Bosutinib Versus Placebo for Autosomal Dominant Polycystic Kidney Disease

Vladimir Tesar, Kazimierz Ciechanowski, York Pei, Irina Barash, Megan Shannon, Ray Li, Jason H. Williams, Matteo Levisetti, Steven Arkin, Andreas Serra

Supplemental Materials

Additional Eligibility Criteria

- Systolic blood pressure <140 mm Hg or diastolic blood pressure <90 mm Hg at screening
- Left ventricular ejection fraction ≥50%
- No history of prolonged QTc interval or predose QTc <450 milliseconds
- Alanine aminotransferase and/or aspartate aminotransferase ≤2.5 times the upper limit of normal
- Total bilirubin ≤2 times the upper limit of normal

Frequency of Safety Monitoring

TEAEs were continuously monitored throughout the study. Urinalysis was assessed at screening and days 15, 30 and months 3, 6, 9, 12, 15, 18, 21, 24, 25 during the initial treatment period and at months 28, 31, 34, 37 during the extended treatment period as well as at the final treatment completion visit; creatinine was assessed at screening and days 15, 30 and months 2–9, 12, 15–25 during the initial treatment period and months 26–37 during the extended treatment period and at the final treatment completion visit; liver function testing (including total protein, albumin, total bilirubin, direct bilirubin, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase) was assessed at screening and days 7, 15, 30 and months 2–9, 12, 15–25 during the initial treatment period and at months 26–37 during the extended treatment period and at the final treatment completion visit; physical examinations and vital signs were assessed at screening and days 1, 15, 30 and months 2, 3, 6, 9, 12, 15, 18, 21, 24, 25 during the initial treatment period and at months 28, 31, 34, and 37 during the extended treatment period as well as at the final treatment completion visit; 12-lead electrocardiograms were assessed at screening and days 1, 15, as clinically needed until month 9,

month 12, as clinically needed between months 15–24, and month 25 during the initial treatment period; echocardiogram and multigated acquisition scan were assessed at screening, as clinically indicated during days 1, 7, 15, and 30, and at month 6, 12, as clinically indicated during months 15–24, and at month 25 during the initial treatment period.

Table S1. Summary of TKV and eGFR Over Time by Treatment Group (mITT)

	Bosutinib			
	200 mg/d (n=27)	**400 mg/d (n=6)**	**400/200 mg/d (n=21)**	**Placebo (n=33)**
TKV				
Baseline				
n	27	6	21	33
Median (range) TKV, mL	1358.75 (803.50−4064.95)	1378.05 (793.40 −2147.75)	1366.55 (803.70−2771.55)	1551.00 (814.55−3702.00)
Month 12				
n	26	4	21	30
Median (range) TKV, mL	1437.13 (737.90−4312.95)	1552.28 (937.40−2369.85)	1429.55 (719.55−2588.00)	1658.30 (838.30−3831.60)
Median (range) change from baseline, %	0.46 (–14.98−13.63)*	6.47 (–0.09 to 34.09)	1.448 (–10.87 to 24.46)	6.35 (–9.27 to 19.01)
End of initial treatment period				
n	23	3	20	30
Median (range) TKV, mL	1403.45 (730.45−4819.55)	849.10 (823.30−2546.50)	1313.78 (707.20−2636.45)	1727.30 (832.45−3945.35)
Median (range) change from baseline, %	5.29 (–17.50 to 26.34)†	–3.16 (–7.07 to 18.57)	0.06 (–15.85 to 17.03)	11.05 (–11.85 to 28.00)
eGFR				
Baseline				
n	27	6	21	33
Mean (SD) eGFR, mL/min/1.73 m^2	91.06 (16.32)	73.50 (16.74)	92.91 (22.39)	86.64 (15.50)
Month 12				
n	26	4	21	31
Mean (SD) eGFR, mL/min/1.73 m^2	84.72 (19.23)	66.81 (12.43)	81.39 (23.15)	87.72 (17.69)
Mean (SD) change from baseline, %	–6.91 (12.32)‡	–8.23 (11.07)	–12.48 (13.52)	1.52 (11.36)
Month 24				
n	23	3	20	30
Mean (SD) eGFR, mL/min/1.73 m^2	81.54 (21.31)	58.42 (12.23)	81.06 (25.68)	79.74 (18.10)
Mean (SD) change from baseline, %	–9.42 (16.88)§	–25.72 (11.75)	–14.62 (15.46)	–8.85 (14.20)
End of initial treatment period				
n	23	3	20	30
Mean (SD) eGFR, mL/min/1.73 m^2	85.01 (18.36)	66.77 (10.63)	84.31 (24.76)	84.95 (21.29)
Mean (SD) change from baseline, %	–5.45 (11.45)‖	–14.77 (10.24)	–10.40 (16.48)	–2.66 (21.64)

eGFR=estimated glomerular filtration rate; mITT=modified intent-to-treat population; TKV=total kidney volume.

*P=0.011 and †P=0.063 based on Wilcoxon Rank Sum test comparing percentage change in TKV from baseline for bosutinib 200 mg/d vs placebo.

‡P=0.024, §P=0.713, and ‖P=0.622 based on Wilcoxon Rank Sum test comparing percentage change in eGFR from baseline for bosutinib 200 mg/d vs placebo.

Table S2. Summary of TKV Over Time Stratified by Baseline TKV >1500 mL Versus ≥750 to 1500 mL

	Bosutinib			
	200 mg/d (n=27)	400 mg/d (n=7)	400/200 mg/d (n=21)	Placebo (n=33)
Baseline TKV >1500 mL				
Baseline				
n	11	3	10	18
Median (range) TKV, mL	2042.05 (1510.00− 4064.95)	1966.35 (1842.45−2147.75)	1767.88 (1549.55−2771.55)	2019.35 (1509.35− 3702.00)
Month 12				
n	11	2	10	16
Median (range) TKV, mL	2211.15 (1468.45− 4312.95)	2167.20 (1964.55−2369.85)	1863.90 (1478.15−2588.00)	2184.58 (1457.65− 3831.60)
Median (range) change from baseline, %	–2.40 (–9.28 to 13.06)	5.13 (–0.09 to 10.34)	0.28 (–10.87 to 24.46)	5.94 (–3.43 to 11.41)
End of initial treatment period				
n	9	1	9	16
Median (range) TKV, mL	2077.30 (1392.45−4819.55)	2546.50 (N/A)	1781.85 (1463.95−2636.45)	2379.10 (1461.55− 3945.35)
Median (range) change from baseline, %	5.29 (–7.78 to 26.34)	18.57 (N/A)	–0.61 (–12.44 to 17.03)	–3.45 (10.67−28.00)
Baseline TKV ≥750−1500 mL				
Baseline				
n	16	4	11	15
Median (range) TKV, mL	1057.38 (803.50−1437.65)	850.15 (793.40−913.65)	1132.65 (803.70−1366.55)	1186.85 (814.55−1408.00)
Month 12				
n	15	2	11	14
Median (range) TKV, mL	1078.85 (737.90−1461.60)	1038.70 (937.40−1140.00)	1144.10 (719.55−1429.55)	1210.95 (838.30−1604.25)
Median (range) change from baseline, %	0.922 (–14.98 to 13.63)	18.35 (2.60−34.09)	1.45 (–10.47 to 8.11)	6.97 (–9.27 to 19.01)
End of initial treatment period				
n	14	2	11	14
Median (range) TKV, mL	1084.93 (730.45−1474.40)	826.20 (823.30−849.10)	1022.70 (707.20−1357.70)	1296.75 (832.45−1711.20)
Median (range change from baseline, %	5.24 (–17.50 to 19.62)	–5.11 (–7.07 to –3.16)	0.74 (–15.85 to 10.49)	11.32 (–11.85 to 21.91)

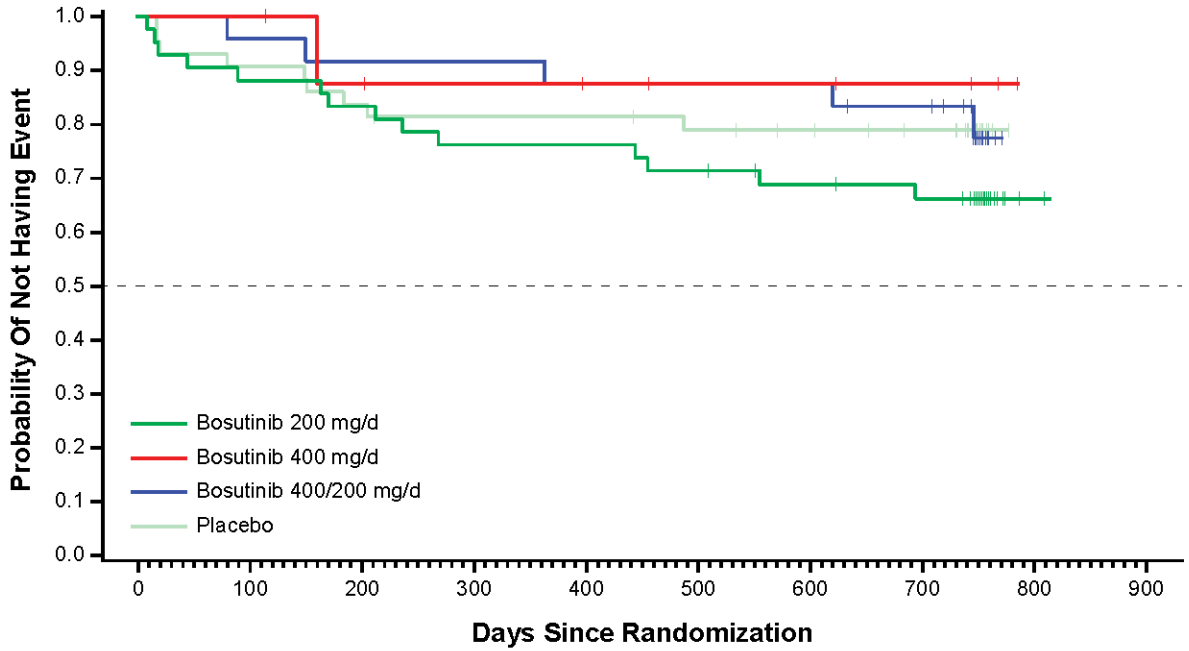
N/A=not applicable; TKV=total kidney volume.

Table S3. Treatment-Related TEAEs Occurring in ≥5% of the Safety Population

	Bosutinib									
	200 mg/d (n=58)		400 mg/d (n=31)		400/200 mg/d (n=24)		Placebo (n=56)		Total (n=169)	
TEAE, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	22 (38)	1 (2)	26 (84)	3 (10)	17 (71)	0	6 (11)	1 (2)	71 (42)	5 (3)
Nausea	17 (29)	0	15 (48)	0	12 (50)	0	7 (13)	0	51 (30)	0
ALT increased	18 (31)	4 (7)	16 (52)	4 (13)	12 (50)	2 (8)	2 (4)	0	48 (28)	10 (6)
AST increased	16 (28)	0	11 (36)	4 (13)	6 (25)	0	1 (2)	0	34 (20)	4 (2)
Vomiting	5 (9)	0	11 (36)	2 (7)	9 (38)	0	1 (2)	0	26 (15)	2 (1)
Abdominal pain upper	2 (3)	0	6 (19)	0	8 (33)	0	2 (4)	0	18 (11)	0
Blood CPK increased	8 (14)	0	3 (10)	0	4 (17)	0	3 (5)	0	18 (11)	0
Fatigue	2 (3)	0	8 (26)	0	1 (4)	0	5 (9)	0	16 (10)	0
Lipase increased	5 (9)	2 (3)	5 (16)	3 (10)	3 (13)	0	3 (5)	1 (2)	16 (10)	6 (4)
Abdominal pain	3 (5)	1 (2)	7 (23)	0	2 (8)	0	3 (5)	0	15 (9)	1 (1)
Headache	4 (7)	0	3 (10)	0	1 (4)	0	4 (7)	0	12 (7)	0
Anemia	5 (9)	0	3 (10)	0	3 (13)	1 (4)	0	0	11 (7)	1 (1)
Abdominal distension	3 (5)	0	2 (7)	0	1 (4)	0	3 (5)	0	9 (5)	0
Amylase increased	2 (3)	0	3 (10)	0	3 (13)	0	1 (2)	0	9 (5)	0
Dizziness	4 (7)	0	2 (7)	0	2 (8)	0	1 (2)	0	9 (5)	0
Dyspepsia	3 (5)	0	2 (7)	0	2 (8)	0	2 (4)	0	9 (5)	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; TEAE=treatment-emergent adverse event.

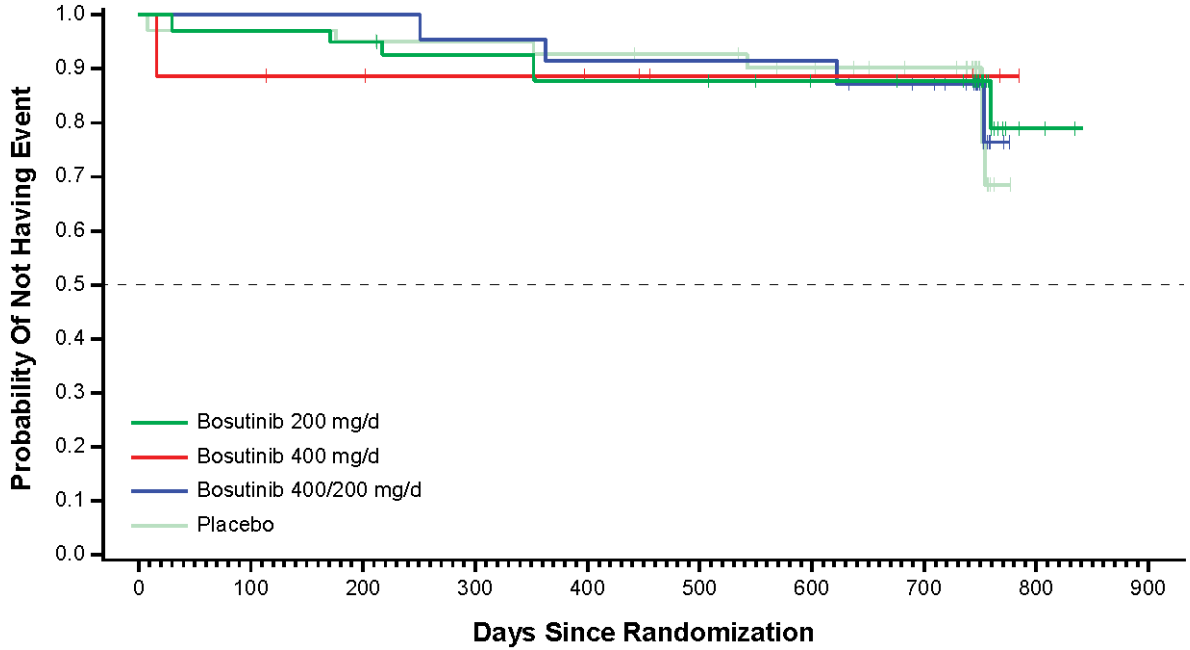
Figure S1. Kaplan-Meier Plot of Time to Onset or Worsening of Hypertension From Randomization



Patients at risk, n

Bosutinib 200 mg/d	42	37	35	32	32	30	27	25	1	0
Bosutinib 400 mg/d	9	9	7	6	5	4	4	3	0	0
Bosutinib 400/200 mg/d	24	23	22	22	21	21	21	19	0	0
Placebo	43	39	36	34	34	32	29	26	0	0

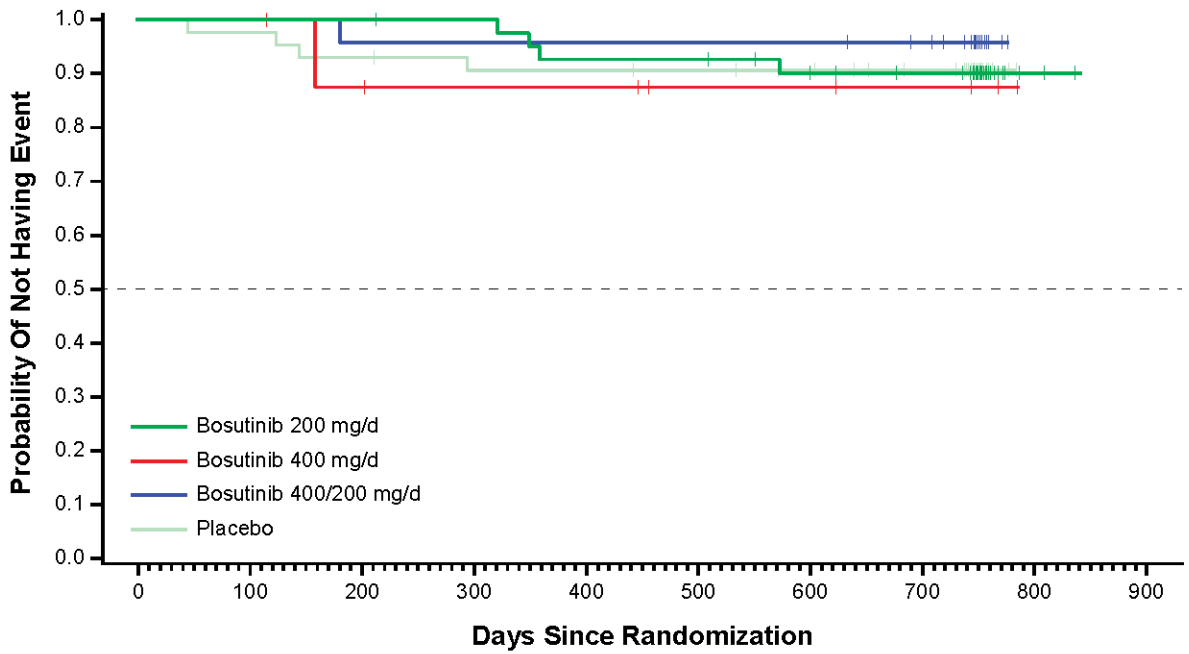
Figure S2. Kaplan-Meier Plot of Time to Onset or Worsening of Polycystic Kidney Disease–Related Chronic Back/Flank (Renal) Pain From Randomization



Patients at risk, n

Bosutinib 200 mg/d	42	41	40	38	36	36	33	31	2	0
Bosutinib 400 mg/d	9	8	7	6	5	3	3	3	0	0
Bosutinib 400/200 mg/d	24	24	24	23	22	22	22	19	0	0
Placebo	43	42	41	40	39	38	34	30	0	0

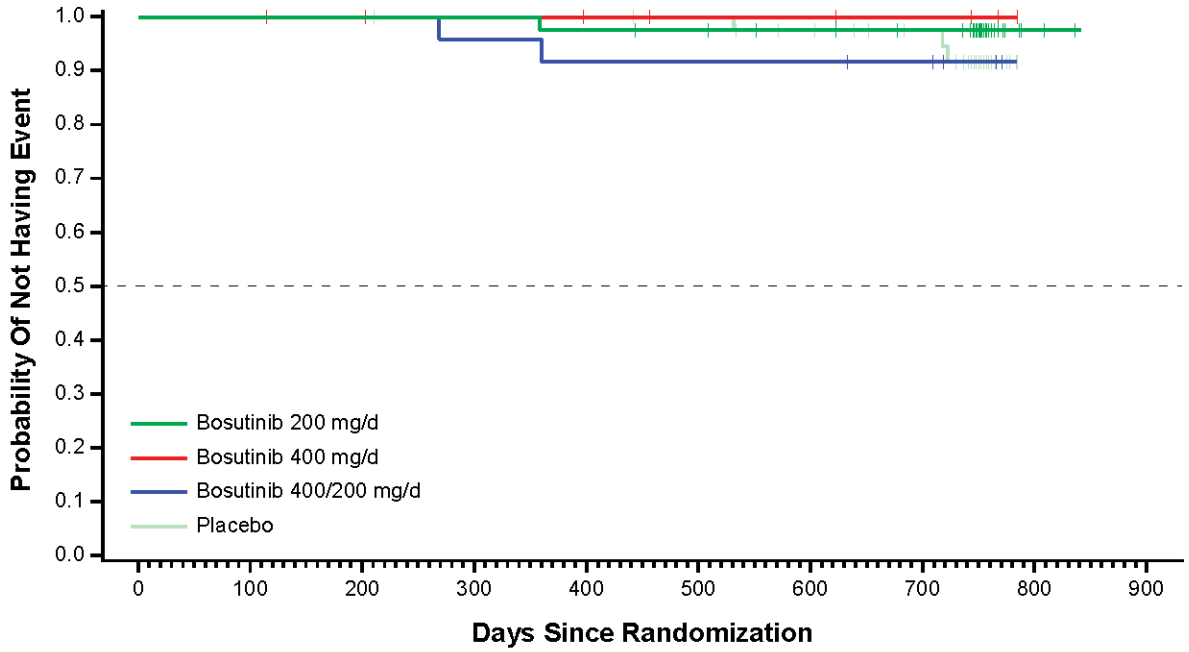
Figure S3. Kaplan-Meier Plot of Time to Onset or Worsening of Hematuria From Randomization



Patients at risk, n

Bosutinib 200 mg/d	42	42	42	41	38	38	34	32	2	0
Bosutinib 400 mg/d	9	9	7	6	6	4	4	3	0	0
Bosutinib 400/200 mg/d	24	24	23	23	23	23	23	21	0	0
Placebo	43	42	40	38	38	37	34	30	0	0

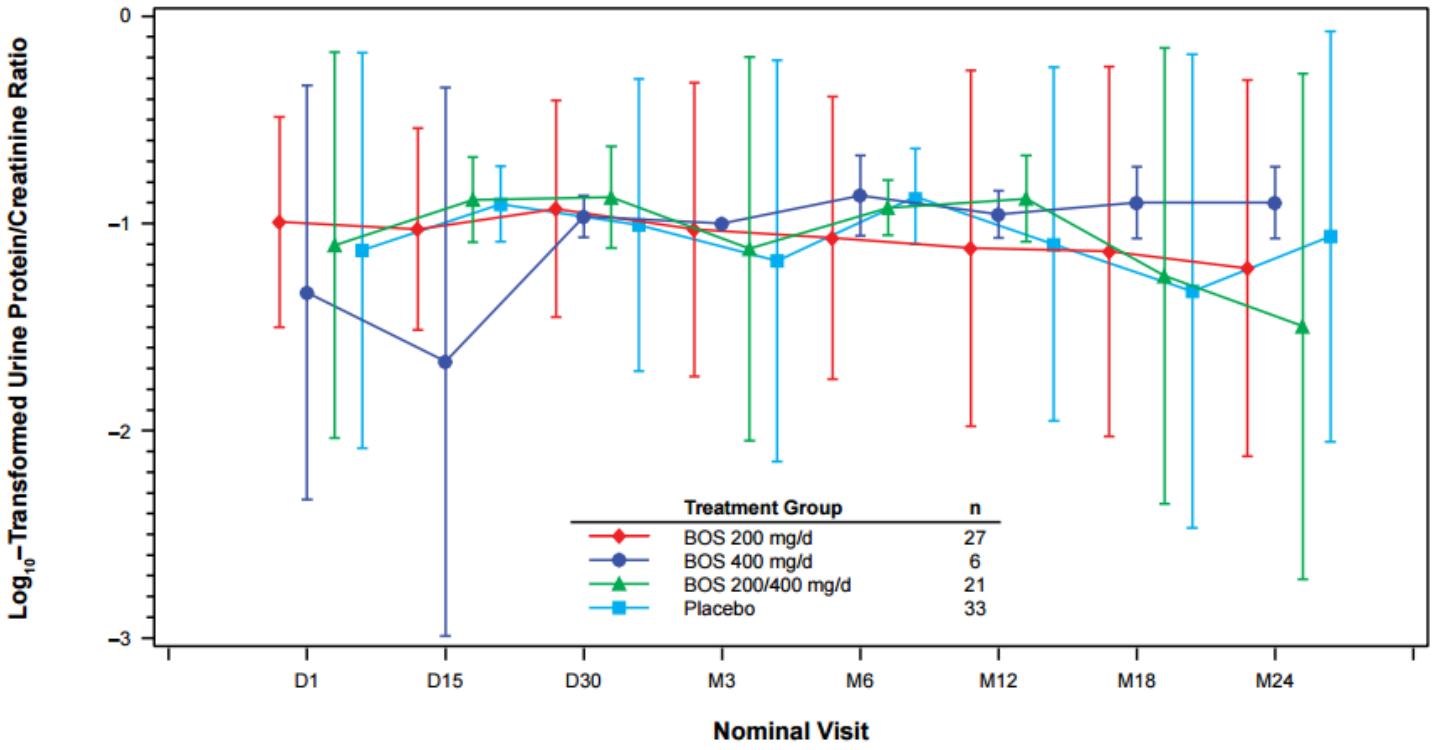
Figure S4. Kaplan-Meier Plot of Time to Onset or Worsening of Proteinuria From Randomization



Patients at risk, n

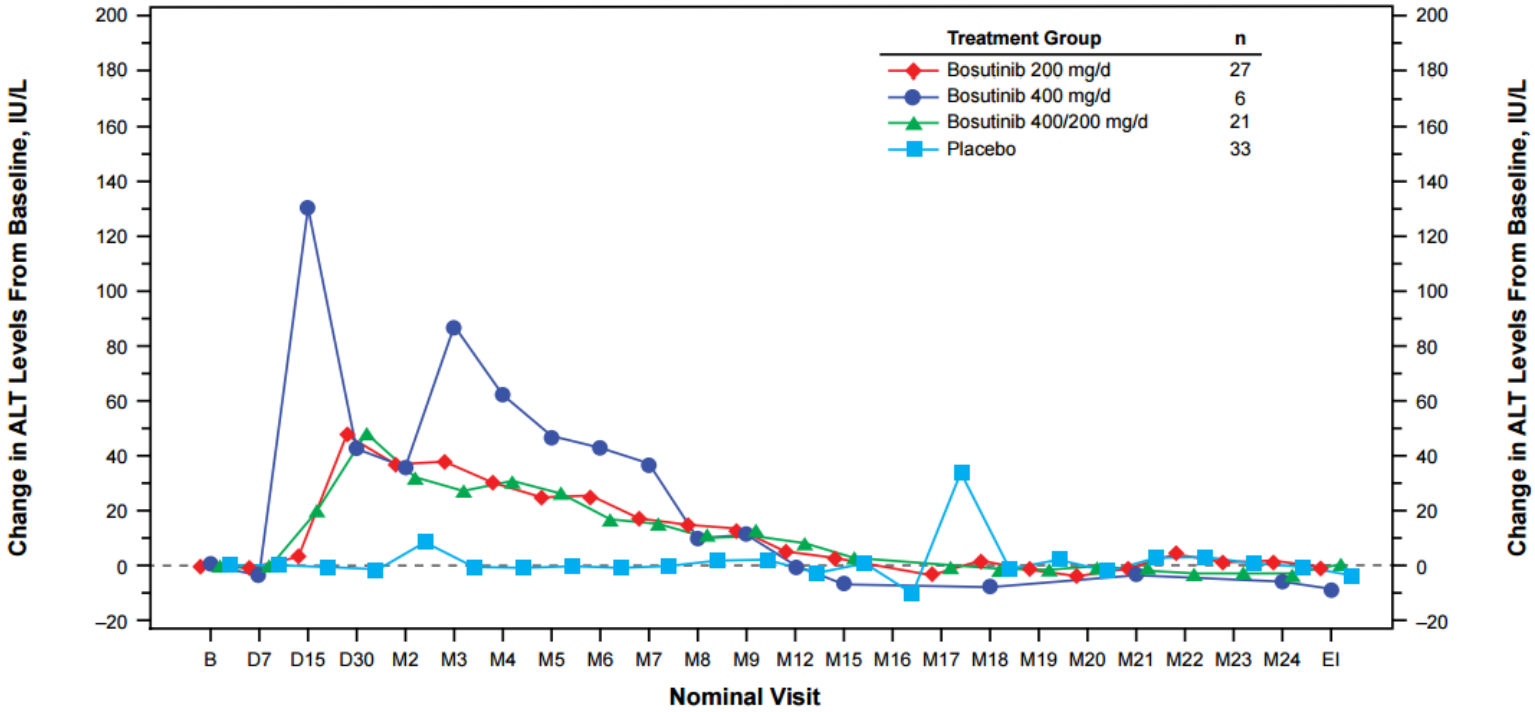
Bosutinib 200 mg/d	42	42	42	41	40	39	36	34	2	0
Bosutinib 400 mg/d	9	9	8	7	6	4	4	3	0	0
Bosutinib 400/200 mg/d	24	24	24	23	22	22	22	21	0	0
Placebo	43	43	43	42	42	41	37	33	0	0

Figure S5. Mean (SD) Log_{10}-Transformed Urine Protein/Creatinine Ratio by Treatment and Visit



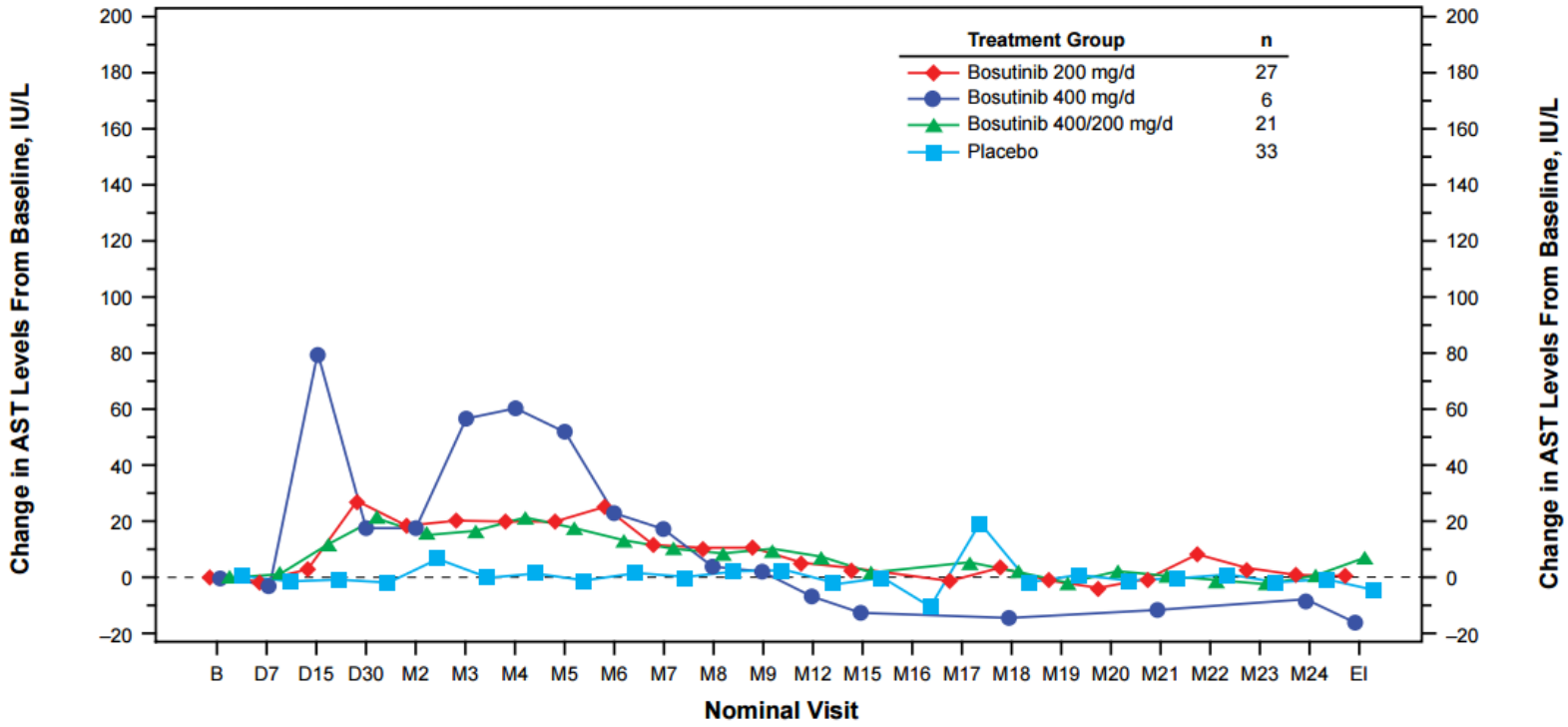
BOS=bosutinib; D=day; M=month.

Figure S6. Mean Change From Baseline in ALT Values Over Time by Treatment



ALT=alanine aminotransferase; B=baseline; D=day; EI=end of initial treatment; M=month.

Figure S7. Mean Change From Baseline in AST Values Over Time by Treatment



AST=aspartate aminotransferase; B=baseline; D=day; EI=end of initial treatment; M=month.