

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Repeated Oral Doses of Pazopanib on Cardiac Conduction in Patients with Solid Tumors

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ONLINE SUPPLEMENTARY MATERIAL

This study investigated the relationship between pazopanib treatment and QTc prolongation in patients with advanced cancer; a positive control (moxifloxacin) was included to validate the sensitivity of the analyses. The online supplementary tables provide additional results regarding the effects of moxifloxacin, specific electrocardiographic (ECG) abnormalities in pazopanib-treated patients, overall safety results, and additional ad-hoc analyses.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S1. Mean baseline Bazett-corrected QT Interval (QTcB) in msec (SD) by Treatment on Day 1 and by Treatment on Days 2 to 9**

Evaluable Population, N = 65				
Baseline (Day -1) Time Point, hr	Placebo_{moxi} (n = 31)	Moxi (n = 34)	Placebo_{paz} (n = 32)	Paz (n = 33)
-0.5	427.1 (19.2)	431.5 (21.1)	430.1 (20.3)	428.5 (20.3)
1	428.2 (19.3)	429.3 (23.2)	428.8 (23.5)	428.8 (19.1)
2	430.8 (17.5)	431.4 (24.5)	429.3 (24.9)	432.9 (17.2)
3	432.2 (18.6)	432.5 (22.0)	431.6 (23.6)	433.1 (16.8)
4	432.7 (16.7)	429.9 (23.4)	430.7 (23.4)	431.7 (17.4)
6	432.3 (18.1)	434.3 (25.3)	431.9 (24.0)	434.7 (20.2)
8	428.9 (18.9)	428.6 (24.0)	427.4 (24.1)	430.0 (19.1)
Intent-to-Treat Population, N = 96				
	Placebo_{moxi} (n = 48)	Moxi (n = 48)	Placebo_{paz} (n = 47)	Paz (n = 48)
-0.5	424.7 (17.8)	432.7 (21.3)	429.3 (20.2)	428.3 (19.0)
1	426.6 (18.6)	431.1 (23.0)	429.4 (22.5)	428.9 (19.3)
2	428.6 (17.4)	431.5 (24.3)	429.7 (23.2)	431.4 (18.0)
3	430.0 (17.1)	433.3 (22.2)	431.9 (22.3)	432.2 (16.6)
4	431.2 (16.1)	431.9 (23.3)	431.9 (22.3)	431.8 (17.2)
6	431.7 (16.8)	435.0 (24.2)	432.7 (21.3)	434.8 (19.9)
8	428.0 (17.2)	429.3 (24.6)	428.5 (22.9)	429.6 (19.0)

Abbreviations: Moxi, moxifloxacin; Paz, pazopanib; SD, standard deviation.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S2. Mean baseline Fridericia-corrected QT Interval (QTcF) in msec (SD) by Treatment on Day 1 and by Treatment on Days 2 to 9**

Evaluable Population, N = 65				
Baseline (Day -1) Time Point, hr	Placebo_{moxi} (n = 31)	Moxi (n = 34)	Placebo_{paz} (n = 32)	Paz (n = 33)
-0.5	409.1 (19.0)	414.7 (17.1)	415.9 (21.4)	408.5 (14.5)
1	413.6 (16.5)	416.2 (17.8)	416.8 (20.8)	413.2 (12.6)
2	415.2 (15.8)	417.0 (18.9)	417.4 (22.1)	414.9 (11.2)
3	416.0 (16.2)	417.4 (19.0)	418.4 (21.6)	415.1 (12.7)
4	415.9 (16.3)	413.0 (18.0)	416.4 (20.8)	412.4 (12.6)
6	411.9 (16.9)	416.8 (21.0)	415.8 (22.0)	413.2 (16.2)
8	409.4 (16.8)	413.8 (19.8)	414.0 (21.2)	409.4 (15.2)
Intent-to-Treat Population, N = 96				
	Placebo_{moxi} (n = 48)	Moxi (n = 48)	Placebo_{paz} (n = 47)	Paz (n = 48)
-0.5	408.7 (17.0)	415.3 (17.9)	414.8 (20.7)	409.6 (13.7)
1	413.7 (15.2)	417.3 (18.4)	417.5 (20.1)	414.0 (12.7)
2	414.8 (14.6)	416.1 (19.2)	417.2 (20.2)	414.5 (12.2)
3	416.2 (15.1)	417.9 (19.4)	419.1 (20.8)	415.7 (12.5)
4	415.2 (14.9)	415.1 (18.9)	417.1 (20.4)	413.9 (12.1)
6	412.0 (15.3)	417.0 (20.0)	415.4 (19.6)	414.5 (15.7)
8	409.1 (15.0)	413.3 (20.3)	413.0 (20.5)	410.2 (14.3)

Abbreviations: Moxi, moxifloxacin; Paz, pazopanib; SD, standard deviation.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S3. Least-Squares Mean Difference in QTc Change from Baseline for Patients Receiving Moxifloxacin Compared with Placebo**

Evaluable Population, N = 65			
Day 1 Time Point, hr	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	-1.45 (-8.04, 5.14)	1.54 (-5.21, 8.30)	0.12 (-7.22, 7.47)
1	5.94 (-0.47, 12.36)	7.39 (0.85, 13.93)	7.21 (0.01, 14.41)
2	5.28 (-1.13, 11.70)	4.40 (-2.14, 10.94)	6.00 (-1.20, 13.20)
3	10.61 (4.20, 17.03)	11.70 (5.17, 18.24)	11.92 (4.73, 19.11)
4	9.30 (2.89, 15.72)	10.13 (3.59, 16.68)	9.42 (2.23, 16.61)
6	6.93 (0.51, 13.35)	6.88 (0.34, 13.42)	7.75 (0.56, 14.95)
8	9.26 (2.84, 15.68)	13.17 (6.63, 19.71)	11.09 (3.89, 18.28)

Intent-to-Treat Population, N = 96			
	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	0.53 (-5.12, 6.17)	0.68 (-4.87, 6.24)	0.82 (-5.06, 6.70)
1	8.12 (2.63, 13.61)	8.60 (3.25, 13.95)	8.34 (2.61, 14.07)
2	8.85 (3.36, 14.34)	8.65 (3.30, 14.00)	8.86 (3.14, 14.59)
3	10.76 (5.27, 16.25)	11.93 (6.58, 17.28)	11.41 (5.69, 17.14)
4	10.26 (4.78, 15.74)	11.14 (5.79, 16.48)	10.11 (4.40, 15.83)
6	10.85 (5.36, 16.34)	10.50 (5.16, 15.85)	10.51 (4.79, 16.23)
8	11.32 (5.82, 16.81)	12.86 (7.50, 18.21)	11.42 (5.70, 17.14)

Abbreviations: CI, confidence interval; QTcB, Bazett-corrected QT interval; QTcF, Fridericia-corrected QT interval; QTci, calculated individual QT interval.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S4. Least-Squares Mean Difference in QTc Change from Baseline for Patients Receiving Pazopanib Compared with Placebo**

Day 9 Time Point, hr	Evaluable Population, N = 65		
	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	-0.20 (-7.10, 6.70)	-1.29 (-8.83, 6.26)	-0.89 (-8.50, 6.73)
1	3.96 (-2.82, 10.74)	-0.99 (-8.39, 6.41)	1.85 (-5.65, 9.35)
2	1.96 (-4.82, 8.74)	-1.89 (-9.30, 5.52)	0.51 (-6.99, 8.00)
3	2.10 (-4.69, 8.88)	-2.08 (-9.48, 5.33)	0.73 (-6.77, 8.23)
4	1.42 (-5.36, 8.21)	-2.36 (-9.77, 5.04)	0.22 (-7.29, 7.72)
6	4.33 (-2.45, 11.11)	-2.99 (-10.39, 4.42)	1.22 (-6.28, 8.72)
8	4.43 (-2.36, 11.22)	-3.21 (-10.61, 4.19)	1.71 (-5.79, 9.21)

Day 9 Time Point, hr	Intent-to-Treat Population, N = 96		
	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	0.48 (-5.22, 6.19)	-1.48 (-7.83, 4.88)	-1.90 (-8.56, 4.76)
1	2.89 (-2.70, 8.48)	-2.55 (-8.76, 3.65)	1.06 (-6.50, 6.61)
2	1.20 (-4.42, 6.82)	-3.28 (-9.53, 2.97)	-1.20 (-7.78, 5.38)
3	2.16 (-3.47, 7.78)	-3.11 (-9.36, 3.14)	-0.45 (-7.03, 6.14)
4	0.42 (-5.20, 6.05)	-4.00 (-10.24, 2.24)	-1.93 (-8.51, 4.66)
6	3.66 (-1.96, 9.28)	-4.48 (-10.72, 1.76)	-0.31 (-6.89, 6.27)
8	4.33 (-1.29, 9.94)	-5.06 (-11.29, 1.18)	0.52 (-6.05, 7.10)

Regression Analysis for Dependence of QT Correction on RR at Baseline (Intent-to-Treat Population, N = 96)		
QTcF Regression Coefficient (95% CI)	QTcB Regression Coefficient (95% CI)	QTci Regression Coefficient (95% CI)
0.033 (0.024, 0.042)	-0.05 (-0.059, -0.041)	0.005 (-0.003, 0.014)

Abbreviations: CI, confidence interval; QTcB, Bazett-corrected QT interval; QTcF, Fridericia-corrected QT interval; QTci, calculated individual QT interval.

Supplementary Table S5. Holter ECG Abnormalities for Pazopanib-Treated Patients in the Intent-to-Treat Population^a

Abnormality	Pazopanib-Treated Patients, n (%)	
	Baseline (n = 48)	Day 9 (n = 48)
Sinus bradycardia	3 (6)	7 (16)
Ectopic supraventricular beats	3 (6)	6 (14)
First degree AV block ^b	1 (2)	3 (7)
T-wave inversion	1 (2)	4 (9)
T waves flat	4 (8)	8 (18)
T waves biphasic	1 (2)	3 (7)
ST depression	2 (4)	3 (7)

Abbreviations: AV, atrioventricular; ECG, electrocardiogram.

^a Only those abnormalities that increased relative to placebo are listed.

^b PR interval >200 msec.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S6: Treatment-Emergent Adverse Events Among Patients Receiving Either Pazopanib or Placebo**

Adverse Event	Patients, <i>n</i> (%)	
	Pazopanib (<i>n</i> = 48)	Placebo (<i>n</i> = 47)
Fatigue	13 (27)	5 (11)
Nausea	12 (25)	3 (6)
Decreased appetite	8 (17)	1 (2)
Hypertension	7 (15)	0
Weight decreased	5 (10)	0
Diarrhea	4 (8)	1 (2)
Dyspnea	3 (6)	2 (4)
Constipation	3 (6)	2 (4)
Vomiting	3 (6)	0
Paraesthesia	3 (6)	0
Dysphonia	3 (6)	0
Abdominal pain	3 (6)	0
Headache	2 (4)	1 (2)
Pyrexia	2 (4)	1 (2)
Back pain	2 (4)	3 (6)
ALT increased	2 (4)	0
AST increased	2 (4)	0
Dizziness	2 (4)	0
Feeling cold	2 (4)	0
Hypokalemia	1 (2)	4 (9)
Upper abdominal pain	1 (2)	2 (4)
Frequent bowel movements	1 (2)	2 (4)
Hypomagnesemia	1 (2)	1 (2)
Blood alkaline phosphatase increased	1 (2)	1 (2)
Blurred vision	1 (2)	1 (2)
Musculoskeletal pain	0	2 (4)
Hematochezia	0	2 (4)
Hemoptysis	0	2 (4)
Anemia	0	2 (4)
Arthralgia	0	2 (4)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S7. Post-Hoc (0 - 24 hr) Analysis of Least-Squares Mean Difference in Heart Rate Changes from Baseline after Pazopanib Compared with Placebo**

Day 9 Time Point, hr	Evaluable Population, N = 57 ^a	
	Heart Rate Mean Difference in bpm (90% CI)	
-0.5	-0.43 (-5.40, 4.53)	
1	-4.58 (-9.72, 0.56)	
2	-3.48 (-7.87, 0.91)	
3	-3.98 (-8.49, 0.54)	
4	-2.75 (-7.20, 1.70)	
6	-5.43 (-10.89, 0.02)	
8	-7.39 (-12.29, -2.49)	
12	-5.37 (-10.82, 0.09)	
16	-10.11 (-14.85, -5.37)	
20	-0.42 (-7.60, 6.77)	
24	-4.16 (-11.40, 3.07)	
	Intent-to-Treat Population, N = 96	
	Heart Rate Mean Difference in bpm (90% CI)	
-0.5	-1.88 (-5.72, 1.97)	
1	-5.62 (-9.65, -1.59)	
2	-4.52 (-7.95, -1.08)	
3	-5.45 (-8.97, -1.94)	
4	-5.08 (-8.76, -1.40)	
6	-8.90 (-13.31, -4.49)	
8	-10.33 (-14.17, -6.49)	
12	-7.35 (-11.70, -3.00)	
16	-13.28 (-17.18, -9.37)	
20	-4.03 (-9.82, 1.76)	
24	-5.97 (-11.57, -0.37)	

^a In this analysis, an additional 8 patients were deemed nonevaluable because of Holter recording technical problems.

Abbreviations: bpm, beats per minute; CI, confidence interval.

*Cancer Chemotherapy and Pharmacology***Supplementary Table S8. Post-Hoc (0 - 24 hr) Analysis of Least-Squares Mean Difference in QTc Change from Baseline for Patients Receiving Pazopanib Compared with Placebo**

Evaluable Population, N = 57^a			
Day 9 Time Point, hr	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	-0.46 (-6.66, 5.74)	-2.14 (-9.12, 4.84)	-2.46 (-9.03, 4.11)
1	3.80 (-2.20, 9.80)	-2.00 (-8.75, 4.75)	-0.52 (-6.91, 5.86)
2	0.54 (-5.45, 6.54)	-4.50 (-11.24, 2.25)	-2.65 (-9.02, 3.73)
3	0.28 (-5.72, 6.27)	-5.25 (-12.00, 1.49)	-3.48 (-9.86, 2.90)
4	-0.76 (-6.75, 5.24)	-4.83 (-11.57, 1.92)	-2.95 (-9.34, 3.44)
6	3.03 (-2.96, 9.02)	-4.21 (-10.95, 2.53)	-1.90 (-8.28, 4.48)
8	4.05 (-1.95, 10.05)	-4.95 (-11.69, 1.79)	-1.16 (-7.54, 5.22)
12	-1.70 (-7.71, 4.31)	-8.58 (-15.32, -1.83)	-5.97 (-12.36, 0.42)
16	-1.97 (-8.00, 4.07)	-14.43 (-21.19, -7.68)	-8.97 (-15.37, -2.57)
20	1.51 (-4.50, 7.51)	-1.70 (-8.44, 5.05)	-1.84 (-8.23, 4.54)
24	4.11 (-1.88, 10.10)	-0.37 (-7.11, 6.37)	0.44 (-5.94, 6.82)

Intent-to-Treat Population, N = 96			
	QTcF, msec Mean Difference (90% CI)	QTcB, msec Mean Difference (90% CI)	QTci, msec Mean Difference (90% CI)
-0.5	0.78 (-4.23, 5.78)	-2.11 (-7.63, 3.41)	-1.92 (-7.71, 3.86)
1	3.60 (-1.99, 9.20)	-2.22 (-7.53, 3.09)	0.41 (-5.22, 6.03)
2	1.92 (-3.18, 7.01)	-3.21 (-8.57, 2.16)	-0.82 (-6.49, 4.85)
3	2.76 (-2.61, 8.13)	-2.88 (-8.24, 2.49)	-0.70 (-6.37, 4.97)
4	1.21 (-4.07, 6.48)	-3.68 (-9.04, 1.68)	-1.67 (-7.33, 4.00)
6	4.18 (-1.28, 9.64)	-4.59 (-9.95, 0.77)	-1.38 (-7.04, 4.28)
8	4.93 (-0.07, 9.94)	-5.14 (-10.49, 0.21)	-0.32 (-5.98, 5.33)
12	0.90 (-4.78, 6.57)	-6.29 (-11.64, -0.95)	-3.01 (-8.67, 2.64)
16	0.72 (-5.34, 6.78)	-12.12 (-17.49, -6.74)	-6.58 (-12.26, -0.90)
20	3.87 (-2.31, 10.05)	-0.91 (-6.35, 4.53)	0.17 (-5.55, 5.58)
24	4.44 (-0.94, 9.82)	-0.90 (-6.34, 4.54)	-0.62 (-6.35, 5.10)

Abbreviations: QTcB, Bazett-corrected QT interval; QTcF, Fridericia-corrected QT interval; QTci, calculated individual QT interval.

^a In this analysis, an additional 8 patients were deemed nonevaluable because of Holter recording technical problems.