factors (UP/UCr≥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[30] based on enrollment center or country, CKD cause (diabetic or nondiabetic nephropathy), and baseline sCr level (≤3.0 or >3.0 mg/dl). The AST-120 dose was selected based on results from a dose-ranging phase 2 study.[27] 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 hours 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 ≥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 UP/UCr≥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 ≤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

Table 4. Baseline characteristics associated with CKD progression (pooled placebo ITT population)

Characteristic	eGFR Decline (ml/min per 1.73 m^2 per yr)		*P* Values
	eGFR Decline Fast Group (*n*=499;10.22±0.43)	eGFR Decline Slow Group (*n*=500;0.28±0.26)	
CKD cause			
Diabetic nephropathy	214 (42.9)	190 (38.0)	0.12
Nondiabetic nephropathy	285 (57.1)	310 (62.0)	
CKD stage			
3a	1 (0.2)	2 (0.4)	0.58
3b	69 (13.8)	66 (13.2)	
4	349 (69.9)	343 (68.6)	
5	80 (16.0)	89 (17.8)	
sCr, mg/dl	3.16±0.86	3.12±0.87	0.45
eGFR, ml/min per 1.73 m^2	22.33±7.34	21.76±7.12	0.21
UP/UCr	2.41 (1.38); *n*=498	1.60 (1.17); *n*=497	<0.001
Hematuria			
Positive (+)	214 (43.0)	129 (25.8)	<0.001
Negative (–)	284 (57.0)	371 (74.2)	
Systolic BP, mmHg	135.2±13.6	132.4±13.8	0.001
Diastolic BP, mmHg	78.4±9.1	77.2±8.9	0.04
Age, yr	53.4±15.46	57.8±13.68	<0.001
Sex			
Men	320 (64.1)	282 (56.4)	0.01
Race			
White	387 (77.6)	398 (79.6)	0.88
Black or African American	46 (9.2)	43 (8.6)	
Asian	22 (4.4)	20 (4.0)	
Other	44 (8.8)	39 (7.8)	
Use of ACEI or ARB			
Yes	414 (83.0)	427 (85.4)	0.29
Baseline anemia status[a]			
Yes	365 (73.4)	340 (68.8)	0.11
Body mass index, kg/m^2[b]	28.6±6.4	29.6±7.9	0.03

Data are presented as *n* (%) or mean±SD. Median eGFR decline is –3.51 ml/min per 1.73 m^2 per year (–0.292 ml/min per 1.73 m^2 per month). Fast, <median; slow, ≥median. Hematuria (+): trace, 1+, 2+, or 3+.

[a]Anemia was defined as a hemoglobin level <13.5 g/dl (men) or <12.0 g/dl (women).

[b]Body mass index is weight in kilograms divided by square of the height in meters.

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,[31] 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.[32] 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×(1–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.[29] 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

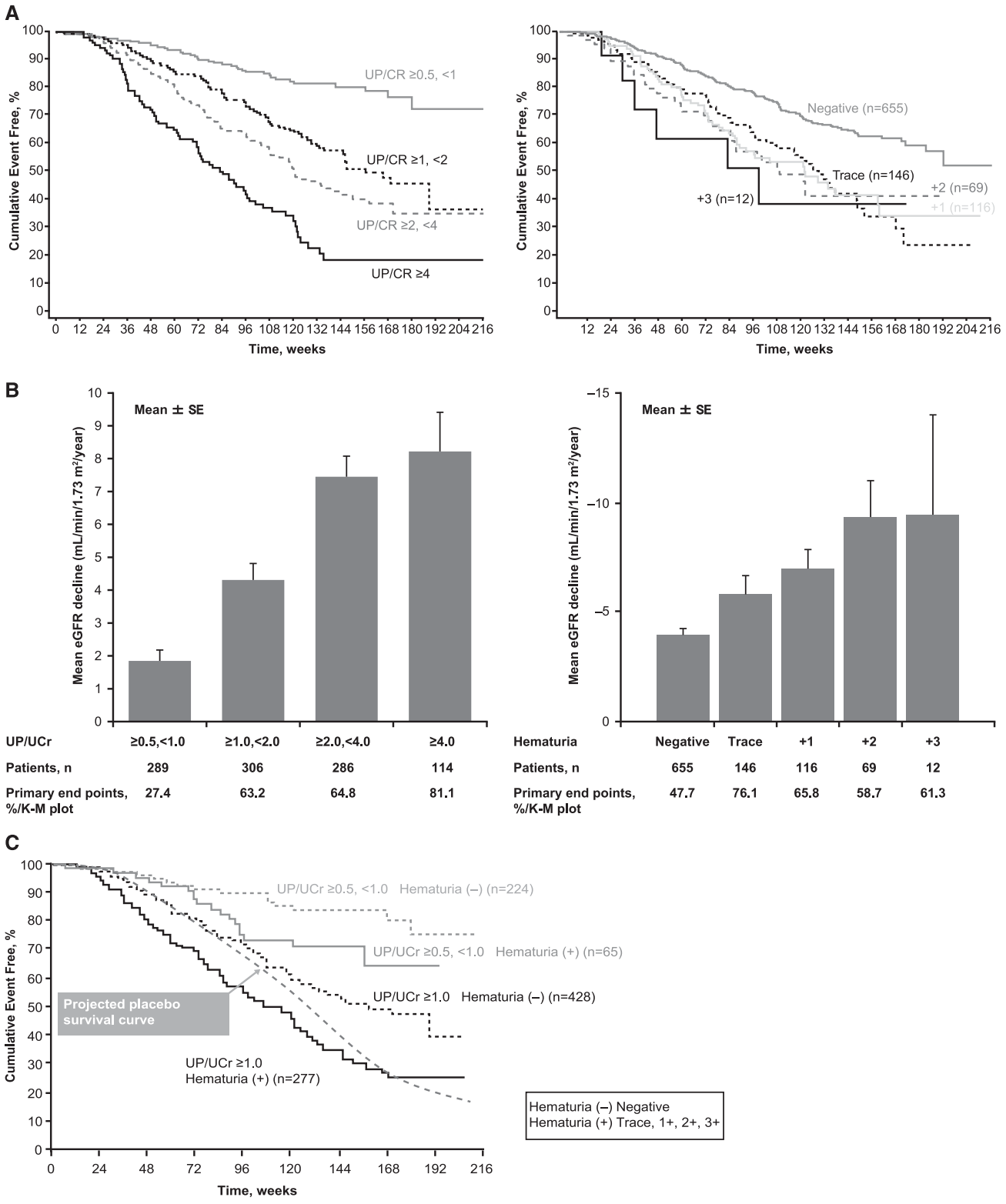

Figure 6. Effect of UP/UCr and hematuria status on renal disease progression. (A) Event rate based on baseline UP/UCr level or hematuria status (pooled placebo ITT population). (B) Mean eGFR decline based on baseline UP/UCr level or hematuria status (pooled placebo ITT population). (C) Event rate based on combined baseline UP/UCr level and hematuria status (pooled placebo ITT population). K-M, Kaplan–Meier.

Table 5. Summary of AEs (safety population)

Description of AE	EPPIC-1 (*n*=1016)				EPPIC-2 (*n*=1012)				Pooled (*n*=1028)			
	AST-120 (*n*=507)		Placebo (*n*=509)		AST-120 (*n*=507)		Placebo (*n*=505)		AST-120 (*n*=1014)		Placebo (*n*=1014)	
	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients
Treatment-emergent AE	2483	436 (86.0)	2589	448 (88.0)	2727	438 (86.4)	2488	425 (84.2)	5210	874 (86.2)	5077	873 (86.1)
Severe	193	105 (20.7)	185	94 (18.5)	227	104 (20.5)	233	110 (21.8)	420	209 (20.6)	418	204 (20.1)
Moderate	854	210 (41.4)	925	214 (42.0)	967	208 (41.0)	874	201 (39.8)	1821	418 (41.2)	1799	415 (40.9)
Mild	1435	121 (23.9)	1476	140 (27.5)	1533	126 (24.9)	1381	114 (22.6)	2968	247 (24.4)	2857	254 (25.0)
Unknown[a]	1	0	3	0	0	0	0	0	1	0	3	0
Treatment-related AE	142	93 (18.3)	147	94 (18.5)	203	109 (21.5)	203	106 (21.0)	345	202 (19.9)	350	200 (19.7)
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.

[a]Each patient who experienced a treatment-emergent AE of unknown status experienced multiple treatment-emergent AEs of another status (severe, moderate, or mild).

Table 6. Summary of eGFR and sCr level at time of dialysis initiation (ITT population)

Demographics	EPPIC-1			EPPIC-2			Pooled		
	n	eGFR	sCr	*n*	eGFR	sCr	*n*	eGFR	sCr
Total	302	10.90±5.25	6.59±3.16	289	9.95±4.67	6.81±3.00	591	10.44±4.99	6.70±3.09
CKD cause									
Diabetic nephropathy	147	13.02±5.19	5.26±2.00	124	11.32±5.02	5.91±2.28	271	12.24±5.17	5.56±2.16
Nondiabetic nephropathy	155	8.88±4.47	7.84±3.54	165	8.92±4.10	7.48±3.30	320	8.90±4.28	7.66±3.41
Sex									
Women	99	8.89±4.49	6.81±3.43	126	8.99±4.22	6.61±3.33	225	8.95±4.33	6.70±3.37
Men	203	11.88±5.33	6.48±3.03	163	10.70±4.87	6.96±2.72	366	11.35±5.15	6.69±2.90
Region									
Europe (with Russia and Ukraine)	113	8.22±3.74	8.23±3.78	108	8.10±4.18	8.31±3.50	221	8.16±3.95	8.27±3.64
Europe (without Russia and Ukraine)	35	10.81±3.40	5.92±1.55	33	10.39±3.35	6.37±2.75	68	10.61±3.35	6.14±2.21
Latin America	43	8.61±3.30	7.19±2.50	74	9.46±4.18	6.56±2.50	117	9.15±3.89	6.79±2.51
North America	146	13.64±5.34	5.13±1.90	107	12.16±4.57	5.47±1.92	253	13.02±5.08	5.28±1.91
Country									
Russia	46	7.65±3.19	8.27±3.20	39	7.70±5.18	8.38±3.57	85	7.67±4.19	8.32±3.35
Ukraine	32	6.22±3.31	10.71±4.66	36	6.43±2.45	10.01±3.19	68	6.33±2.86	10.34±3.94
United States	124	13.73±5.57	5.16±1.96	94	12.49±4.60	5.32±1.86	218	13.20±5.20	5.25±1.93

Data are presented as *n* or mean±SD. eGFR values are given in ml/min per 1.73 m^2. Europe includes Czech Republic, France, Germany, Italy, Spain, and Poland with/without Russia and Ukraine. Latin America includes Argentina, Brazil, and Mexico. North America includes United States and Canada.

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.

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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

(Chair, United States), E. Lakatos (United States), and J. Daugirdas (United States). Members of the EPICC Endpoint Adjudication Committee are as follows: D. Sica (Chair, United States), M. Rocco (United States), and L. Szczech (United States). The EPPIC-1 investigators are as follows: P. Massari, G. Greloni, C. Diaz, J. Santos, C. Mascheroni, P. Novoa, P. Raffaele, and J. Bittar (Argentina); G. Filho, R. dePaula, V. Garcia, S. Draibe, D. Mion Jr, J. Centeno, R. Milagres, D. Carvalho, and D. d'Avila (Brazil); V. Pichette, L. Roy, R. Ting, V. Woo, S. Chow, D. Sapir, and H. Mehta (Canada); O. Viklicky, J. Tocik, J. Suchanova, I. Valkovsky, and M. Peskova (Czech Republic); P. Zaoui, D. Fouque, M. Hourmant, and B. Al Jalaby (France); G. Villa, G. Cancarini, G. Bonforte, and A. Santoro (Italy); J. Barbosa Salas, A. Chew-Wong, H. Perez-Grovas Garza, and F. Gallegos Mendez (Mexico); B. Rutkowski, K. Ciechanowski, R. Malecki, M. Muszytowski, and K. Ostrowski (Poland); V. Anashkin, N. Khurkhurova, V. Dobronravov, N. Dubrovina, V. Ermolenko, E. Kolmakova, D. Volkov, A. Litvinov, A. Rebrov, A. Doronina, S. Yakushin, M. Ballyuzek, G. Dyubanova, O. Sigitova, T. Zateeva, L. Bychkova, O. Zanozina, A. Nazarov, A. Yampolsky, N. Agranovich (Russia); O. Dyadyk, I. Dudar, M. Kolesnyk, F. Kostyev, A. Lyulko, M. Orynchak, V. Strizhak, M. Vlasenko, V. Zhebel, O. Larin, M. Borschivsky, and L. Zub (Ukraine); and M. Acharya, S. Arbes, M. Assouad, P. Berkowitz, E. Brown, D. Coyne, R. Dhingra, E. Galindo-Ramos, S. Goral, A. Jamal, D. Koeper, M. Krause, K. Lempert, B. Levine, J. Lewis, L. Mailloux, B. Mehta, J. Navarro, R. Petrillo, U. Ranjit, R. Rodelas, A. Esquenazi, D. Scott, M. Seek, J. Wetmore, T. Wiegmann, S. Zeig, D. Fischer, A. Gonzalez, R. Minasian, L. Sakhrani, D. Dev, J. Fassler, S. Lew, F. Husserl, L. Weisberg, S. Desai, J. Aiello, A. Bivins, S. Diamond, A. Chen, and R. Zabaneh (United States). The EPPIC-2 investigators are as follows: N. Garcia, L. Juncos, D. Di Tullio, F. Margulis, A. Cusumano, N. Penalba, P. Atchabahian, A. Zucchini, and A. Vallejos (Argentina); F. Veronese, M. Riella, F. Almeida, C. Amodeo, R. Franco, E. Lasmar, and W. Oigman (Brazil); P. Barre, E. Burgess, A. Chiu, and S. Cournoyer (Canada); V. Tesar, M. Ryba, M. Kadlec, and Z. Bitterova (Czech Republic); S. Regner, G. Leimenstoll, and R. Schneidenbach (Germany); S. Vital Flores, R. Correa Rotter, G. Mondragon Ramirez, O. Ron-Torres, S. Diaz Escobedo, and G. Garcia (Mexico); M. Mysliwiec, D. Baczynski, A. Ksiazek, and M. Szurkowski (Poland); V. Arkhiposhkiy, O. Barbarash, E. Minina, V. Kostenko, I. Gordeev, V. Marasaev, Y. Shvarts, E. Smolyarchuk, S. Tereschenko, M. Timofeev, O. Barysheva, E. Vaskina, A. Zemchenkov, R. Libis, V. Zlokazov, O. Lantseva, L. Zibnitskaya, V. Shirshov, and A. Kuzin (Russia); G. Fernandez Juarez, J. Bover, J. Guerediaga Madariaga, M. Sánchez Heras, and P. Bouza Piñeiro (Spain); T. Kostynenko, V. Lesovoy, V. Lizogub, O. Lyulko, L. Martynyuk, L. Pyrih, A. Svintsitskyy, I. Topchiy, I. Vakaliuk, I. Katerenchuk, A. Bazylevych, Z. Semydotska, B. Rebrov, and M. Stanislavchuk (Ukraine); and M. Bernardo, J. Blondin, S. Blumenthal, J. Cangiano, M. Chonchol, M. El-Shahawy, D. Fitz-Patrick, T. Gehr, T. Herman, M. Kaplan, W. Kaye, N. Kopyt, R. Lafayette, J. Lee, L. Lee, V. Lorica, G. Canas, R. McCrary, R. Ramsamooj, E. Reisin, R. Saxena, R. Sturdivant, M. Vernace, M. Weiner, D. Wombolt, M. El-Khatib, M. Smith, P. McCauley, G. Newman, R. Anel, C. Charytan, P. Suchinda, F. Al-Saghir, R. Gruich, M. Moustafa, L. Stern, R. Cottiero, F. Goldstein, D. Artzer, C. Martinez, R. Huseman, R. Schmidt, and M. Feldman (United States).

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