

14.3. Pharmacokinetics Data Summary Tables and Figures

Table 14.3.1.1
Lonafarnib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	50 mg QD (N=2)	50 mg BID (N=2)	75 mg QD (N=1)	75 mg BID (N=1)	100 mg BID (N=9)	Overall (N=15)
Pre-Dose						
N	2	2	1	1	8	14
Mean (SD)	1115.0 (134.35)	2630.0 (1909.19)	1310.0 ()	3460.0 ()	3337.5 (1346.58)	2782.9 (1442.62)
Median	1115.0	2630.0	1310.0	3460.0	3070.0	2730.0
Min, Max	1020.0, 1210.0	1280.0, 3980.0	1310.0, 1310.0	3460.0, 3460.0	1720.0, 5770.0	1020.0, 5770.0
0.5 Hour Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1043.5 (65.76)	2635.0 (2043.54)	1130.0 ()	3320.0 ()	3118.9 (1216.68)	2658.5 (1360.72)
Median	1043.5	2635.0	1130.0	3320.0	2840.0	2830.0
Min, Max	997.0, 1090.0	1190.0, 4080.0	1130.0, 1130.0	3320.0, 3320.0	1720.0, 5380.0	997.0, 5380.0
1.0 Hour Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1065.0 (21.21)	2610.0 (1951.61)	1230.0 ()	3360.0 ()	3218.9 (1279.93)	2727.3 (1396.07)
Median	1065.0	2610.0	1230.0	3360.0	3050.0	2760.0
Min, Max	1050.0, 1080.0	1230.0, 3990.0	1230.0, 1230.0	3360.0, 3360.0	1700.0, 5700.0	1050.0, 5700.0
2.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1175.0 (190.92)	2555.0 (1873.83)	1210.0 ()	3730.0 ()	3303.3 (1136.38)	2808.7 (1335.02)
Median	1175.0	2555.0	1210.0	3730.0	3010.0	2690.0
Min, Max	1040.0, 1310.0	1230.0, 3880.0	1210.0, 1210.0	3730.0, 3730.0	1990.0, 5580.0	1040.0, 5580.0

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Lonafarnib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	50 mg QD (N=2)	50 mg BID (N=2)	75 mg QD (N=1)	75 mg BID (N=1)	100 mg BID (N=9)	Overall (N=15)
3.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1355.0 (304.06)	2535.0 (1732.41)	1310.0 ()	3700.0 ()	3595.6 (1393.87)	3010.0 (1488.48)
Median	1355.0	2535.0	1310.0	3700.0	3100.0	3020.0
Min, Max	1140.0, 1570.0	1310.0, 3760.0	1310.0, 1310.0	3700.0, 3700.0	2040.0, 6660.0	1140.0, 6660.0
4.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1395.0 (431.34)	2805.0 (2085.97)	1610.0 ()	3500.0 ()	3701.1 (1372.56)	3121.3 (1493.37)
Median	1395.0	2805.0	1610.0	3500.0	3410.0	3340.0
Min, Max	1090.0, 1700.0	1330.0, 4280.0	1610.0, 1610.0	3500.0, 3500.0	2040.0, 6610.0	1090.0, 6610.0
6.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1485.0 (219.20)	2995.0 (2199.10)	1820.0 ()	3440.0 ()	3775.6 (1296.23)	3213.3 (1445.01)
Median	1485.0	2995.0	1820.0	3440.0	3360.0	3330.0
Min, Max	1330.0, 1640.0	1440.0, 4550.0	1820.0, 1820.0	3440.0, 3440.0	2080.0, 6430.0	1330.0, 6430.0
8.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1555.0 (91.92)	3085.0 (2227.39)	1750.0 ()	3390.0 ()	3748.9 (1389.90)	3210.7 (1481.10)
Median	1555.0	3085.0	1750.0	3390.0	3320.0	3210.0
Min, Max	1490.0, 1620.0	1510.0, 4660.0	1750.0, 1750.0	3390.0, 3390.0	2110.0, 6660.0	1490.0, 6660.0

Table 14.3.1.1
Lonafarnib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	50 mg QD (N=2)	50 mg BID (N=2)	75 mg QD (N=1)	75 mg BID (N=1)	100 mg BID (N=9)	Overall (N=15)
10.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1435.0 (77.78)	2830.0 (2135.46)	1790.0 ()	3640.0 ()	3574.4 (1278.71)	3075.3 (1398.00)
Median	1435.0	2830.0	1790.0	3640.0	3280.0	3200.0
Min, Max	1380.0, 1490.0	1320.0, 4340.0	1790.0, 1790.0	3640.0, 3640.0	2090.0, 6160.0	1320.0, 6160.0
12.0 Hours Post-Dose						
N	2	2	1	1	9	15
Mean (SD)	1345.0 (21.21)	2705.0 (2199.10)	1670.0 ()	3550.0 ()	3393.3 (1252.40)	2924.0 (1373.57)
Median	1345.0	2705.0	1670.0	3550.0	3050.0	3020.0
Min, Max	1330.0, 1360.0	1150.0, 4260.0	1670.0, 1670.0	3550.0, 3550.0	1920.0, 5890.0	1150.0, 5890.0

Table 14.3.1.2
Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
Pre-Dose			
N	3	11	14
Mean (SD)	124.7 (42.68)	1012.3 (912.48)	822.1 (885.21)
Median	101.0	725.0	519.0
Min, Max	99.2, 174.0	113.0, 3320.0	99.2, 3320.0
0.5 Hour Post-Dose			
N	3	12	15
Mean (SD)	98.6 (18.54)	890.4 (883.68)	732.1 (849.17)
Median	88.5	594.5	402.0
Min, Max	87.3, 120.0	208.0, 3350.0	87.3, 3350.0
1.0 Hour Post-Dose			
N	3	12	15
Mean (SD)	94.9 (9.82)	1149.6 (1197.06)	938.7 (1147.42)
Median	97.8	643.5	586.0
Min, Max	84.0, 103.0	139.0, 4470.0	84.0, 4470.0
2.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	347.1 (344.03)	1411.7 (815.89)	1198.8 (856.86)
Median	223.0	1400.0	986.0
Min, Max	82.4, 736.0	202.0, 2900.0	82.4, 2900.0

Table 14.3.1.2
Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
3.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	846.3 (1040.52)	1701.0 (987.83)	1530.1 (1023.03)
Median	368.0	1470.0	1230.0
Min, Max	131.0, 2040.0	273.0, 3120.0	131.0, 3120.0
4.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	811.0 (638.77)	1595.3 (1054.85)	1438.4 (1018.82)
Median	594.0	1250.0	1150.0
Min, Max	309.0, 1530.0	236.0, 3910.0	236.0, 3910.0
6.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	671.7 (190.42)	1275.8 (822.24)	1155.0 (773.92)
Median	710.0	1135.0	1080.0
Min, Max	465.0, 840.0	418.0, 3230.0	418.0, 3230.0
8.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	692.3 (304.95)	942.0 (545.65)	892.1 (507.84)
Median	610.0	862.5	802.0
Min, Max	437.0, 1030.0	200.0, 1960.0	200.0, 1960.0

Table 14.3.1.2
Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

Time Point	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
10.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	435.3 (103.04)	766.0 (453.57)	699.9 (426.50)
Median	432.0	816.5	551.0
Min, Max	334.0, 540.0	132.0, 1500.0	132.0, 1500.0
12.0 Hours Post-Dose			
N	3	12	15
Mean (SD)	324.0 (83.74)	558.3 (352.38)	511.5 (328.61)
Median	286.0	483.5	441.0
Min, Max	266.0, 420.0	107.0, 1180.0	107.0, 1180.0

Table 14.3.2.1
Lonafarnib Plasma Trough Concentrations (ng/mL) by Dose Level and Visit
(Pharmacokinetic Analysis Set)

Visit	50 mg (N=15)	75 mg (N=13)	100 mg (N=10)	Overall (N=15)
Week 2				
N	12			12
Mean (SD)	1789.5 (729.39)			1789.5 (729.39)
Median	1650.0			1650.0
Min, Max	934.0, 3700.0			934.0, 3700.0
Week 4				
N	1	11		12
Mean (SD)	4250.0 ()	1707.3 (526.16)		1919.2 (889.08)
Median	4250.0	1710.0		1710.0
Min, Max	4250.0, 4250.0	1160.0, 2600.0		1160.0, 4250.0
Week 6				
N	1	4	7	12
Mean (SD)	4440.0 ()	3222.5 (985.85)	1987.1 (759.69)	2603.3 (1125.86)
Median	4440.0	3140.0	1990.0	2585.0
Min, Max	4440.0, 4440.0	2120.0, 4490.0	860.0, 2940.0	860.0, 4490.0
Week 8				
N	1	1	10	12
Mean (SD)	1500.0 ()	3320.0 ()	3046.0 (1002.17)	2940.0 (1016.65)
Median	1500.0	3320.0	2955.0	2955.0
Min, Max	1500.0, 1500.0	3320.0, 3320.0	1700.0, 5080.0	1500.0, 5080.0

Patients are summarized under the dose received at the corresponding visit.
Patients on QD dosing excluded.

Table 14.3.2.1
Lonafarnib Plasma Trough Concentrations (ng/mL) by Dose Level and Visit
(Pharmacokinetic Analysis Set)

Visit	50 mg (N=15)	75 mg (N=13)	100 mg (N=10)	Overall (N=15)
Week 12				
N	2	1	8	11
Mean (SD)	2760.0 (2163.75)	1410.0 ()	3005.0 (1495.72)	2815.5 (1503.69)
Median	2760.0	1410.0	2705.0	2400.0
Min, Max	1230.0, 4290.0	1410.0, 1410.0	1210.0, 6070.0	1210.0, 6070.0
Week 16				
N	2	2	7	11
Mean (SD)	3055.0 (2708.22)	3135.0 (445.48)	2344.3 (914.89)	2617.3 (1183.05)
Median	3055.0	3135.0	1870.0	2820.0
Min, Max	1140.0, 4970.0	2820.0, 3450.0	1430.0, 3770.0	1140.0, 4970.0

Patients are summarized under the dose received at the corresponding visit.
Patients on QD dosing excluded.

Table 14.3.2.2
Ritonavir Plasma Trough Concentrations (ng/mL) by Dose Level and Visit
(Pharmacokinetic Analysis Set)

Visit	100 mg (N=15)		
Week 2			
N	12		
Mean (SD)	802.9 (761.82)		
Median	481.0		
Min, Max	95.5, 2530.0		
Week 4			
N	12		
Mean (SD)	769.2 (740.55)		
Median	526.5		
Min, Max	162.0, 2600.0		
Week 6			
N	12		
Mean (SD)	613.8 (569.91)		
Median	489.5		
Min, Max	45.2, 2160.0		
Week 8			
N	12		
Mean (SD)	569.0 (433.48)		
Median	475.0		
Min, Max	113.0, 1640.0		

Patients on QD dosing excluded.

Table 14.3.2.2
Ritonavir Plasma Trough Concentrations (ng/mL) by Dose Level and Visit
(Pharmacokinetic Analysis Set)

Visit	100 mg (N=15)
Week 12	
N	11
Mean (SD)	618.5 (574.92)
Median	341.0
Min, Max	99.7, 1820.0
Week 16	
N	11
Mean (SD)	703.7 (820.04)
Median	431.0
Min, Max	67.8, 3030.0

Patients on QD dosing excluded.

Table 14.3.3.1
Lonafarnib Pharmacokinetic Parameters by Dose Level
(Pharmacokinetic Analysis Set)

Parameter (unit)	50 mg QD (N=2)	50 mg BID (N=2)	75 mg QD (N=1)	75 mg BID (N=1)	100 mg BID (N=9)	Overall (N=15)
AUC 0-tau (ng*hr/mL)						
N	2	2	1	1	9	15
Mean (SD)	16517 (1816.2)	33755 (25021)	19140 ()	42215 ()	42701 (15655)	36414 (17079)
CV (%)	11.0	74.1			36.7	46.9
Median	16517	33755	19140	42215	38488	36535
Min, Max	15233, 17801	16063, 51448	19140, 19140	42215, 42215	24135, 74954	15233, 74954
Average Concentration (ng/mL)						
N	2	2	1	1	9	15
Mean (SD)	1376 (151.35)	2813 (2085.1)	1595 ()	3518 ()	3558 (1304.6)	3034 (1423.2)
CV (%)	11.0	74.1			36.7	46.9
Median	1376	2813	1595	3518	3207	3045
Min, Max	1269, 1483	1339, 4287	1595, 1595	3518, 3518	2011, 6246	1269, 6246
CL/F (L/hr)						
N	2	2	1	1	9	15
Mean (SD)	3.0 (0.33)	2.0 (1.51)	3.9 ()	1.8 ()	2.6 (0.86)	2.6 (0.91)
CV (%)	11.0	74.1			32.9	34.9
Median	3.0	2.0	3.9	1.8	2.6	2.7
Min, Max	2.8, 3.3	1.0, 3.1	3.9, 3.9	1.8, 1.8	1.3, 4.1	1.0, 4.1
Cmax (ng/mL)						
N	2	2	1	1	9	15
Mean (SD)	1595 (148.49)	3085 (2227.4)	1820 ()	3730 ()	3889 (1362.1)	3327 (1493.3)
CV (%)	9.3	72.2			35.0	44.9
Median	1595	3085	1820	3730	3470	3410
Min, Max	1490, 1700	1510, 4660	1820, 1820	3730, 3730	2110, 6660	1490, 6660

Table 14.3.3.1
Lonafarnib Pharmacokinetic Parameters by Dose Level
(Pharmacokinetic Analysis Set)

Parameter (unit)	50 mg QD (N=2)	50 mg BID (N=2)	75 mg QD (N=1)	75 mg BID (N=1)	100 mg BID (N=9)	Overall (N=15)
Trough Concentration (ng/mL)						
N	2	2	1	1	9	15
Mean (SD)	1345 (21.21)	2705 (2199.1)	1670 ()	3550 ()	3393 (1252.4)	2924 (1373.6)
CV (%)	1.6	81.3			36.9	47.0
Median	1345	2705	1670	3550	3050	3020
Min, Max	1330, 1360	1150, 4260	1670, 1670	3550, 3550	1920, 5890	1150, 5890
Tmax (hr)						
N	2	2	1	1	9	15
Mean (SD)	6.0 (2.83)	8.0 (0.00)	6.0 ()	2.0 ()	5.2 (2.05)	5.5 (2.20)
CV (%)	47.1	0.0			39.2	39.8
Median	6.0	8.0	6.0	2.0	6.0	6.0
Min, Max	4.0, 8.0	8.0, 8.0	6.0, 6.0	2.0, 2.0	3.0, 8.0	2.0, 8.0

Table 14.3.3.2
Ritonavir Pharmacokinetic Parameters by Dose Level
(Pharmacokinetic Analysis Set)

Parameter (unit)	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
AUC 0-inf (ng*hr/mL)			
N	2	11	13
Mean (SD)	6856 (3437.1)	13562 (8762.6)	12530 (8444.6)
CV (%)	50.1	64.6	67.4
Median	6856	12058	9444
Min, Max	4426, 9287	3022, 32027	3022, 32027
Percent Extrapolated (%)			
N	2	11	13
Mean (SD)	0.868 (0.7085)	0.492 (0.4102)	0.550 (0.4495)
CV (%)	81.627	83.403	81.764
Median	0.868	0.410	0.410
Min, Max	0.367, 1.369	0.139, 1.633	0.139, 1.633
AUC 0-tau (ng*hr/mL)			
N	3	12	15
Mean (SD)	6484 (2507.4)	13566 (8355.2)	12150 (8021.6)
CV (%)	38.7	61.6	66.0
Median	5834	12560	9413
Min, Max	4366, 9253	3005, 31983	3005, 31983
Average Concentration (ng/mL)			
N	3	12	15
Mean (SD)	540.4 (208.95)	1131 (696.26)	1012 (668.46)
CV (%)	38.7	61.6	66.0
Median	486.2	1047	784.4
Min, Max	363.9, 771.1	250.4, 2665	250.4, 2665

Table 14.3.3.2
Ritonavir Pharmacokinetic Parameters by Dose Level
(Pharmacokinetic Analysis Set)

Parameter (unit)	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
CL/F (L/hr)			
N	3	12	15
Mean (SD)	17.0 (6.05)	11.3 (8.70)	12.4 (8.38)
CV (%)	35.7	77.2	67.6
Median	17.1	8.0	10.6
Min, Max	10.8, 22.9	3.1, 33.3	3.1, 33.3
Cmax (ng/mL)			
N	3	12	15
Mean (SD)	1221 (741.74)	1914 (1169.8)	1776 (1111.8)
CV (%)	60.7	61.1	62.6
Median	1030	1500	1290
Min, Max	594.0, 2040	584.0, 4470	584.0, 4470
Trough Concentration (ng/mL)			
N	3	12	15
Mean (SD)	324.0 (83.74)	558.3 (352.38)	511.5 (328.61)
CV (%)	25.8	63.1	64.2
Median	286.0	483.5	441.0
Min, Max	266.0, 420.0	107.0, 1180	107.0, 1180
Ke (1/hr)			
N	2	11	13
Mean (SD)	0.138 (0.0580)	0.160 (0.0599)	0.156 (0.0578)
CV (%)	42.016	37.557	36.979
Median	0.138	0.164	0.164
Min, Max	0.097, 0.179	0.048, 0.275	0.048, 0.275

Table 14.3.3.2
Ritonavir Pharmacokinetic Parameters by Dose Level
(Pharmacokinetic Analysis Set)

Parameter (unit)	100 mg QD (N=3)	100 mg BID (N=12)	Overall (N=15)
Half-life (hr)			
N	2	11	13
Mean (SD)	5.5 (2.30)	5.3 (3.27)	5.3 (3.05)
CV (%)	41.8	61.7	57.4
Median	5.5	4.2	4.2
Min, Max	3.9, 7.1	2.5, 14.4	2.5, 14.4
Tmax (hr)			
N	3	12	15
Mean (SD)	5.0 (2.65)	3.3 (1.48)	3.6 (1.80)
CV (%)	52.9	45.7	50.1
Median	4.0	3.0	3.0
Min, Max	3.0, 8.0	1.0, 6.0	1.0, 8.0
Varea/F			
N	2	11	13
Mean (SD)	146.5 (122.16)	80.3 (66.53)	90.5 (74.50)
CV (%)	83.4	82.8	82.3
Median	146.5	62.2	62.2
Min, Max	60.2, 232.9	19.0, 255.2	19.0, 255.2

Figure 14.3.4.1
Mean (\pm SE) of Lonafamib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

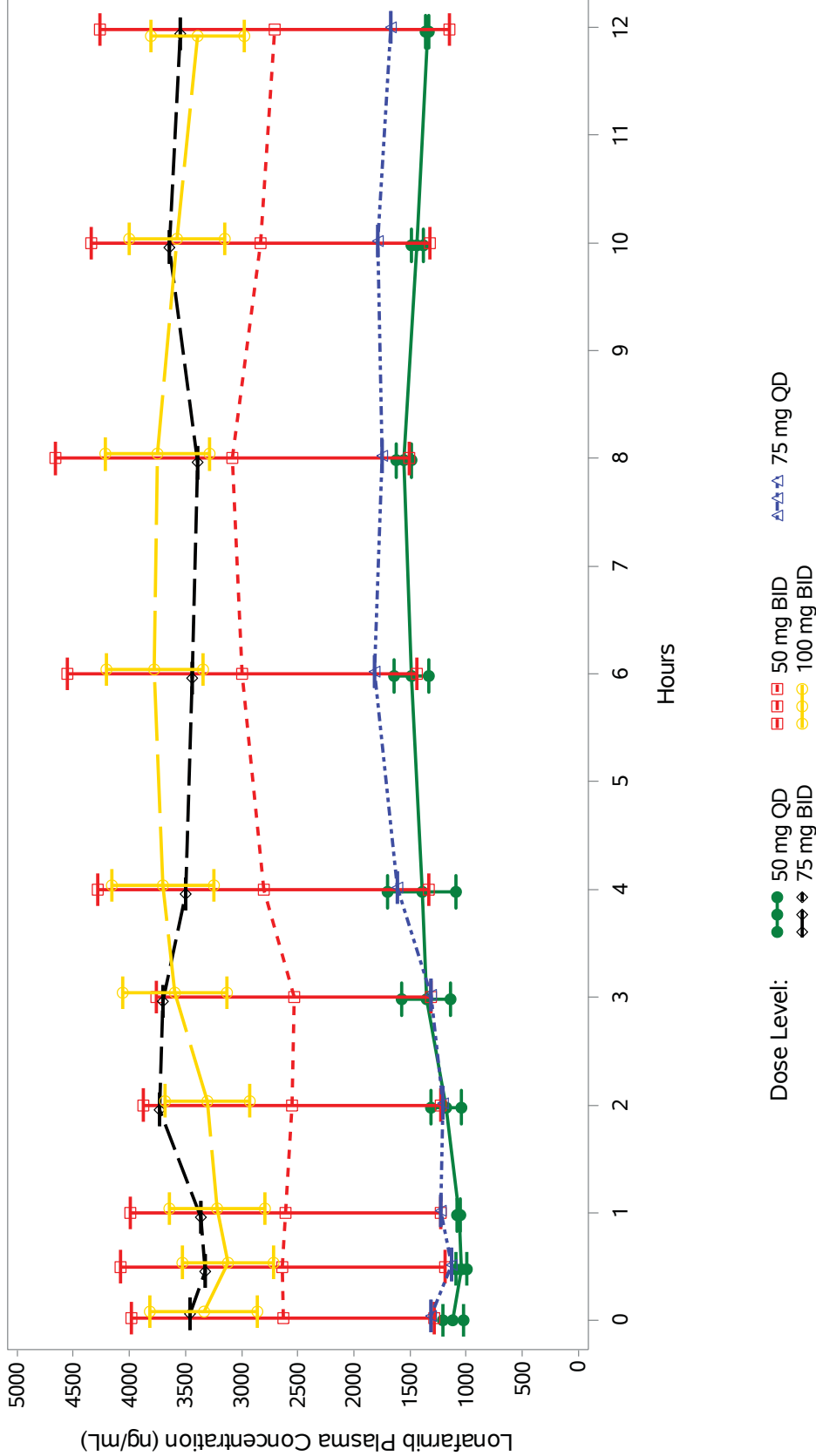
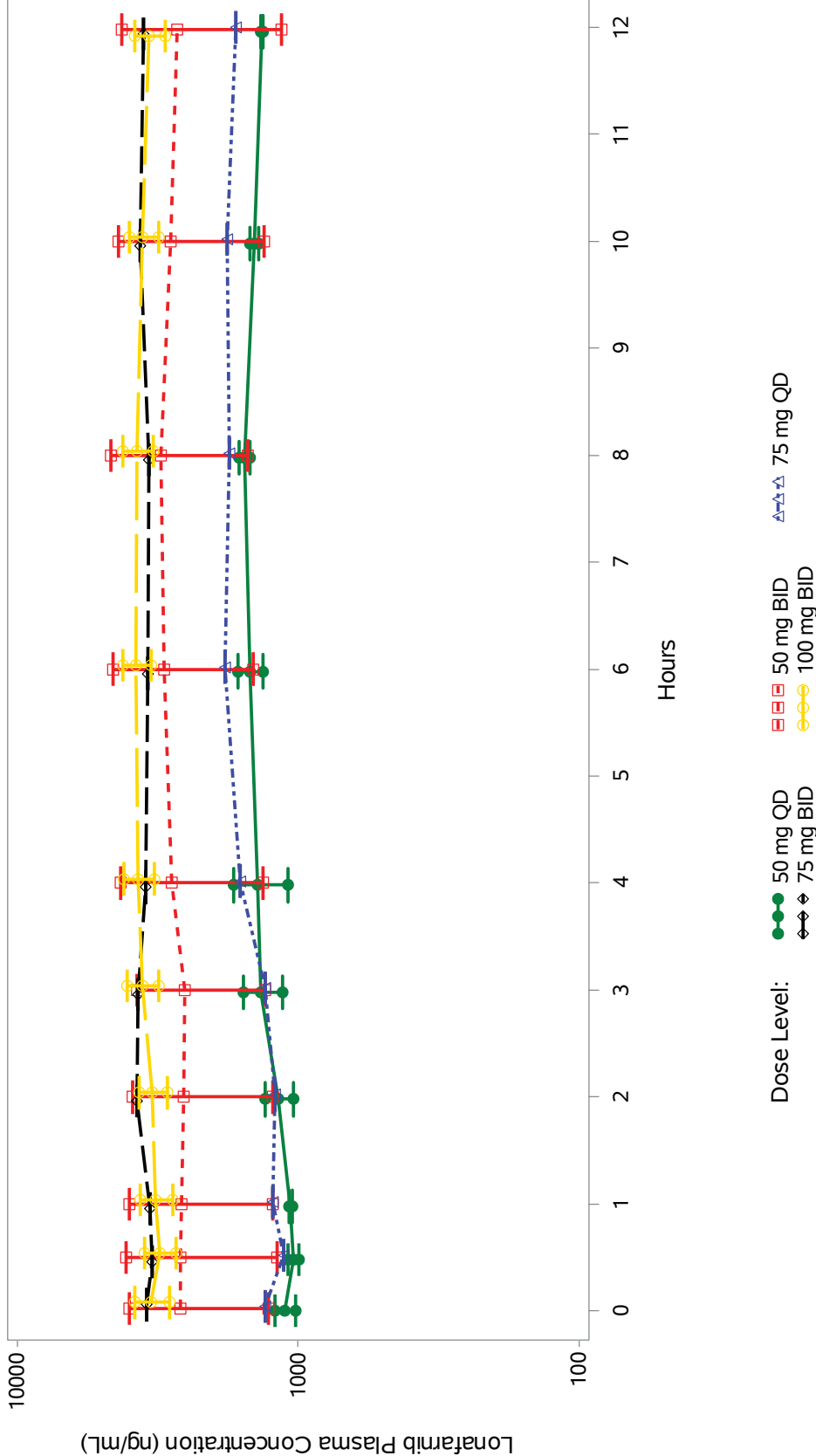
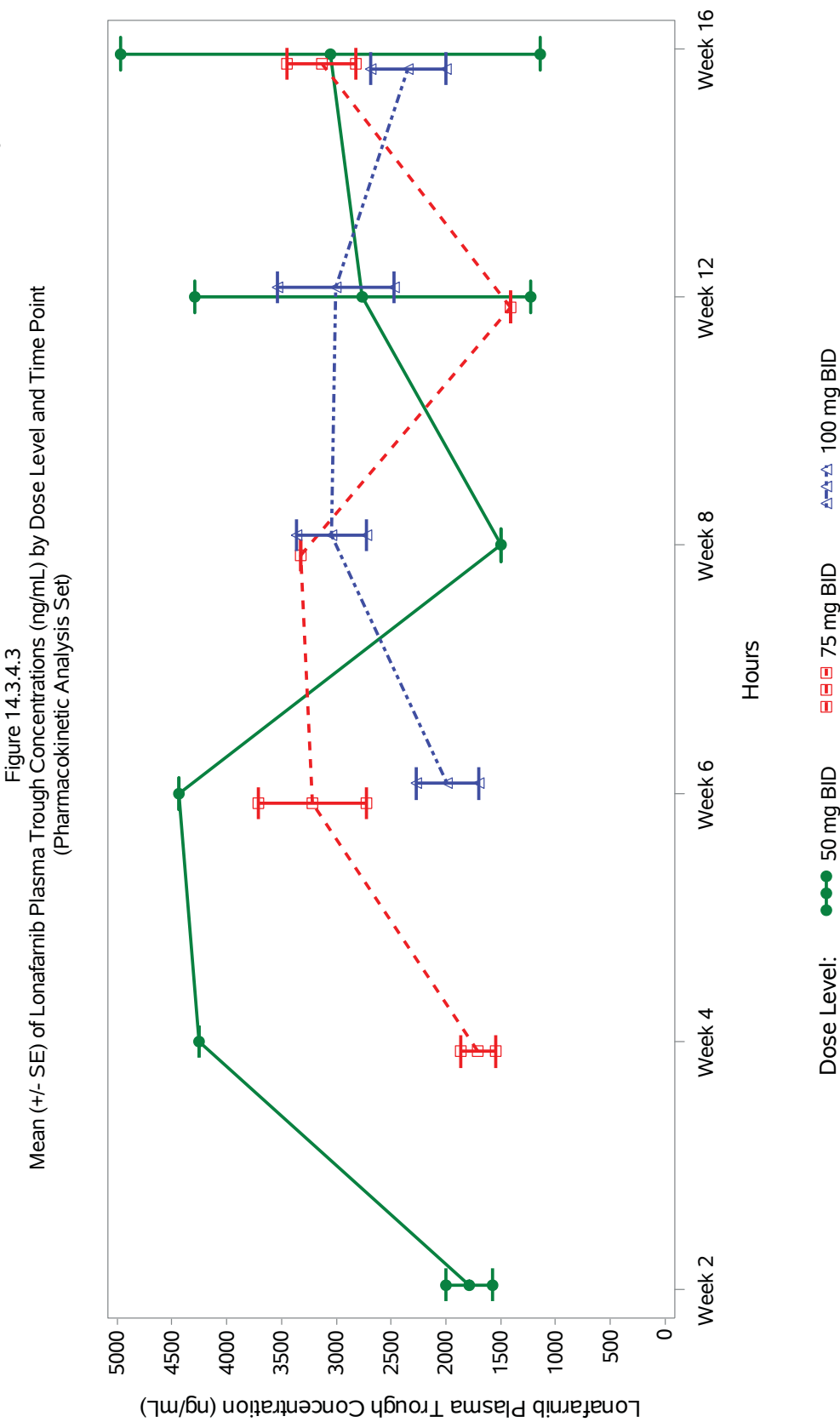


Figure 14.3.4.2
Log of Mean (\pm SE) of Lonafarnib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)





Patients on QD dosing excluded.

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Figure 14.3.4.4
Mean (\pm SE) of Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

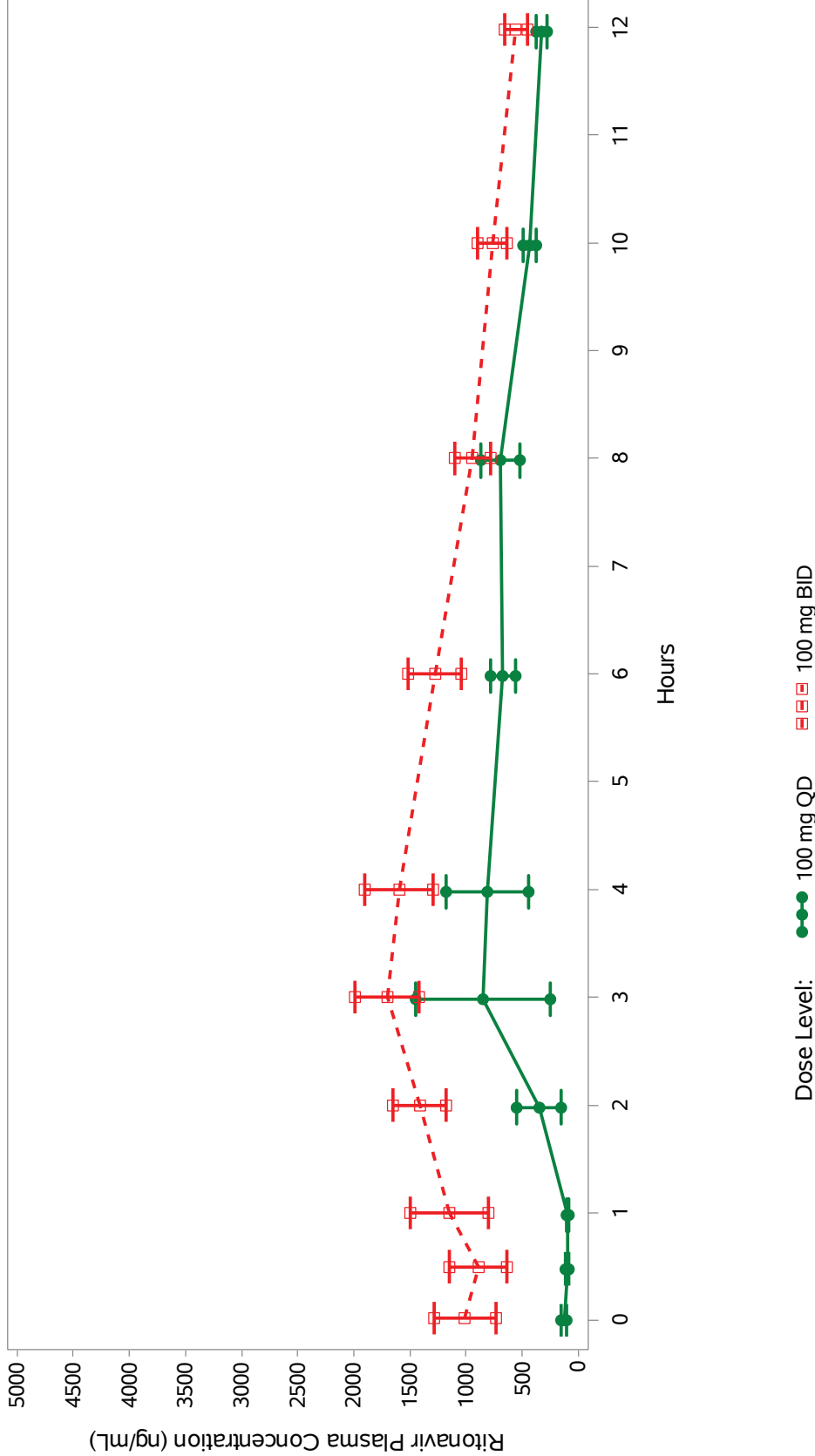


Figure 14.3.4.5
Log of Mean (+/- SE) of Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

