

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, 5880.0 | 997.0, 5880.0 |
| 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 |

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) |
|----------------------------|-------------------|--------------------|-------------------|--------------------|---------------------|-------------------|
| 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=10) | 100 mg (N=15) | 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 (+/- SE) of Lonafamib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

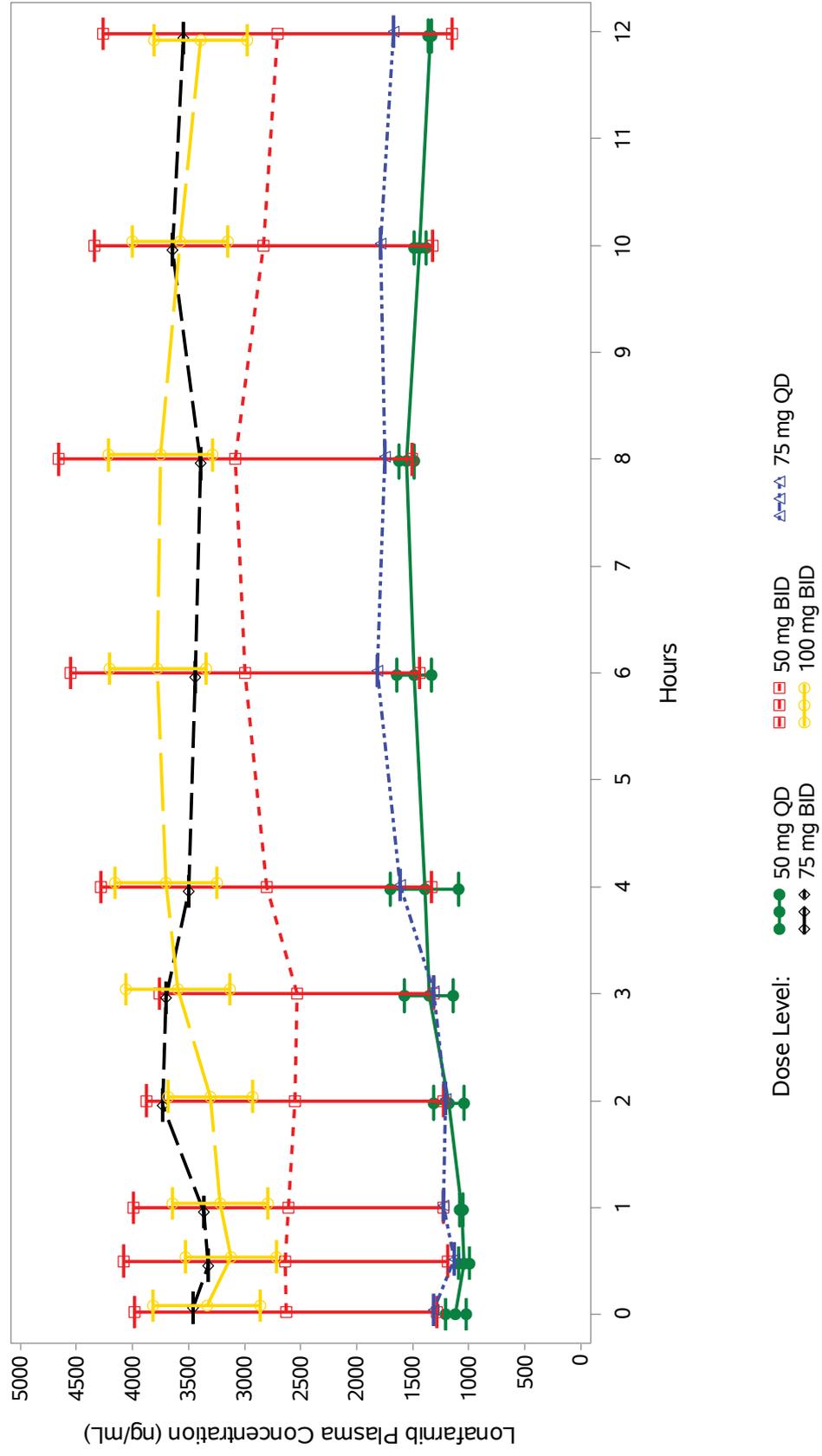


Figure 14.3.4.2
Log of Mean (+/- SE) of Lonafarnib Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

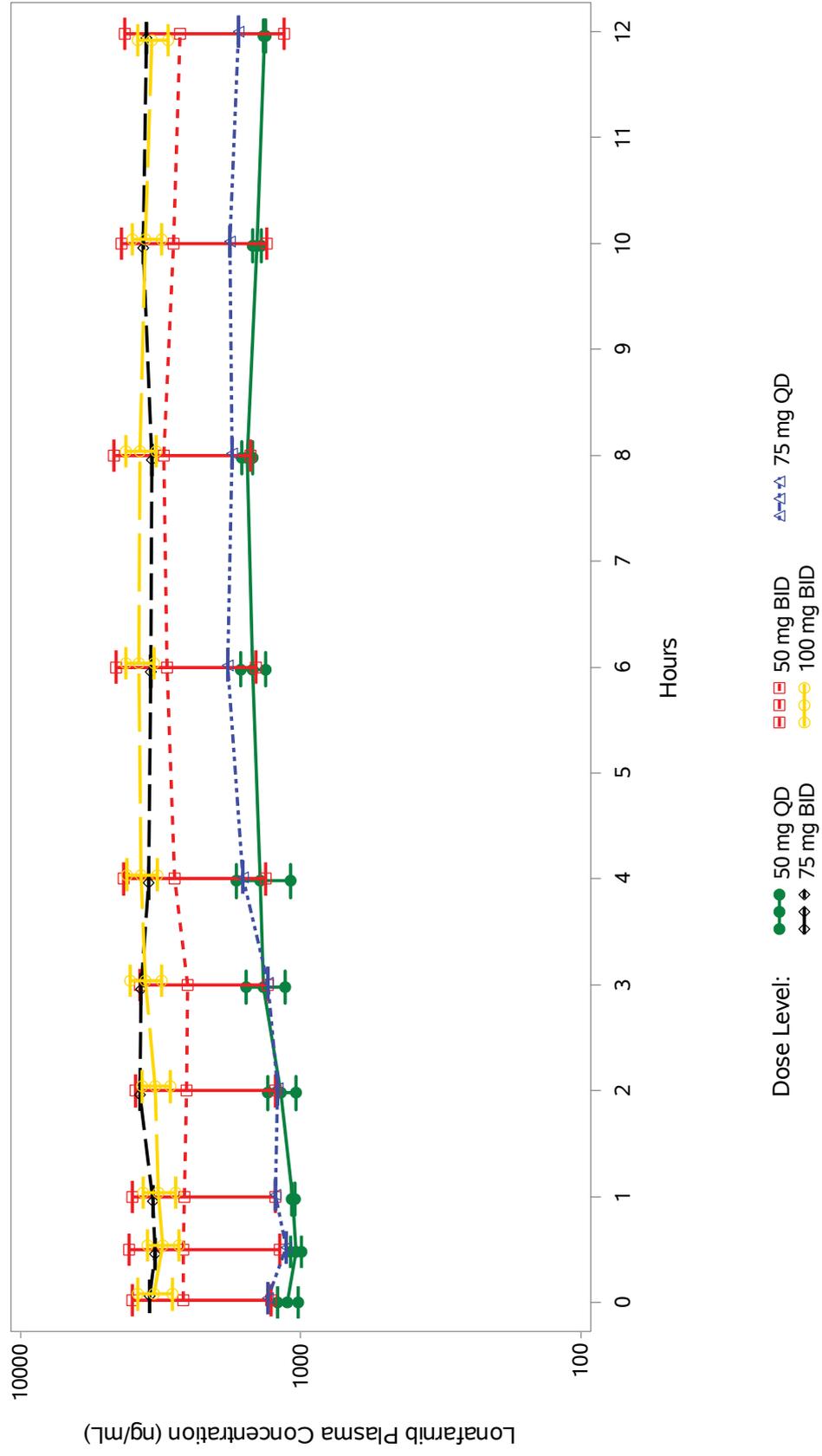
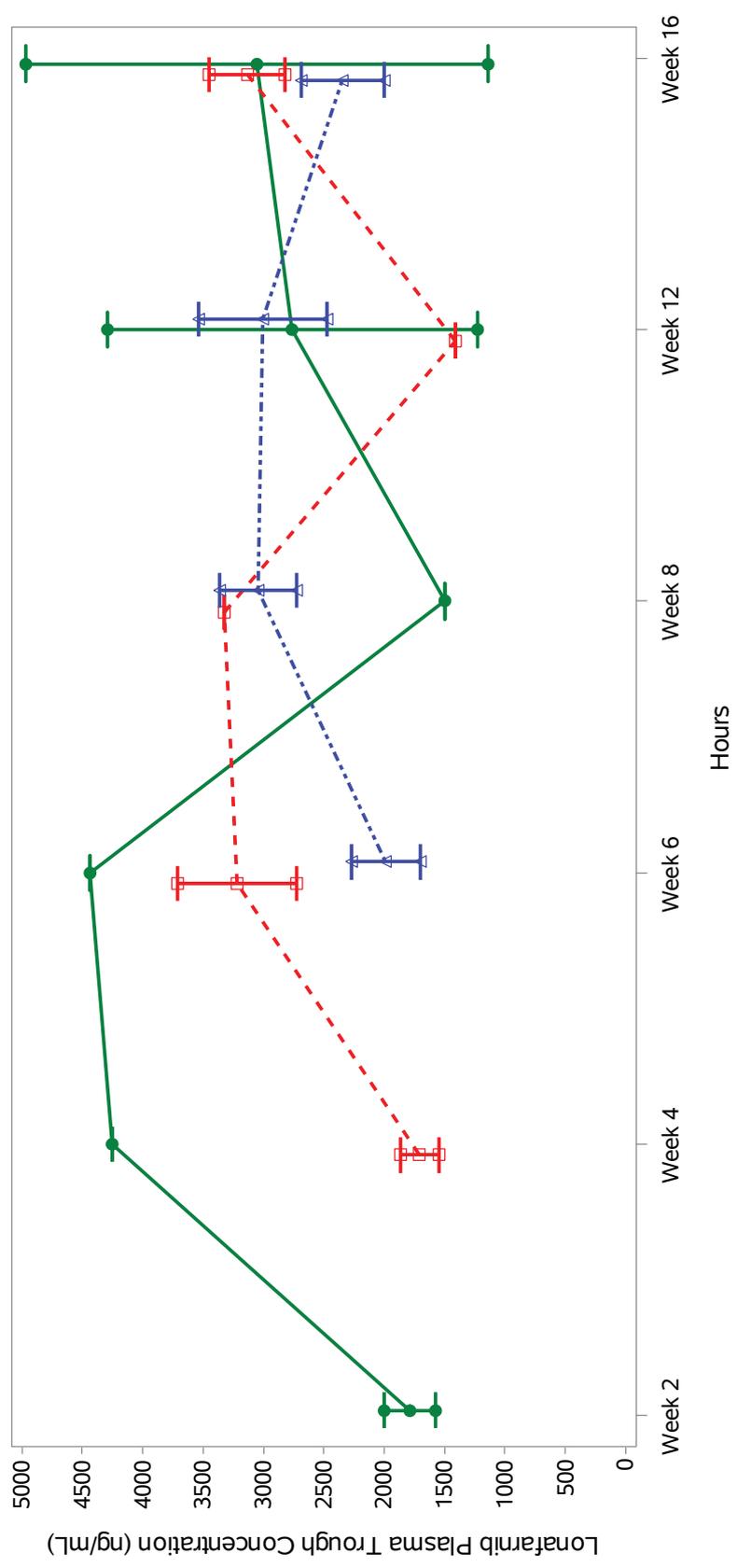


Figure 14.3.4.3
Mean (+/- SE) of Lonafarnib Plasma Trough Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)



Patients on QD dosing excluded.

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

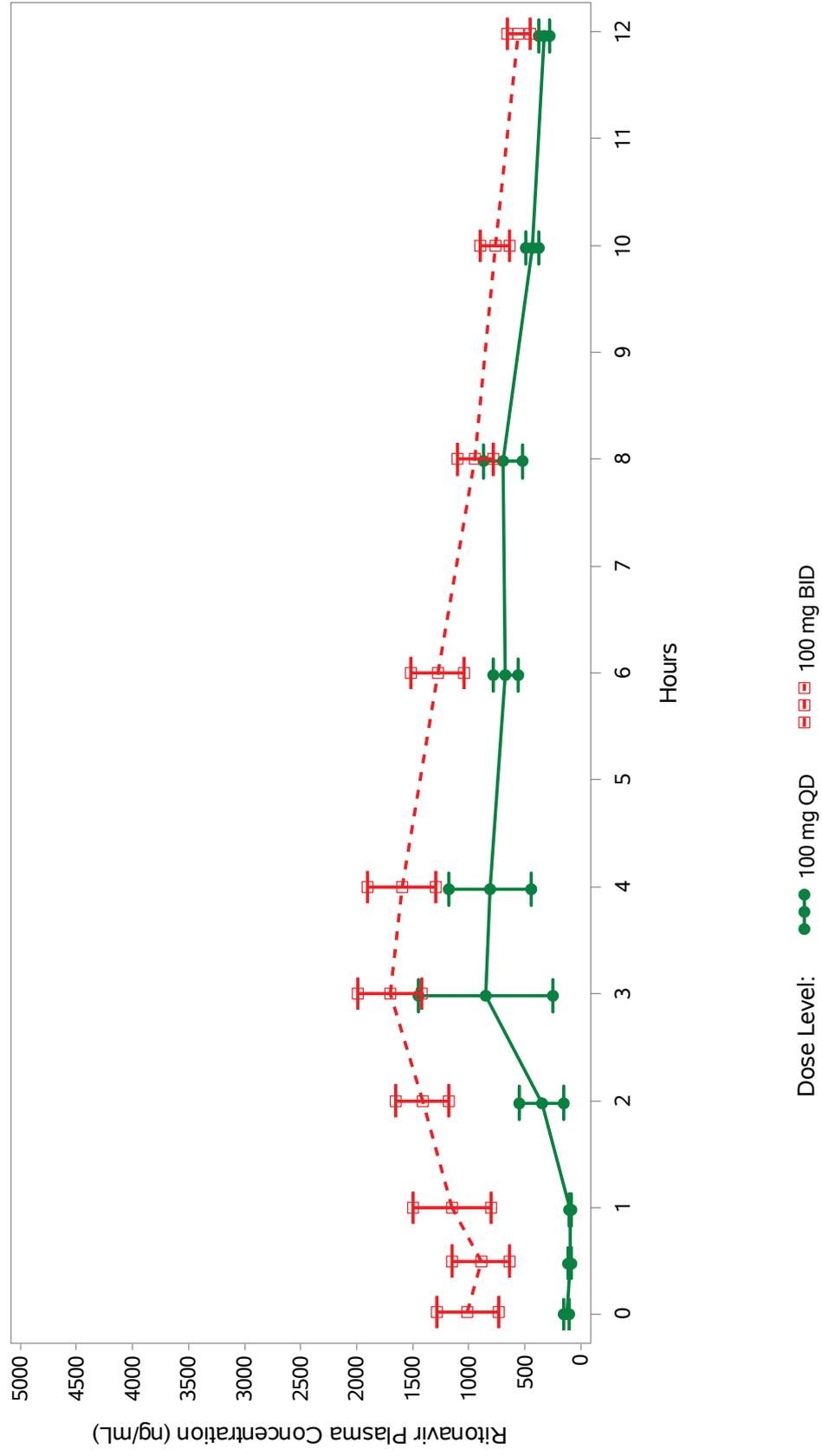


Figure 14.3.4.5
Log of Mean (+/- SE) of Ritonavir Plasma Concentrations (ng/mL) by Dose Level and Time Point
(Pharmacokinetic Analysis Set)

