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Prostacyclin analog beraprost sodium efficacy in primary glomerular disease or nephrosclerosis: Analysis of the Japanese subgroup in CASSIOPEIR study

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Abstract

We conducted a multicenter, randomized, double-blind, placebo-controlled, phase IIb/III study (CASSIOPEIR) using a renal composite endpoint (i.e., doubling of SCr or end-stage renal disease) in seven Asian countries/region. CASSIOPEIR compared TRK-100STP (120 μg and 240 μg) with placebo in patients with non-diabetic CKD patients with primary glomerular disease or nephrosclerosis ($n = 892$). However, the superiority of TRK-100STP over placebo was not observed. A prior phase II study on which the Phase IIb/III study design was based included only Japanese patients. We therefore evaluated TRK-100STP efficacy and safety in a subgroup of Japanese patients using the CASSIOPEIR dataset. As the timing of treatment initiation is important in CKD, we conducted additional subgroup analyses based on the baseline serum creatinine (SCr) and eGFR. ITT analysis was performed in a Japanese subgroup ($n = 339$) in which the primary endpoint was the first occurrence of renal composite endpoint. Significant differences were observed for TRK-100STP 240 μg vs. placebo ($P = 0.0493$; HR 0.69 [95% CI: 0.47, 1.00]), but no significant difference was observed between TRK-100 120 μg and placebo ($P = 0.3523$; HR 0.85). More prominent improvement was observed with TRK-100STP 240 μg vs. placebo for baseline SCr < 3.0 mg/dL ($P = 0.0031$; HR 0.43); SCr < 3.5 mg/dL ($P = 0.0237$, HR 0.59); and eGFR ≥ 10 mL/min/1.73 m^2 ($P = 0.0339$, HR0.67), respectively. No significant changes in urinary albumin/creatinine ratio and blood pressure were observed. TRK-100STP was generally well tolerated and most adverse drug reactions were mild or moderate in severity. In conclusion, in the Japanese subgroup of CASSIOPEIR, TRK-100STP 240 μg/day significantly improved the renal composite endpoint compared with placebo, with greater efficacy in subjects with SCr < 3.5 or eGFR ≥ 10 mL/min/1.73 m^2.

KEYWORDS

beraprost sodium, CASSIOPEIR, chronic kidney disease, Japanese subgroup, prostacyclin, TRK-100STP

1 | INTRODUCTION

Prostacyclin is an autacoid synthesized primarily in vascular endothelial cells that plays a key role in maintaining blood flow in organs, including the kidneys. Beraprost sodium (BPS) is an orally active prostacyclin derivative [1] that is licensed and prescribed widely in Asian countries for the treatment of peripheral artery disease (PAD) and pulmonary hypertension [2]. BPS has also been shown to be effective in renal impaired animal models such as glomerular disease [3,4] and diabetic nephropathy [5,6]. Recently, tubulointerstitial hypoxia has been highlighted as a final common pathway to end-stage renal disease (ESRD) [7,8]. Renal blood flow is reduced when renal glomeruli are damaged by pathological factors such as inflammation and hypertension. Lack of oxygen, particularly in the tubulointerstitium of the outer-medullary region (which is susceptible to hypoxia), triggers further damage to renal glomeruli which causes renal function to progressively decline [9].

In animal models, BPS suppressed renal cell apoptosis and disappearance of renal micro-vessels. It is also reported that BPS maintained renal blood flow and reduced histological damage in chronic kidney disease (CKD) rats [10], and these effects of BPS lead to an improvement in hypoxia in the kidney [11] and reduced associated mortality [12]. In CKD cats, the mechanism of tubulointerstitial fibrosis is similar to that in humans, confirming its usefulness as a model of human CKD [13]. BPS significantly inhibited the increase in serum creatinine (SCr) levels in a randomized controlled trial in cats [14].

The usefulness of BPS has also been demonstrated in several exploratory human clinical studies [15,16]. Based on the findings of these studies, we conducted a phase II, randomized, placebo-controlled comparative study of TRK-100STP, a sustained-release form of BPS, in Japanese patients with non-diabetic CKD. The results suggested suppression of the deterioration rate of parameters of renal function (i.e., SCr, estimate glomerular filtration rate [eGFR] and serum cystatin C) in subjects treated with either 120 and 240 μg BPS, even though a dose–response relationship was not evident [17].

To demonstrate the efficacy of BPS for CKD, a study using renal composite endpoints of ESRD and doubling of SCr is considered necessary. As the phase II study was unable to establish a recommended dose, a subsequent phase IIb/III study of TRK-100STP targeting non-diabetic CKD was designed [18] based on the results of the phase II study. This, the CASSIOPEIR (**C**hronic Renal Failure **As**ian **S**tudy w**i**th **O**ral **P**GI_2 Derivative for **E**valuating **I**mprovement of **R**enal Function) study was conducted in seven countries/region (i.e., Japan, China, Hong Kong, Taiwan, Korea, Malaysia and Thailand) and was registered at ClinicalTrials.gov (NCT01090037). Although CASSIOPEIR was unable to demonstrate efficacy on the renal composite endpoints [19], this finding is consistent with other multi-regional studies conducted on CKD patients that reported varying levels of drug efficacy depending on the country or region [20,21]. It was therefore considered useful to evaluate the efficacy and safety in a subgroup of Japanese patients (who were the target population of the initial phase II study) using the dataset of the phase IIb/III study.

The timing of treatment initiation is important in the treatment of CKD given that achieving any level of disease improvement by drug therapy is hard in patients with a significantly reduced renal function such as CKD stage G5. One limitation to demonstrate TRK-100STP efficacy in CASSIOPEIR was suspected to be the higher criterion for SCr at study entry (2.0–4.5 mg/dL), compared with other studies using renal composite endpoints. Accordingly, a subgroup analysis by SCr and eGFR at study entry was performed. To investigate the reason for the difference in efficacy between subjects enrolled in Japan compared with other Asian countries, BPS plasma levels were analyzed using samples collected for population pharmacokinetic (PPK) analysis, in addition to an analysis of the effect of other baseline parameters.

2 | PATIENTS AND METHODS

The protocol of the CASSIOPEIR study was previously reported [18]. To summarize, this study was a multicenter, randomized, double-blind, placebo-controlled comparative study of TRK-100STP (120 or 240 μg/day) in non-diabetic CKD patients with primary glomerular disease or nephrosclerosis. The definition of primary glomerular disease in this study was that the principal investigator at each institution judged that the disease was primary glomerular disease based on the medical record and other information, and a definitive diagnosis by biopsy was not necessarily required. The definition of primary glomerular disease was the same as in our previous Ph-II study [17], and was specified in the protocol. In addition, secondary glomerular diseases such as diabetic nephropathy, lupus nephritis, ANCA-related nephritis, so on, are excluded in the exclusion criteria of the protocol [18].

The treatment period was for 2–4 years and a total of 892 subjects were enrolled and randomized at 160 study institutions. The primary endpoint was doubling SCr or time to the onset of ESRD and this could include introduction of dialysis, renal transplantation or increase in SCr of up to 6.0 mg/dL. In this study, country and institution-based block randomization was used, and the effects of confounding factors, either known or unknown, have been balanced also in the Japanese subpopulation of the study.

The study was approved by the local research Ethics Committee of each participating center and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to participating in any study-related activities. Using the dataset of this study, a post hoc analysis of the renal composite endpoints and safety were evaluated in the subgroup of Japanese patients. In addition, the efficacy of TRK-100STP by lower baseline SCr (<2.5, <3.0, and <3.5 mg/dL) and eGFR (≥10, ≥15 mL/min/1.73 m^2) using the Japanese equation for eGFR [22] were also evaluated.

The intent-to-treat (ITT) population was employed for efficacy analysis. For the primary endpoint, a closed-testing procedure starting from the highest dose was used to compare each active dose group vs. the placebo group for multiplicity adjustment of testing. A pairwise comparison between the TRK-100STP 240 μg and placebo groups was therefore performed by Log–rank test at a two-sided 5% significance level. If statistical significance was observed in the previous step, then, a pairwise comparison between the TRK-100STP 120 μg and placebo groups was performed.

The secondary endpoints were doubling of SCr and rate of ESRD (which included the introduction of dialysis, increase in SCr ≥6.0 mg/dL, and renal transplantation). Analyses of secondary endpoints and other subgroups were performed by Log–rank test and no adjustment for multiplicity was performed. The hazard ratio (HR) and 95% confidence interval (CI) were calculated by the Cox proportional hazards model.

2.1 | Measurement and analysis of plasma beraprost level

Plasma samples of all patients were collected for PPK analysis. Among the pharmacokinetics analysis set (PKAS) [18], data obtained during 8, 12, 36, 48, 72, and 84 weeks of treatment (i.e., non-trough points having morning medication) were analyzed. The plasma level of BPS was measured at Toray Research Center (TRC, Tokyo, Japan) according to protocol. Data analysis on the samples was conducted after the unblinding of the whole study according to the procedure set before unblinding.

3 | RESULTS

3.1 | Subject disposition and characteristics

The trial profile of the Japanese subgroup is shown in Figure 1. A total of 339 patients from 88 sites were randomized to receive either TRK-100STP or placebo during

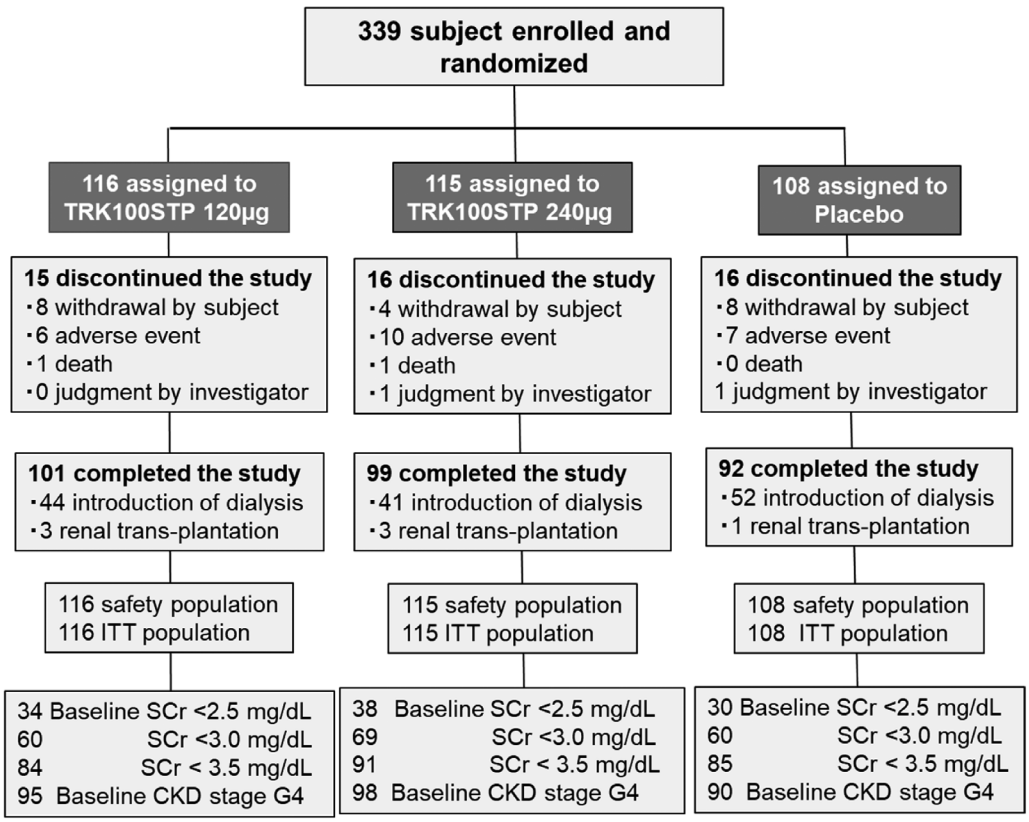

FIGURE 1 Trial subject disposition

TABLE 1 Demographics and baseline characteristics of the subgroup of Japanese subjects

	TRK-100STP 120 μg (*n* = 116)	TRK-100STP 240 μg (*n* = 115)	Placebo (*n* = 108)	Total (*n* = 339)
Age, years				
Mean (SD)	59.7 (11.6)	60.3 (10.8)	59.0 (13.1)	59.7 (11.6)
Median (range)	63.0 (27–75)	63.0 (29–75)	61.5 (21–75)	62.0 (21–75)
Sex, *n* (%)				
Male	74 (63.8)	77 (67.0)	74 (68.5)	225 (66.4)
Female	42 (36.2)	38 (33.0)	34 (31.5)	114 (33.6)
Primary disease, *n* (%)				
Primary glomerular disease	89 (76.7)	85 (73.9)	81 (75.0)	225 (75.2)
Nephrosclerosis	27 (23.3)	30 (26.1)	27 (25.0)	84 (24.8)
Primary glomerular disease—specific condition identified by renal biopsy (in subjects who underwent biopsy), *n* (%)				
IgA nephropathy	29 (74.4)	28 (60.9)	27 (61.4)	84 (65.1)
Focal glomerulosclerosis (focal segmental glomerulosclerosis)	4 (10.3)	7 (15.2)	7 (15.9)	18 (14.0)
Membranous nephropathy	1 (2.6)	2 (4.3)	0 (0.0)	3 (2.3)
Membranoproliferative glomerulonephritis	1 (2.6)	1 (2.2)	2 (4.5)	4 (3.1)
Mesangial proliferative glomerulonephritis	3 (7.7)	3 (6.5)	3 (6.8)	9 (7.0)
Other proliferative nephritis (including non-IgA nephropathy)	0 (0.0)	4 (8.7)	1 (2.3)	5 (3.9)
Unidentified	1 (2.6)	0 (0.0)	2 (4.5)	3 (2.3)
Others	0 (0.0)	1 (2.2)	2 (4.5)	3 (2.3)
Concomitant medications, *n* (%)				
ACEI or ARB	107 (92.2)	107 (93.0)	100 (92.6)	314 (92.6)
Baseline body weight, kg	63.7 (13.7)	62.4 (12.9)	61.6 (11.1)	62.6 (12.6)
Baseline SCr, mg/dL				
Mean (SD)	3.007 (0.662)	2.900 (0.595)	2.964 (0.619)	2.957 (0.626)
Slope of 1/SCr vs time, dL/mg■4 weeks [a]				
Mean (SD)	−0.00821 (0.00309)	−0.00815 (0.00311)	−0.00928 (0.00439)	−0.00853 (0.00359)
Baseline eGFR (MDRD), mL /min/1.73 m^2				
Mean (SD)	15.8 (4.7)	16.2 (4.5)	15.9 (4.1)	16.0 (4.4)
Baseline eGFR (CKD-EPI), mL/min/1.73 m^2				
Mean (SD)	21.0 (6.9)	21.3 (6.4)	21.0(6.1)	21.1 (6.5)
Baseline eGFR (Japanese equation), mL/min/1.73 m^2				
	17.4 (4.7)	17.3 (5.2)	17.7 (4.9)	17.5 (5.0)
Urinary albumin/ creatinine (mg/g creatinine)				
Mean (SD)	881 (669)	964 (783)	1155 (872)	996 (782)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; SCr, serum creatinine; MDRD, modification of diet in renal disease.
[a]Slope of 1/SCr vs time during 1 year before treatment, which is an indicator of the rate of CKD progression before treatment.

the treatment period. The safety analysis and ITT analysis were performed using these patients.

The mean follow-up periods for Japanese patients were 777.6 ± 387.5 days (mean ± SD) for placebo, 803.8 ± 432.5 days for 120 μg, and 829.8 ± 407.8 days for 240 μg, respectively. Demographics and baseline characteristics of the subgroup of Japanese subjects are summarized in Table 1. Background factors that are generally considered to have a large effect on CKD progression were not notably different between the groups.

Several notable differences were identified between the Japanese subjects and those enrolled from other countries

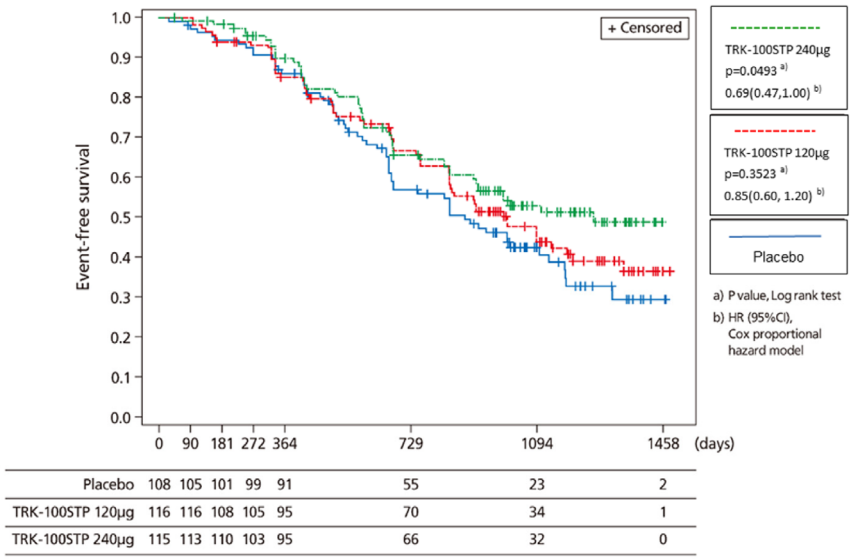

FIGURE 2 Kaplan–Meier plots of renal composite endpoints in the Japanese population). a) *P*-value, log–rank test; (b) HR (95% CI), Cox proportional hazard model

(Table A1). In the Japanese subpopulation, the rate of use of the combination of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) was high (92.6% vs. 62.1%). Furthermore, the age (average [SD]: 59.7 [11.6] vs. 51.3 [12.9]), male proportion (66.4% vs. 57.0%) and nephrosclerosis proportion (24.8% vs. 17.4%) were all higher in the Japanese population. There was no difference in other background parameters (Table 1 and Table A1).

3.2 | Effect on blood pressure and urinary albumin/creatinine ratio

Baseline blood pressures (systolic and diastolic) were comparable between the three treatment groups (Table A2). There were no significant differences in changes from baseline blood pressure values among the three groups. No differences in baseline urinary albumin to creatinine ratio or in changes from baseline were observed among the three groups (Table A2).

3.3 | Primary analytical endpoint efficacy

A significant difference was observed in the renal composite endpoint between the TRK-100STP 240 μg dose group and the placebo group ($P = 0.0493$; HR 0.69 [95% CI: 0.47, 1.00]) (Figure 2). As statistical significance was observed in this step then a pairwise comparison between the TRK-100STP 120 μg and placebo groups was performed. No significant difference was observed between the TRK-100STP 120 μg group and the placebo group ($P = 0.3523$; HR 0.85 [95% CI: 0.60, 1.20]).

3.4 | Secondary endpoints

The HR for renal transplantation in the Japanese population was 2.71 in the TRK-100STP 120 μg group ($P = 0.3679$) and 2.62 in the TRK-100STP 240 μg group (0.3866), which may be due to the small number of events (i.e., 3-6). The HR of the remaining secondary endpoints ranged between 0.72–0.97 in the TRK-100STP 120 μg group and 0.70–0.80 in the TRK-100STP 240 μg group (Table 2).

3.5 | Subgroup analysis

Results of subgroup analysis based on the renal composite endpoints by baseline SCr and eGFR are shown in Table 3. Significant differences were observed between the TRK-100STP 240 μg and placebo groups in patients with baseline values of SCr <3.0 and 3.5 mg/dL. Kaplan–Meier plots for the patients with an SCr of <3.0 mg/dL are shown in Figure 3. In the 120 μg group, TRK-100STP efficacy was not demonstrated in any SCr subgroup. The proportion of patients with baseline CKD stage G3b/G4/G5 was 6/94/1% and was 3/90/7% and 2/80/18%, respectively, in the subpopulations with SCr of <2.5, <3.0, and <3.5 mg/dL.

In the inter-group comparison of renal composite endpoints by baseline eGFR, a significant difference ($P = 0.0339$) and decrease in HR (HR = 0.67) was observed for the 240 μg in baseline eGFR ≥ 10 mL/min/1.73 m^2, and decrease in HR was observed in eGFR ≥15 mL/min/1.73 m^2. Considering CKD stage G4 represented the majority in patients with baseline SCr below 2.5–3.5 mg/mL, the efficacy of 240 μg of TRK-100STP was considered to be remarkable in

TABLE 2 Secondary endpoints in the Japanese population

Secondary endpoint		120 μg ($n = 116$) vs. placebo ($n = 108$)	240 μg (0 = 115) vs. placebo ($n = 108$)	Incidence rate/(person-years)		
				Placebo	120 μg	240 μg
Doubling of SCr	HR (95% CI)[a] *P*-value [b]	0.72 (0.45, 1.15) 0.1641	0.70 (0.43, 1.12) 0.1327	0.16120	0.12174	0.11703
ESRD	Hazard ratio (95% CI) [a] *P*-value [b]	0.81 (0.56, 1.18) 0.2713	0.73 (0.49, 1.06) 0.0976	0.24953	0.20456	0.18269
Introduction of dialysis	HR (95% CI) [a] *P*-value [b]	0.72 (0.48, 1.08) 0.1080	0.71 (0.47, 1.06) 0.0931	0.21028	0.15489	0.15183
Increase in SCr ≥ 6.0 mg/dL	HR (95% CI) [a] *P*-value [b]	0.97 (0.62, 1.53) 0.9092	0.80 (0.50, 1.27) 0.3386	0.15595	0.15216	0.12529
Transplantation	HR (95% CI) [a] *P*-value [b]	2.71 (0.35, 54.8) 0.3679	2.62 (0.33, 53.1) 0.3866	0.00393	0.01050	0.01079

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; SCr, serum creatinine.
[a]Cox proportional hazard mode.
[b]Log–rank test.

TABLE 3 Comparison of renal composite endpoints by baseline SCr

Baseline SCr or eGFR		Placebo	TRK-100STP 120 μg	TRK-100STP 240 μg
SCr < 2.5 mg/dL	Number	30	34	38
	HR (95% CI)[a]		0.56 (0.24, 1.26)	0.50 (0.21, 1.11)
	P-value[b]		0.1605	0.0824
SCr < 3.0 mg/dL	Number	60	60	69
	HR (95% CI)[a]		0.67 (0.39, 1.15)	0.43 (0.24, 0.76)
	P-value[b]		0.1457	0.0031
SCr <3.5 mg/dL	Number	85	84	91
	HR (95% CI)[a]		0.77 (0.49, 1.19)	0.59 (0.37, 0.94)
	P-value[b]		0.2318	0.0237
eGFR ≥ 15 mL/min/1.73 m^2	Number	76	78	86
	HR (95% CI)[a]		0.82 (0.52, 1.29)	0.64 (0.39, 1.02)
	P-value[b]		0.3589	0.0618
eGFR ≥ 10 mL/min/1.73 m^2	Number	109	119	115
	HR (95% CI)[a]		0.82 (0.58,1.16)	0.67 (0.46,0.97)
	P-value[b]		0.2361	0.0339

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SCr, serum creatinine.
[a]Cox proportional hazard model.
[b]Log–rank test.

patient with CKD Stage G4 or eGFR ≥ 10 mL/min/1.73 m^2 (Figure 4).

In Table A3, the slope (4w to last observation) of 1/SCr vs time during the treatment period (4w to last observation) was shown in the subgroups with a baseline SCr of 2–2.5, 2–3.0, and 2–3.5 mg/dL, respectively. Although there was no significant difference, there was a trend toward a slower decline in renal function in the BPS 240 μg group than in the placebo group.

Changes in the urinary albumin/creatinine ratio and blood pressure are shown in Table A2. No remarkable differences were observed between baseline and the final evaluation point for both parameters.

3.6 | Plasma BPS level and the effects on the renal composite endpoint

In the 240 μg treatment group, mean plasma levels in patients in whom blood sampling time was recorded as 2–6 h after taking the drug, which was around the T_{max} of TRK-100STP single administration [23]. Plasma concentrations of BPS in Japanese subjects were as follows: Week 8:309 ± 184 pg/mL; Week 12:337 ± 202 pg/mL; Week 36:303 ± 186 pg/mL; Week 48:291 ± 165 pg/mL; Week 72:329 ± 220 pg/mL; and Week 84:308 ± 187 pg/mL (mean ± SD). In populations from the other countries the combined values were: Week 8:252 ± 188; Week

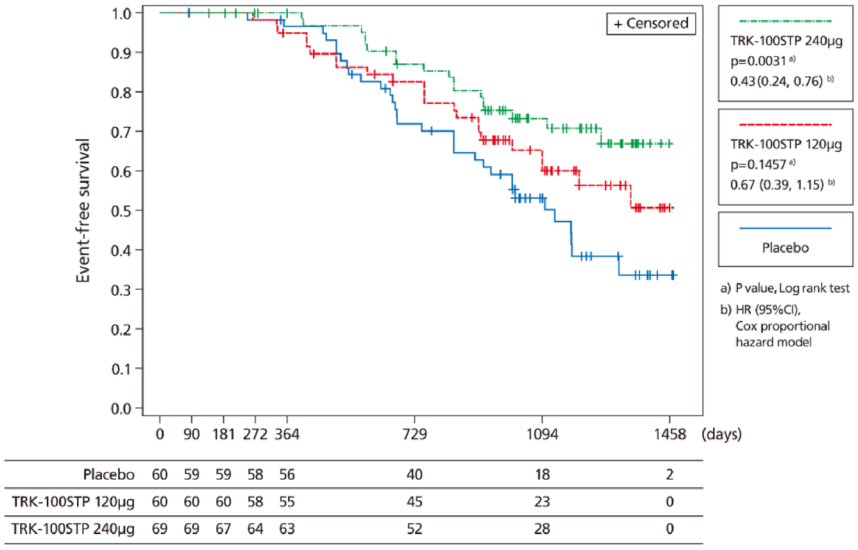

FIGURE 3 Kaplan–Meier plots of renal composite endpoints in Japanese patients with a baseline SCr <3.0 mg/dL. (a) *P*-value, log–rank test; (b) HR (95% CI), Cox proportional hazard model

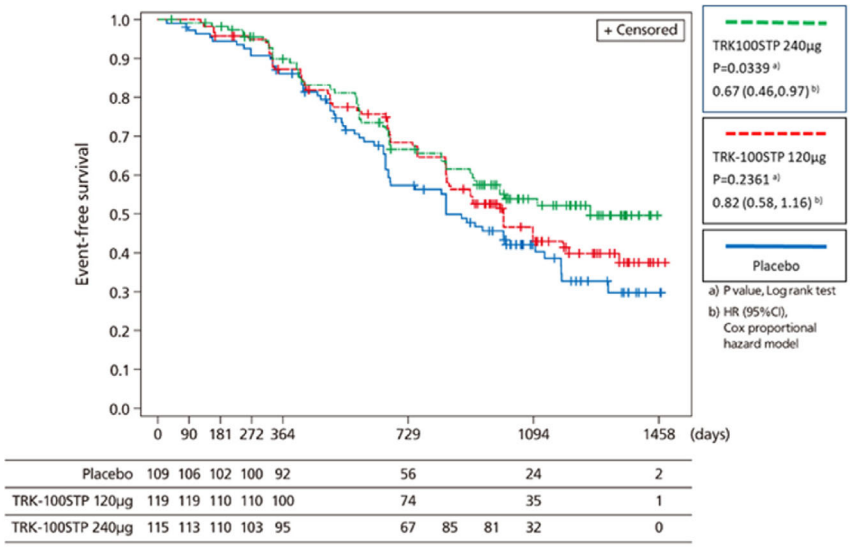

FIGURE 4 Kaplan–Meier plots of renal composite endpoints in Japanese patients with a baseline >10 mL/min/1.73 m^2. (a) *P*-value, log–rank test, (b) HR (95% CI), Cox proportional hazard model

12:268 ± 179; Week 36:231 ± 165; Week 48:247 ± 161; Week 72:258 ± 183; and Week 84:250 ± 185 pg/mL. Plasma concentrations of BPS at all time points were found to be higher in the Japanese population compared with all other countries combined. Patients with a mean plasma concentration of BPS above 50 pg/mL were identified among patients who took the drug 2–6 hours (around T_{max}) before blood sampling in the clinical records. A total of 98/115 (85%) Japanese patients were identified on the basis of having had at least 1 point of measurement at 2–6 h after taking the drug. In contrast, in populations from countries other than Japan, 81 of 183 (56%) patients were identified in this way. Thus, instances of more than 50 pg were particularly frequent in Japan than the countries other than Japan. Analysis was performed using the renal composite endpoint only in these patients. The HR declined further in Japan (HR = 0.60) and the HR in Asian countries other than Japan was 0.85, indicating a tendency to approach the HR in Japan (Table 5).

3.7 | Safety and tolerability

The safety outcomes are summarized in Table 4. The incidence of adverse drug reactions (ADRs) was 28.7% in the placebo group, 33.6% in the 120 μg group and 33.9% in the 240 μg group. The majority of ADRs were mild or moderate in severity. The incidence of serious adverse effects (SAEs) and severe adverse effects was similar among the three groups.

In the Japanese population, side effects that were reported by more than 10% of subjects in ether group and

TABLE 4 Summary of adverse events and side effects

	Placebo	TRK-100STP 120 μg	TRK-100STP 240 μg
Number of subjects for safety analysis (SAF)	108	116	115
Adverse events	105 (97.2%)	111 (95.7%)	111 (96.5%)
Adverse drug reactions (ADRs)	31 (28.7%)	39 (33.6%)	39 (33.9%)
Serious adverse events that resulted in death	0 (0.0%)	1 (0.9%)	1 (0.9%)
Serious adverse events (excluding events resulting in death)	45 (41.7%)	39 (33.6%)	44 (38.3%)
Severe adverse events	13 (12.0%)	8 (6.9%)	12 (10.4%)
Adverse event that resulted in withdrawal of dosing	15 (13.9%)	18 (15.5%)	17 (14.8%)
Adverse event that resulted in temporary discontinuation of dosing	14 (13.0%)	13 (11.2%)	9 (7.8%)

TABLE 5 Renal composite endpoint in patients with plasma concentrations around T_{max} above the minimum effective dose (50 pg/mL)

Sub-group		Placebo	TRK-100STP 120 μg	TRK-100STP 240 μg
Japan+Asia	Number	272	175	198
	HR (95% CI)[a]		0.95 (0.24, 1.26)	0.72 (0.55, 0.94)
	P-value[b]		$P = 0.6514$	$P = 0.0140$
Japan	Number	106	84	98
	HR (95% CI)[a]		0.75 (0.51, 1.10)	0.60 (0.40, 0.89)
	P-value[b]		$P = 0.1459$	$P = 0.0104$
Asia	Number	166	91	100
	HR (95% CI)[a]		1.15 (0.81,1.63)	0.84 (0.58,1.20)
	P-value[b]		$P = 0.4318$	$P = 3457$

[a]Cox proportional hazard model.
[b]Log–rank test.

were more common in the BPS group than in the placebo group were as follows. Diarrhea (9.3% in the placebo group, 9.5% in the 120 μg group, 13.0% in the 240 μg group), headache (6.5%, 9.5%, 16.5%), back pain (5.6%, 14.7%, 8.7%), fall (4.6%, 12.9%, 11.3%), hypertension (5.6%, 9.5%, 10.4%).

4 | DISCUSSION

Most phase III clinical studies of other drugs in this therapeutic area that have used the renal composite endpoint have targeted diabetic nephropathy. In contrast, the CASSIOPEIR study targeted primary glomerular diseases (which have a high prevalence among Japanese patients) and nephrosclerosis (the incidence of which is increasing worldwide). Recently, the high efficacy of SGLT2 inhibitor canagliflozin for the renal composite endpoint has been demonstrated and many drugs targeting blood glucose are also expected to be used the treatment of diabetic CKD. However, in non-diabetic nephropathy, there is still no consensus on the optimal approach, with the exception of treatment with ACEI/ARB or other antihypertensive drugs. In the present subgroup analysis of the Japanese sub-population enrolled to the CASSIOPEIR study, TRK-100STP 240 μg was demonstrated to be effective based on the renal composite endpoints. In addition, the clinical benefits were more pronounced in patients with baseline SCr <3.5 mg/dL or eGFR ≥10 mL/min/1.73 m^2.

In this study, the drug administration period was set to 2–4 years, and the administration period differed depending on the entry time of the patient. Therefore, it is natural that the number of subjects decreased at 2 years. As shown in Figure 2, the 240 μg group was superior to placebo until the fourth year after the start of administration, and the difference was observed to be 10% or more at many points, especially after the first year. In addition, comparisons between groups were made using the log–rank test. This test is not based on

the value at one-time point but summarizes the number of observed and expected events for each time point and therefore evaluates all time points. For these reasons, the small number of cases at the later time point is not considered to have had any particular influence on the results of the statistical evaluation.

There are several important observations from this sub-group analysis. First, for the Japanese subpopulation, the effectiveness of TRK-100STP 240 μg was comparable to what was expected at the time the CASSIOPEIR study was designed. As previously reported, the design of the CASSIOPEIR study was based on the results of phase II study conducted only in Japanese subjects. As a result of this investigation, a significant difference for TRK-100STP 240 μg was found. Second, the usefulness of TRK-100STP was not accompanied by changes in the urinary albumin/creatinine ratio or blood pressure. This is consistent with the 6-month administration of TRK-100STP having the effect of suppressing renal function deterioration without decreasing blood pressure or the urinary protein level [17]. Whether renal function deterioration in CKD patients can be suppressed without depending on a decrease in urinary protein is currently under discussion. A recent meta-analysis revealed that suppression of renal function deterioration in diabetic nephropathy patients is associated with a decrease in the urinary protein level [24]. It was suggested that, at least for the treatment of non-diabetic CKD patients with BPS, the renal composite endpoints are improved regardless of urinary albumin.

In recent years, an increasing body of non-clinical and clinical evidence suggests that tubulointerstitial hypoxia is the final common pathway that leads to ESRD [7,9,13]. There is consequently strong interest in how effective the renal hypoxia targeting approaches such as beraprost is when using a renal composite endpoint. Although the target disease was diabetic nephropathy (i.e., in contrast to the target of the present study), the HR in other studies using renal composite endpoints, such as RENAAL [20], IDNT and CREDENCE was 0.84, 0.77, and 0.66, respectively. The HR of TRK-100STP in the Japanese 240 μg group was 0.69 and was 0.50, 0.43, 0.59, 0.64, and 0.67 in the subpopulations with SCr of <2.5mg/dL, <3.0mg/dL, <3.5 mg/dL and eGFR ≥15, >10 mL/min/1.73 m^2, respectively. Thus, it was suggested that 240 μg of TRK-100STP was highly effective, as compared to other drugs that have demonstrated efficacy for kidney disease. The average baseline values of SCr or eGFR in subjects in the RENAAL, IDNT and CREDENCE studies were 1.9 mg/dL, 1.65–1.69 mg/dL, and 56.2 mL/min/1.72 m^2, respectively. Therefore, the characteristic of the effect of TRK-100STP was that it was observed in patients with baseline CKD stage G4 where there was insufficient evidence of the effects of other drugs. Consequently, targeting renal hypoxia may be an attractive therapeutic approach for the treatment of non-diabetic CKD patients.

In the previous phase II study [17], a comparable suppression of renal function deterioration was observed in both the 120 and 240 μg TRK-100STP treatment groups. In this analysis, higher efficacy was noted for 240 μg group. This may have been because the SCr at study entry was higher in the phase IIb/III study (i.e., at 2.0–4.5 mg/dL) than in the phase II study (i.e., at 1.3–4.0 mg/dL for females, 1.5–4.5 mg/dL for males), and because the treatment period was 6 months in the phase II study and 2–4 years in the phase IIb/III study [18]. As such, TRK-100STP at a dose of 120 μg was considered to be less effective in such patients. Furthermore, the dose-dependency of human renal composite endpoints was consistent with observations of BPS efficacy in CKD model rats [4] where BPS completely inhibited the increase in SCr at higher dose. It is notable that complete inhibition of SCr elevation in IRIS (International Renal Interest Society) stages 2 and 3 was also observed in CKD cats [14]. Therefore, in humans, it may be expected that increasing the dose results in higher efficacy. Given that the administration of TRK-100STP at 180 μg up to 360 μg per day to patients with pulmonary arterial hypertension is approved in Japan, and also that TRK-100STP 240 μg was generally well tolerated in the present study, there was sufficient rationale to investigate the administration of TRK-100STP at a higher dose in patients with CKD.

In the CASSIOPEIR study, treatment with TRK-100STP is employed, in principle, as an adjunct to existing treatments. No limitation was set against concomitant ACEIs/ARBs use, although dose alternation and newly initiated prescription was restricted [18]. Overall, 92.6% of subjects in Japan received ACEI/ARB and this was substantially comprised of combination therapy of BPS with ACEI/ARB [19]. Recently, a confirmatory study of the ACEI and ARB combination was conducted in patients with diabetic nephropathy; however, concomitant use did not appear to enhance efficacy and was instead reported to increase the incidence of ADRs. Furthermore, the effects of an add-on to existing therapies including ACEI/ARB have been investigated in phase III studies of oral charcoal [21] and a renin inhibitor; however, these studies failed to demonstrate an enhanced treatment effect. Therefore, BPS, which is effective when combined with ACEI/ARB, is a useful treatment option and it can be inferred that the mechanism of action of BPS in CKD is different from that of ACEI/ARB.

As the lack of efficacy reported for mixed overall populations of patients [19] appears to be due to the relative ineffectiveness of BPS in subjects from countries

except Japan, we investigated differences in baseline characteristics between Japan and other countries. In addition to the high rate of use of ACEI/ARB combination (92.6% vs. 62.1%), baseline age, ratio of males, and ratio of glomerulonephritis were slightly higher in the Japanese sub-population compared to other countries. However, to date, no evidence has been obtained that could explain the differences in efficacy between Japan and other countries.

We investigated another possibility, namely whether there was a difference in the BPS exposure level between Japan and the other countries. The mean plasma level in the Japanese patients was higher than that in patients from the other countries, suggesting that Japanese patients are potentially exposed to higher plasma levels of BPS. The effects of BPS on CKD are contributed by actions such as antiplatelet, vasodilation, protection of vascular endothelial cells, and suppression of production of inflammatory cytokines [23]. Of these, protection of endothelial cells is considered to be particularly important, and it is rarely observed with other drugs. The protective effect of BPS on cultured human aortic endothelial cells was observed in a dose-dependent manner from 0.1 nM [25] (minimum effective concentration). In the CASSIOPEIR study, only patients with plasma concentrations near T_{max} above the minimum effective concentration (set at 50 pg/mL or 0.12 nM) can be expected to be effective. The high proportion of these patients in Japan (85% vs. 55%) may have led to differences in efficacy between subjects from Japan compared with other countries. This estimate was supported by the results (Table 5) for the renal composite endpoint, which was limited to patients with exposures above the minimum effective concentration (50 pg/mL) around T_{max}.

PK studies of BPS immediate-release tablets have been conducted in Japan [26], Europe [27], and South Korea [28] and have not shown significant differences in any PK parameters. Similar results were noted for TRK-100STP in a study comparing PK among Japanese, Chinese, and Koreans (unpublished data). Thus, there were no apparent ethnicity-based differences in PK profiles suggested as a possible factor. Another suspected factor was that as drug ingestion was self-reported in the study, the drug adherence rate may have been higher among Japanese subjects (leading to higher plasma exposure levels) compared to other countries. The recorded total medication rate in the 240 μg group was higher in Japanese subjects compared to other Asian countries (average ± SD: 93.9 ± 12.6% vs. 88.0 ± 19.1%). In addition, when 120 μg of TRK-100STP is administered to a healthy person, the plasma concentration of 50 pg/mL or more even after 12 hours from administration. Furthermore, C_{max} and AUC increase in patients with reduced renal function [29]. It is strongly suggested that the "subjects that do not reach minimum effective concentration even at T_{max}," which were more common in countries other than Japan, are highly likely not to have actually taken medication at the time point.

In a study involving CKD patients, medication compliance led to an important difference in efficacy outcomes [30]. In non-diabetic CKD patients with an SCr of 2.0–4.5 mg/dL targeted in the CASSIOPEIR study, there was a little or no subjective symptoms associated with a declined renal function. Thus, it is difficult to maintain high medication compliance in a 2-year or longer study period and regional differences may be present. The difference in the effects of TRK-100STP between subjects in Japan and those in other Asian countries was not sufficiently clarified in this study, and further investigation is necessary, including a difference in disease and medical treatment environment for renal diseases.

In terms of its safety profile, TRK-100STP was well tolerated in all patient subgroups, including Japanese patients.

An important potential limitation of this study included the fact that it was a sub-group and post-hoc analysis of a multicenter, randomized, double-blind, placebo-controlled comparative study.

5 | CONCLUSION

In the Japanese subgroup of the CASSIOPEIR study, TRK-100STP at a dose of 240 μg was suggested to be effective for the primary renal composite endpoints, with efficacy more pronounced in the group of subjects with SCr <3.5 mg/dL or eGFR≥10 mL/min/1.73 m^2. In terms of safety profile, TRK-100STP was well tolerated across all patients including the Japanese subgroup.

ETHICAL APPROVAL

This trial has been approved by competent regulatory authorities of Japan, In accordance with the laws of Japan, the trial has been conducted after obtaining documented approval from Institutional Review Board/Independent Ethics Committee in each site according to ICH-GCP guidelines.

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pharmacovigilance, study design, data collection, data analysis, data interpretation, and writing of the clinical study report.

CONFLICTS OF INTERESTS

Hajimu Kurumatani and Kiyonobu Okada are employees of Toray. Masanao Isono was a Toray employee during the study. Hideki Origasa received consultancy fees from Toray during the study. Toshiro Fujita received grants and personal fees from Astellas, grants from Toray, grants and personal fees from Boehringer Ingelheim, grants from Chugai, grants from Fukuda Denshi, grants from Kyowa Hakko Kirin, grants from Mitsubishi Tanabe, grants from Mochida, grants from Omron, grants from Pfizer, and grants and personal fees from Takeda. Hidetomo Nakamoto received personal fees from Astellas and Toray during the conduct of the study, personal fees from Kissei, Tokyo Mitsubishi, Baxter, Terumo, Astellas, and Toray, and grants from Chugai and Kyowa Hakko Kirin.

AUTHOR CONTRIBUTIONS

Hajimu Kurumatani: Conceptualization of the idea, study design, data collection and drafted the paper. Kiyonobu Okada: Study design and statistical analysis. Hideki Origasa: Statistical advice. Masanao Isono: Conceptualization of the idea, study design, data collection. Toshiro Fujita: Conceptualization of the idea, study design and acted as medical adviser of CASSIOPEIR. Hidetomo Nakamoto: Conceptualization of the idea, study design. All authors participated in reviewing and interpreting the data and providing comments and revisions to the manuscript. All authors approved the final version of the manuscript prior to submission.

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APPENDIX

TABLE A1 Demographics and baseline characteristics of subjects other than Japanese

	TRK-100STP 120 μg (*n* = 180)	TRK-100STP 240 μg (*n* = 183)	Placebo (*n* = 183)	Total (*n* = 546)
Age, years				
Mean (SD)	52.1 (12.9)	50.9 (13.2)	51.0 (12.7)	51.3 (12.9)
Median (range)	53.0(24-75)	52.0 (19-75)	51.0 (19-74)	52.0 (19–75)
Sex, *n* (%)				
Male	92 (51.1)	102 (55.7)	117 (63.9)	311 (57.0)
Female	88 (48.9)	81 (44.3)	66 (36.1)	235 (43.0)
Primary disease, *n* (%)				
Primary glomerular disease	147 (81.7)	151 (82.5)	153 (83.6)	451 (82.6)
Nephrosclerosis	33 (18.3)	32(17.5)	30 (16.4)	95 (17.4)
Primary glomerular disease - specific condition identified by renal biopsy (in subjects who underwent biopsy), *n* (%)				
IgA nephropathy	45 (75.0)	35 (53.0)	44 (73.3)	124 (66.7)
Focal glomerulosclerosis (focal segmental glomerulosclerosis)	8 (13.3)	15 (22.7)	8 (13.3)	31 (16.7)
Membranous nephropathy	0 (0.0)	3 (4.5)	3 (5.0)	6 (3.2)
Membranoproliferative glomerulonephritis	0 (0.0)	1 (1.5)	1 (1.7)	2 (1.1)
Mesangial proliferative glomerulonephritis	0 (0.0)	5 (7.6)	1 (1.7)	6 (3.2)
Other proliferative nephritis (including non-IgA nephropathy)	2 (3.3)	1 (1.5)	2 (3.3)	5 (2.7)
Unidentified	1 (1.7)	3 (4.5)	0 (0.0)	4 (2.2)
Others	4 (6.7)	3 (4.5)	1 (1.7)	8 (4.3)
Concomitant medications, *n* (%)				
ACEI or ARB	101 (56.1)	122 (66.7)	116 (63.4)	339 (62.1)
Baseline body weight, kg	64.4 (12.2)	61.9 (12.4)	63.3 (12.59	63.2 (12.4)
Baseline SCr, mg/dL				
Mean (SD)	2.984 (0.614)	3.038 (0.637)	2.950 (0.667)	2.991 (0.640)
Slope of 1/SCr vs time, dL/mg■4 weeks[a]				
Mean (SD)	−0.00985 (0.00484)	−0.01077 (0.00708)	−0.01045 (0.00633)	−0.01036 (0.00616)
Baseline eGFR (MDRD), mL/min/1.73 m^2				
Mean (SD)	15.5 (4.8)	15.8 (4.6)	16.6 (5.0)	16.0 (4.8)
Baseline eGFR (CKD-EPI), mL/min/1.73 m^2				
Mean (SD)	21.3 (7.0)	21.7 (6.7)	22.8(7.3)	21.9 (7.1)
Baseline eGFR (Japanese equation), mL/min/1.73 m^2				
Mean (SD)	18.6 (5.5)	17.4 (5.3)	17.7 (5.2)	17.9 (5.4)
Urinary albumin/creatinine				
(mg/g creatinine)	822 (728)	820 (737)	859 (734)	833 (732)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; SCr, serum creatinine; MDRD, modification of diet in renal disease.
[a]Slope of 1/SCr vs. time during 1 year before treatment, which is an indicator of the rate of CKD progression before treatment.

TABLE A2 Effects of TRK-100STP on blood pressure and urinary albumin/creatinine in Japanese subpopulation

	Placebo	TRK-100STP 120 μg	TRK-100STP 240 μg
Blood pressure (sitting), mm Hg			
Systolic at W0[a]	128.7 (14.9)	128.0 (12.0)	130.0 (14.2)
Systolic at last assessment time point	132.9 (17.2)	130.4 (16.5)	130.9 (16.6)
Diastolic at W0[a]	76.5 (10.7)	75. 7 (8.5)	75.8 (9.4)
Diastolic at last assessment time point	76.5 (10.6)	75.2 (10.0)	74.8 (11.4)
Albumin/creatinine (urine), mg/g			
At W0[a]	1155 (872)	881 (669)	964 (783)
At last assessment time point	1266 (925)	1021 (931)	1158 (1089)

TABLE A3 Comparison of slope of 1/serum creatinine (SCr) vs. time by baseline SCr

Baseline SCr	Group	Number	Slope of 1/SCr vs. time (SD) (dL/mg^{-4} weeks)	Difference vs. placebo	*P*-value
SCr < 2.5 mg/dL	Placebo	30	−0.00573 (0.00631)		
	120 μg	33	−0.00500 (0.00550)	−0.00072 (0.00590)	0.6310
	240 μg	38	−0.00500 (-0.00576)	−0.00072 (0.00601)	0.6273
SCr < 3.0 mg/dL	Placebo	61	−0.00572 (0.00498)		
	120 μg	58	−0.00538 (0.00593)	−0.00035 (0.00546)	0.7308
	240 μg	69	−0.00382 (0.00820)	−0.00190 (0.00688)	0.1081
SCr < 3.5 mg/dL	Placebo	85	−0.00570 (0.00502)		
	120 μg	82	−0.00583 (0.00703)	0.00013 (0.00703)	0.8908
	240 μg	90	−0.00442 (0.00750)	−0.00128 (0.00642)	0.1843