Table 70: FDA Medical Officer Summary of measures of central tendency for DORI-05 Selected Serum Chemistry Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Levofloxacin		
		n	Mean (SD)	Median	n	Mean (SD)	Median
ALT (IU/L)	Baseline	367	23.51 (18.01)	18.00	360	26.41 (23.26)	20.00
	Change from Baseline to EOT	327	8.65 (24.45)	3.0	322	6 (24.76)	2.0
	Median Change Baseline to EOT by Gender			F: 2 M: 3.5			F: 4 M: 0
AST (IU/L)	Baseline	367	23.90 (18.41)	20.00	360	26.65 (19.73)	22.0
	Change from Baseline to EOT	327	4.06 (19.54)	1.0	323	1.58 (22.04)	0.0
	Median Change Baseline to EOT by Gender			F: 1 M: 2			F: 1 M: -1
Bilirubin, Total (µmol/L)	Baseline	367	11.10 (7.46)	9.23	360	11.68 (7.80)	9.23
	Change from Baseline to EOT	326	-4.20 (7.53)	-2.91	323	-4.22 (7.05)	-2.91
	Median Change Baseline to EOT by Gender			F: -3.42 M: -1.71			F: -3.42 M: -1.71
CPK, Total (IU/L)	Baseline	367	95.04 (122.10)	65.0	360	114.46 (371.34)	66.0
	Change from Baseline to EOT	327	-32.63 (132.70)	-16	323	-53.73 (373.86)	-16
	Median Change Baseline to EOT by Gender			F: -16 M: -18			F: -17.5 M: -12
Creatinine (µmol/L)	Baseline	367	89.99 (39.11)	79.56	360	89.45 (39.99)	79.56
	Change from Baseline to EOT	327	-8.91 (29.42)	-8.8	323	-5.19 (20.11)	0.0
	Median Change Baseline to EOT by Gender			F: -8.84 M: -8.84			F: -8.84 M: 0
Glucose (non-fasting) (mmol/L)	Baseline	364	6.22 (2.47)	5.61	357	6.17 (2.78)	5.50
	Change from Baseline to EOT	325	-0.12 (2.18)	-0.11	316	-0.15 (2.85)	-0.06
	Median Change Baseline to EOT by Gender			F: -0.17 M: -0.11			F: -0.06 M: 0.06
Magnesium (mmol/L)	Baseline	367	0.86 (0.14)	0.85	360	0.86 (0.14)	0.84
	Change from Baseline to EOT	327	0.01 (0.11)	0.00	322	0.00 (0.11)	0.00
	Median Change Baseline to EOT by Gender			F: 0.01 M: 0.00			F: 0 M: -0.01
Phosphorous (mmol/L)	Baseline	367	1.12 (0.29)	1.13	360	1.12 (0.33)	1.10
	Change from Baseline to EOT	327	0.08 (0.48)	0.07	322	0.07 (0.32)	0.07
	Median Change Baseline to EOT by Gender			F: 0.06 M: 0.06			F: 0.1 M: 0.06
Potassium (mmol/L)	Baseline	366	4.16 (0.70)	4.10	359	4.16 (0.72)	4.10
	Change from Baseline to EOT	327	0.13 (0.87)	0.10	321	0.13 (0.63)	0.10
	Median Change Baseline to EOT by Gender			F: 0.2 M: 0.1			F: 0.1 M: 0
Sodium (mmol/L)	Baseline	367	139.82 (3.66)	140.00	360	140.06 (3.70)	140.00
	Change from Baseline to EOT	327	0.75 (3.32)	1.00	323	0.51 (3.57)	0.00
	Median Change Baseline to EOT by Gender			F: 1 M: 0			F: 0.5 M: 0

F=female, M=male

As depicted in the table above, there were no substantial differences in the measures of central tendency for select serum chemistry parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem and levofloxacin arms of study DORI-05.

Table 71: FDA Medical Officer Summary of measures of central tendency for DORI-06 Selected Serum Chemistry Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Levofloxacin (from DORI-05)		
		n	Mean (SD)	Median	n	Mean (SD)	Median
ALT (IU/L)	Baseline	398	23.99 (19.93)	18.0	360	26.41 (23.26)	20.00
	Change from Baseline to EOT	319	13.34 (37.15)	4.0	322	6 (24.76)	2.0
	Median Change Baseline to EOT by Gender			F: 4 M: 4			F: 4 M: 0
AST (IU/L)	Baseline	398	23.18 (14.51)	19.0	360	26.65 (19.73)	22.0
	Change from Baseline to EOT	319	8.17 (43.25)	2.0	323	1.58 (22.04)	0.0
	Median Change Baseline to EOT by Gender			F: 2 M: 2			F: 1 M: -1
Bilirubin, Total (µmol/L)	Baseline	398	10.76 (8.09)	8.55	360	11.68 (7.80)	9.23
	Change from Baseline to EOT	320	-3.65 (7.67)	-1.97	323	-4.22 (7.05)	-2.91
	Median Change Baseline to EOT by Gender			F: -3.08 M: -0.94			F: -3.42 M: -1.71
CPK, Total (IU/L)	Baseline	399	113.07 (238.95)	62.0	360	114.46 (371.34)	66.0
	Change from Baseline to EOT	320	-30.12 (233.35)	-15	323	-53.73 (373.86)	-16
	Median Change Baseline to EOT by Gender			F: -15 M: -14			F: -17.5 M: -12
Creatinine (µmol/L)	Baseline	399	88.44 (41.20)	79.56	360	89.45 (39.99)	79.56
	Change from Baseline to EOT	320	-12.60 (32.49)	-8.8	323	-5.19 (20.11)	0.0
	Median Change Baseline to EOT by Gender			F: -8.84 M: -8.84			F: -8.84 M: 0
Glucose (non-fasting) (mmol/L)	Baseline	397	6.60 (2.88)	5.88	357	6.17 (2.78)	5.50
	Change from Baseline to EOT	317	-0.50 (2.22)	-0.33	316	-0.15 (2.85)	-0.06
	Median Change Baseline to EOT by Gender			F: -0.33 M: -0.22			F: -0.06 M: 0.06
Magnesium (mmol/L)	Baseline	399	0.86 (0.14)	0.86	360	0.86 (0.14)	0.84
	Change from Baseline to EOT	321	0.02 (0.11)	0.00	322	0.00 (0.11)	0.00
	Median Change Baseline to EOT by Gender			F: 0.00 M: 0.00			F: 0 M: -0.01
Phosphorous (mmol/L)	Baseline	399	1.09 (0.25)	1.10	360	1.12 (0.33)	1.10
	Change from Baseline to EOT	320	0.08 (0.29)	0.06	322	0.07 (0.32)	0.07
	Median Change Baseline to EOT by Gender			F: 0.1 M: 0.0			F: 0.1 M: 0.06
Potassium (mmol/L)	Baseline	397	4.10 (0.55)	4.10	359	4.16 (0.72)	4.10
	Change from Baseline to EOT	317	0.16 (0.57)	0.10	321	0.13 (0.63)	0.10
	Median Change Baseline to EOT by Gender			F: 0.2 M: 0.05			F: 0.1 M: 0
Sodium (mmol/L)	Baseline	398	138.73 (4.13)	139.0	360	140.06 (3.70)	140.00
	Change from Baseline to EOT	320	1.3 (3.55)	1.00	323	0.51 (3.57)	0.00
	Median Change Baseline to EOT by Gender			F: 1.0 M: 0.0			F: 0.5 M: 0

F=female, M=male

There were no substantial differences in the measures of central tendency for select serum chemistry parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem arm of DORI-06 and the levofloxacin arm of DORI-05.

Table 72: FDA Medical Officer Summary of measures of central tendency for DORI-07 Selected Serum Chemistry Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Meropenem		
		n	Mean (SD)	Median	n	Mean (SD)	Median
ALT (IU/L)	Baseline	224	30.46 (26.55)	22.0	225	27.90 (31.32)	20
	Change from Baseline to EOT	194	10.03 (40.21)	7.0	196	15.58 (43.02)	7.0
	Median Change Baseline to EOT by Gender			F: 6 M: 8			F: 4 M: 8
AST (IU/L)	Baseline	224	29.38 (22.48)	21.0	225	31.04 (59.91)	21
	Change from Baseline to EOT	193	9.21 (39.01)	7.0	196	9.38 (31.50)	6.0
	Median Change Baseline to EOT by Gender			F: 5 M: 8			F: 5 M: 6
Bilirubin, Total (µmol/L)	Baseline	225	18.63 (14.16)	15.05	225	15.51 (13.57)	13
	Change from Baseline to EOT	195	-8.30 (13.68)	-6.84	196	-6.60 (13.25)	-5.13
	Median Change Baseline to EOT by Gender			F: -5.13 M: -6.93			F: -1.71 M: -6.58
CPK, Total (IU/L)	Baseline	224	175.58 (218.92)	118.5	225	197.38 (458.36)	121.0
	Change from Baseline to EOT	194	-48.31 (210.15)	-29	196	-83.73 (572.47)	-40
	Median Change Baseline to EOT by Gender			F: -20 M: -33			F: -38.5 M: -39.5
Creatinine (µmol/L)	Baseline	225	82.27 (34.28)	79.56	225	76.88 (26.17)	70.72
	Change from Baseline to EOT	195	-12.87 (33.47)	-8.8	196	-2.44 (106.58)	-8.84
	Median Change Baseline to EOT by Gender			F: -8.84 M: -8.84			F: -8.84 M: -8.84
Glucose (non-fasting) (mmol/L)	Baseline	225	7.12 (2.43)	6.44	223	6.91 (2.54)	6.33
	Change from Baseline to EOT	194	-0.98 (2.52)	-0.78	194	-0.72 (2.62)	-0.39
	Median Change Baseline to EOT by Gender			F: -0.78 M: -0.78			F: -0.19 M: -0.47
Magnesium (mmol/L)	Baseline	225	0.82 (0.16)	0.80	225	0.86 (0.15)	0.85
	Change from Baseline to EOT	195	0.06 (0.14)	0.05	196	0.06 (0.13)	0.05
	Median Change Baseline to EOT by Gender			F: 0.19 M: 0.12			F: 0.05 M: 0.06
Phosphorous (mmol/L)	Baseline	225	1.11 (0.29)	1.10	225	1.06 (0.33)	1.07
	Change from Baseline to EOT	195	0.08 (0.39)	0.13	196	0.03 (0.50)	0.03
	Median Change Baseline to EOT by Gender			F: 0.16 M: 0.11			F: 0.03 M: 0.0
Potassium (mmol/L)	Baseline	224	4.19 (0.69)	4.20	225	4.18 (0.57)	4.10
	Change from Baseline to EOT	194	0.04 (0.86)	0.10	196	0.19 (0.86)	0.20
	Median Change Baseline to EOT by Gender			F: 0.1 M: 0.0			F: 0.05 M: 0.20
Sodium (mmol/L)	Baseline	225	138.92 (4.07)	139	225	139.16 (3.29)	139.0
	Change from Baseline to EOT	195	0.65 (4.21)	1.0	196	0.42 (3.69)	1.00
	Median Change Baseline to EOT by Gender			F: 1.0 M: 0.5			F: 1.0 M: 1.0

F=female, M=male

There were no substantial differences in the measures of central tendency for select serum chemistry parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem and meropenem arms of DORI-07.

Table 73: FDA Medical Officer Summary of measures of central tendency for DORI-08 Selected Serum Chemistry Laboratory Tests: Baseline Mean, Median, and Change from Baseline to End of IV Therapy with Gender Stratification

Parameter	Baseline Value and Change from Baseline	Doripenem			Mepenem		
		n	Mean (SD)	Median	n	Mean (SD)	Median
ALT (IU/L)	Baseline	213	30.34 (34.67)	20.0	221	57.15 (404.87)	19.0
	Change from Baseline to EOT	188	12.95 (39.37)	6.0	194	13.16 (47.23)	9.0
	Median Change Baseline to EOT by Gender			F: 6.0 M: 7.0			F: 5 M: 11
AST (IU/L)	Baseline	213	33.02 (44.26)	20.0	221	215.2 (2689.09)	21
	Change from Baseline to EOT	188	7.02 (40.37)	8.0	194	4.74 (89.57)	6.0
	Median Change Baseline to EOT by Gender			F: 8.0 M: 8.0			F: 5 M: 8
Bilirubin, Total (µmol/L)	Baseline	213	17.34 (13.36)	13.68	221	15.50 (10.49)	12.49
	Change from Baseline to EOT	188	-7.62 (10.89)	-5.13	194	-7.27 (8.81)	-5.13
	Median Change Baseline to EOT by Gender			F: -3.42 M: -7.87			F: -5.13 M: -7.01
CPK, Total (IU/L)	Baseline	213	304.18 (1195.0)	136	221	188.23 (305.33)	109.0
	Change from Baseline to EOT	188	-107.28 (1199.57)	-24	194	95.58 (645.24)	-11
	Median Change Baseline to EOT by Gender			F: -24 M: -24			F: -21 M: -7
Creatinine (µmol/L)	Baseline	213	80.97 (33.43)	70.72	221	82.72 (35.67)	79.56
	Change from Baseline to EOT	188	-11.52 (25.01)	-8.8	194	-12.35 (21.62)	-8.8
	Median Change Baseline to EOT by Gender			F: -8.84 M: -8.84			F: -8.84 M: -8.84
Glucose (non-fasting) (mmol/L)	Baseline	213	6.84 (2.81)	6.16	218	6.25 (1.85)	5.99
	Change from Baseline to EOT	187	-0.75 (3.02)	-0.44	194	-0.25 (2.37)	-0.31
	Median Change Baseline to EOT by Gender			F: -0.34 M: -0.50			F: -0.33 M: -0.28
Magnesium (mmol/L)	Baseline	213	0.82 (0.15)	0.80	221	0.81 (0.16)	0.80
	Change from Baseline to EOT	188	0.04 (0.14)	0.05	194	0.08 (0.18)	0.07
	Median Change Baseline to EOT by Gender			F: 0.04 M: 0.05			F: 0.05 M: 0.08
Phosphorous (mmol/L)	Baseline	213	1.07 (0.31)	1.07	221	1.14 (0.4)	1.10
	Change from Baseline to EOT	188	0.09 (0.41)	0.10	194	-0.05 (0.34)	-0.03
	Median Change Baseline to EOT by Gender			F: 0.10 M: 0.10			F: -0.06 M: 0.0
Potassium (mmol/L)	Baseline	213	4.11 (0.56)	4.10	219	4.21 (0.76)	4.10
	Change from Baseline to EOT	188	-0.04 (0.83)	-0.10	192	-0.10 (0.82)	0.0
	Median Change Baseline to EOT by Gender			F: -0.20 M: 0.0			F: -0.1 M: 0.0
Sodium (mmol/L)	Baseline	213	138.65 (3.42)	139.0	221	138.91 (3.36)	139.0
	Change from Baseline to EOT	188	0.98 (4.10)	1.0	194	1.14 (3.94)	1.0
	Median Change Baseline to EOT by Gender			F: 1.0 M: 1.0			F: 1.0 M: 1.0

F=female, M=male

There were no substantial differences in the measures of central tendency for select serum chemistry parameters at baseline, changes from baseline to EOT, or in the analysis by gender stratification between the doripenem and the meropenem arms of DORI-08.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following series of tables from the Sponsor's Clinical Study Reports provides data regarding the number of subjects who experienced post-baseline shifts in toxicity grade for various laboratory parameters. Laboratory abnormalities were classified by the Sponsor using the toxicity grades defined by the Division of Microbiology and Infectious Diseases[2] which were slightly modified by the Sponsor to include a normal grade and to remove clinical manifestations. This classification included Grades from 0 (i.e., within normal limits) to 4. For examination of potential hepatic injury, Hy's High Risk (HHR) Classification was used; [3] this was defined by an alanine amino transferase (ALT) > 3 times upper limit of normal (ULN) and a total bilirubin > 1.5 times ULN at the same time point. Individual subjects who had marked outlier laboratory parameter toxicity grades will be discussed in Section 7.1.7.3.3.

Table 74: Sponsor Shift Table from Baseline to Maximum Post-Baseline Grade in Hematology (Study DORI-05, ITT, Sponsor Table 32 from Clinical Study Report)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin (g/L)												
Baseline												
Grade 0	301 (85.8%)	17 (4.8%)	5 (1.4%)	0	0	323 (92.0%)	298 (89.8%)	16 (4.8%)	0	0	0	314 (94.6%)
Grade 1	3 (0.9%)	11 (3.1%)	2 (0.6%)	1 (0.3%)	0	17 (4.8%)	3 (0.9%)	5 (1.5%)	3 (0.9%)	0	0	11 (3.3%)
Grade 2	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	1 (0.3%)	5 (1.4%)	0	0	6 (1.8%)	0	0	6 (1.8%)
Grade 3	0	0	2 (0.6%)	1 (0.3%)	2 (0.6%)	5 (1.4%)	0	0	0	0	0	0
Grade 4	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)
Total	305 (86.9%)	28 (8.0%)	11 (3.1%)	3 (0.9%)	4 (1.1%)	351 (100%)	301 (90.7%)	21 (6.3%)	9 (2.7%)	1 (0.3%)	0	332 (100%)
Neutrophils + Bands (%)												
Baseline												
Grade 0	231 (72.4%)	8 (2.5%)	1 (0.3%)	0	0	240 (75.2%)	235 (77.3%)	3 (1.0%)	1 (0.3%)	0	0	239 (78.6%)
Grade 1	59 (18.5%)	11 (3.4%)	0	0	0	70 (21.9%)	44 (14.5%)	8 (2.6%)	0	1 (0.3%)	0	53 (17.4%)
Grade 2	8 (2.5%)	0	1 (0.3%)	0	0	9 (2.8%)	7 (2.3%)	2 (0.7%)	0	0	0	9 (3.0%)
Grade 3	0	0	0	0	0	0	2 (0.7%)	1 (0.3%)	0	0	0	3 (1.0%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	298 (93.4%)	19 (6.0%)	2 (0.6%)	0	0	319 (100%)	288 (94.7%)	14 (4.6%)	1 (0.3%)	1 (0.3%)	0	304 (100%)
Abs Neutrophils (x 109/L)												
Baseline												
Grade 0	244 (96.1%)	6 (2.4%)	2 (0.8%)	0	1 (0.4%)	253 (99.6%)	216 (93.9%)	4 (1.7%)	2 (0.9%)	2 (0.9%)	2 (0.9%)	226 (98.3%)
Grade 1	0	0	0	0	0	0	2 (0.9%)	0	0	0	0	2 (0.9%)
Grade 2	0	0	0	0	0	0	1 (0.4%)	0	0	0	0	1 (0.4%)
Grade 3	0	0	0	0	0	0	1 (0.4%)	0	0	0	0	1 (0.4%)
Grade 4	0	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0
Total	244 (96.1%)	6 (2.4%)	2 (0.8%)	0	2 (0.8%)	254 (100%)	220 (95.7%)	4 (1.7%)	2 (0.9%)	2 (0.9%)	2 (0.9%)	230 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Platelet Count (x 109/L)												
Baseline												
Grade 0	343 (99.4%)	0	0	0	0	343 (99.4%)	313 (98.4%)	1 (0.3%)	0	0	0	314 (98.7%)
Grade 1	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.6%)	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 2	0	0	0	0	0	0	3 (0.9%)	0	0	0	0	3 (0.9%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	344 (99.7%)	1 (0.3%)	0	0	0	345 (100%)	317 (99.7%)	1 (0.3%)	0	0	0	318 (100%)
WBC (x 109/L)												
Baseline												
Grade 0	198 (57.4%)	19 (5.5%)	7 (2.0%)	2 (0.6%)	0	226 (65.5%)	196 (59.9%)	12 (3.7%)	1 (0.3%)	4 (1.2%)	1 (0.3%)	214 (65.4%)
Grade 1	25 (7.2%)	5 (1.4%)	3 (0.9%)	1 (0.3%)	0	34 (9.9%)	29 (8.9%)	9 (2.8%)	2 (0.6%)	1 (0.3%)	0	41 (12.5%)
Grade 2	24 (7.0%)	4 (1.2%)	3 (0.9%)	0	0	31 (9.0%)	23 (7.0%)	6 (1.8%)	3 (0.9%)	1 (0.3%)	0	33 (10.1%)
Grade 3	34 (9.9%)	6 (1.7%)	6 (1.7%)	6 (1.7%)	0	52 (15.1%)	19 (5.8%)	11 (3.4%)	4 (1.2%)	4 (1.2%)	0	38 (11.6%)
Grade 4	1 (0.3%)	0	0	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	0	0	0	0	1 (0.3%)
Total	282 (81.7%)	34 (9.9%)	19 (5.5%)	10 (2.9%)	0	345 (100%)	268 (82.0%)	38 (11.6%)	10 (3.1%)	10 (3.1%)	1 (0.3%)	327 (100%)

Abs = absolute; N = number of patients in the analysis set; WBC = white blood cell.
Note: The denominator of the percentage is the number of patients with both a baseline grade and at least 1 post-baseline grade for that laboratory parameter. Toxicity grading was based on the Peninsula Pharmaceuticals, Inc. (PPI)-modified NIH

Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Grading Scale (PPImDMID). Measured analyte values only were used to calculate grades; clinical signs and symptoms were not applied.
Source: Table 15.3.2.2-1

As evidenced from the tables above, most subjects in Study DORI-05 had Grade 0 baseline hematology parameters, which were maintained during study participation. Most of the toxicity grade shifts observed involved an increase of only one grade.

The Sponsor reported that one patient (Patient 201/07094) in the doripenem treatment arm and 2 patients (Patients 203/07105 and 204/09082) in the levofloxacin treatment arm had maximum shifts in absolute neutrophil count from Grade 0 at baseline to Grade 4. For all 3 patients, the maximum shift to Grade 4 occurred by Day 3 but returned to Grade 0 by the EOT(IV) assessment. All patients continued to have Grade 0 absolute neutrophil counts at the TOC and LFU visits. Given that the Grade 4 absolute neutrophil count returned to Grade 0 while the patients continued to receive IV study drug therapy, it is unlikely that these shifts were caused by IV study drug administration. Instead the observed decreases in absolute neutrophil count probably reflected the patients' underlying infectious process.

Medical Officer Comment: No subject had been assigned the Patient # 204/09082 in DORI-05. The Sponsor's reference to Patient 204/09082 should be corrected to Patient # 204/09072, who had an absolute neutrophil count of 220/mm^3 on Day 3. The absolute neutrophil count for each of the subjects dropped to <500/mm^3 during the study, but increased to normal levels by TOC while continuing to receive study drug. Resolution of the neutropenia despite continued exposure to study drug suggests that the decreases in absolute neutrophil count were unlikely to be related to the study drug.

Table 75: Sponsor Shift Table from Baseline to Maximum Post-Baseline Grade in Chemistry (Study DORI-05, ITT, Sponsor Table 33 from Clinical Study Report)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Alkaline Phosphatase (IU/L)												
Baseline												
Grade 0	311 (85.9%)	23 (6.4%)	1 (0.3%)	0	0	335 (92.5%)	300 (85.0%)	30 (8.5%)	1 (0.3%)	0	0	331 (93.8%)
Grade 1	4 (1.1%)	21 (5.8%)	1 (0.3%)	0	0	26 (7.2%)	2 (0.6%)	18 (5.1%)	1 (0.3%)	0	0	21 (5.9%)
Grade 2	0	0	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.3%)	0	0	1 (0.3%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	315 (87.0%)	44 (12.2%)	3 (0.8%)	0	0	362 (100%)	302 (85.6%)	48 (13.6%)	3 (0.8%)	0	0	353 (100%)
ALT (SGPT) (IU/L)												
Baseline												
Grade 0	282 (77.9%)	37 (10.2%)	13 (3.6%)	3 (0.8%)	0	335 (92.5%)	255 (72.2%)	48 (13.6%)	9 (2.5%)	4 (1.1%)	1 (0.3%)	317 (89.8%)
Grade 1	8 (2.2%)	11 (3.0%)	4 (1.1%)	0	0	23 (6.4%)	4 (1.1%)	16 (4.5%)	11 (3.1%)	1 (0.3%)	0	32 (9.1%)
Grade 2	0	3 (0.8%)	1 (0.3%)	0	0	4 (1.1%)	0	1 (0.3%)	2 (0.6%)	0	0	3 (0.8%)
Grade 3	0	0	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	290 (80.1%)	51 (14.1%)	18 (5.0%)	3 (0.8%)	0	362 (100%)	259 (73.4%)	65 (18.4%)	23 (6.5%)	5 (1.4%)	1 (0.3%)	353 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
AST (SGOT) (IU/L)												
Baseline												
Grade 0	306 (84.5%)	27 (7.5%)	10 (2.8%)	1 (0.3%)	0	344 (95.0%)	276 (78.2%)	38 (10.8%)	7 (2.0%)	1 (0.3%)	0	322 (91.2%)
Grade 1	10 (2.8%)	5 (1.4%)	2 (0.6%)	0	0	17 (4.7%)	9 (2.5%)	13 (3.7%)	3 (0.8%)	3 (0.8%)	0	28 (7.9%)
Grade 2	1 (0.3%)	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.6%)
Grade 3	0	0	0	0	0	0	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	317 (87.6%)	32 (8.8%)	12 (3.3%)	1 (0.3%)	0	362 (100%)	287 (81.3%)	52 (14.7%)	10 (2.8%)	4 (1.1%)	0	353 (100%)
BUN (mmol/L)												
Baseline												
Grade 0	317 (88.1%)	14 (3.9%)	2 (0.6%)	0	0	333 (92.5%)	303 (87.1%)	18 (5.2%)	0	0	0	321 (92.2%)
Grade 1	11 (3.1%)	12 (3.3%)	0	0	0	23 (6.4%)	7 (2.0%)	17 (4.9%)	0	0	0	24 (6.9%)
Grade 2	0	2 (0.6%)	2 (0.6%)	0	0	4 (1.1%)	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.6%)
Grade 3	0	0	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	328 (91.1%)	28 (7.8%)	4 (1.1%)	0	0	360 (100%)	310 (89.1%)	36 (10.3%)	1 (0.3%)	1 (0.3%)	0	348 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Calcium (mmol/L) (hypo grade)												
Baseline												
Grade 0	288 (79.6%)	38 (10.5%)	7 (1.9%)	0	0	333 (92.0%)	283 (80.4%)	27 (7.7%)	1 (0.3%)	1 (0.3%)	0	312 (88.6%)
Grade 1	8 (2.2%)	12 (3.3%)	3 (0.8%)	1 (0.3%)	0	24 (6.6%)	18 (5.1%)	12 (3.4%)	1 (0.3%)	0	0	31 (8.8%)
Grade 2	2 (0.6%)	2 (0.6%)	0	0	0	4 (1.1%)	2 (0.6%)	5 (1.4%)	0	0	0	7 (2.0%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	1 (0.3%)	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.6%)
Total	298 (82.3%)	53 (14.6%)	10 (2.8%)	1 (0.3%)	0	362 (100%)	304 (86.4%)	45 (12.8%)	2 (0.6%)	1 (0.3%)	0	352 (100%)
Calcium (mmol/L) (hyper grade)												
Baseline												
Grade 0	341 (94.2%)	12 (3.3%)	1 (0.3%)	0	0	354 (97.8%)	333 (94.6%)	10 (2.8%)	0	0	0	343 (97.4%)
Grade 1	4 (1.1%)	2 (0.6%)	1 (0.3%)	0	0	7 (1.9%)	6 (1.7%)	3 (0.9%)	0	0	0	9 (2.6%)
Grade 2	0	0	1 (0.3%)	0	0	1 (0.3%)	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	345 (95.3%)	14 (3.9%)	3 (0.8%)	0	0	362 (100%)	339 (96.3%)	13 (3.7%)	0	0	0	352 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Creatinine (imol/L)												
Baseline												
Grade 0	288 (79.6%)	14 (3.9%)	2 (0.6%)	1 (0.3%)	0	305 (84.3%)	278 (78.8%)	22 (6.2%)	0	0	0	300 (85.0%)
Grade 1	17 (4.7%)	18 (5.0%)	2 (0.6%)	0	0	37 (10.2%)	20 (5.7%)	18 (5.1%)	4 (1.1%)	0	0	42 (11.9%)
Grade 2	3 (0.8%)	6 (1.7%)	8 (2.2%)	1 (0.3%)	0	18 (5.0%)	2 (0.6%)	2 (0.6%)	6 (1.7%)	0	0	10 (2.8%)
Grade 3	0	0	1 (0.3%)	1 (0.3%)	0	2 (0.6%)	0	0	0	0	1 (0.3%)	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	308 (85.1%)	38 (10.5%)	13 (3.6%)	3 (0.8%)	0	362 (100%)	300 (85.0%)	42 (11.9%)	10 (2.8%)	0	1 (0.3%)	353 (100%)
GGT (IU/L)												
Baseline												
Grade 0	254 (70.2%)	36 (9.9%)	10 (2.8%)	1 (0.3%)	0	301 (83.1%)	230 (65.2%)	31 (8.8%)	12 (3.4%)	5 (1.4%)	0	278 (78.8%)
Grade 1	4 (1.1%)	20 (5.5%)	13 (3.6%)	5 (1.4%)	0	42 (11.6%)	4 (1.1%)	25 (7.1%)	11 (3.1%)	8 (2.3%)	1 (0.3%)	49 (13.9%)
Grade 2	0	2 (0.6%)	8 (2.2%)	2 (0.6%)	1 (0.3%)	13 (3.6%)	0	1 (0.3%)	16 (4.5%)	3 (0.8%)	1 (0.3%)	21 (5.9%)
Grade 3	0	0	1 (0.3%)	3 (0.8%)	2 (0.6%)	6 (1.7%)	0	0	1 (0.3%)	4 (1.1%)	0	5 (1.4%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	258 (71.3%)	58 (16.0%)	32 (8.8%)	11 (3.0%)	3 (0.8%)	362 (100%)	234 (66.3%)	57 (16.1%)	40 (11.3%)	20 (5.7%)	2 (0.6%)	353 (100%)
Magnesium (mmol/L)												
Baseline												
Grade 0	288 (79.6%)	26 (7.2%)	3 (0.8%)	0	0	317 (87.6%)	278 (78.8%)	34 (9.6%)	2 (0.6%)	0	1 (0.3%)	315 (89.2%)
Grade 1	20 (5.5%)	19 (5.2%)	2 (0.6%)	0	0	41 (11.3%)	14 (4.0%)	18 (5.1%)	1 (0.3%)	0	0	33 (9.3%)
Grade 2	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	3 (0.8%)	2 (0.6%)	3 (0.8%)	0	0	0	5 (1.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0	0
Total	309 (85.4%)	46 (12.7%)	6 (1.7%)	1 (0.3%)	0	362 (100%)	294 (83.3%)	55 (15.6%)	3 (0.8%)	0	1 (0.3%)	353 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Phosphorus (mmol/L) Baseline												
Grade 0	308 (85.1%)	18 (5.0%)	2 (0.6%)	0	0	328 (90.6%)	286 (81.0%)	33 (9.3%)	5 (1.4%)	0	0	324 (91.8%)
Grade 1	20 (5.5%)	5 (1.4%)	2 (0.6%)	0	0	27 (7.5%)	12 (3.4%)	7 (2.0%)	2 (0.6%)	0	0	21 (5.9%)
Grade 2	3 (0.8%)	0	1 (0.3%)	1 (0.3%)	0	5 (1.4%)	7 (2.0%)	0	0	0	0	7 (2.0%)
Grade 3	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.6%)	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	332 (91.7%)	24 (6.6%)	5 (1.4%)	1 (0.3%)	0	362 (100%)	306 (86.7%)	40 (11.3%)	7 (2.0%)	0	0	353 (100%)
Potassium (mmol/L (hyper grade) Baseline												
Grade 0	340 (94.2%)	7 (1.9%)	0	0	5 (1.4%)	352 (97.5%)	337 (95.5%)	5 (1.4%)	3 (0.8%)	0	1 (0.3%)	346 (98.0%)
Grade 1	5 (1.4%)	0	0	0	0	5 (1.4%)	2 (0.6%)	1 (0.3%)	0	0	1 (0.3%)	4 (1.1%)
Grade 2	1 (0.3%)	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	2 (0.6%)	1 (0.3%)	0	0	0	3 (0.8%)	2 (0.6%)	0	0	0	0	2 (0.6%)
Total	348 (96.4%)	8 (2.2%)	0	0	5 (1.4%)	361 (100%)	342 (96.9%)	6 (1.7%)	3 (0.8%)	0	2 (0.6%)	353 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Sodium (mmol/L) (hypo grade) Baseline												
Grade 0	296 (81.8%)	23 (6.4%)	0	0	0	319 (88.1%)	294 (83.3%)	26 (7.4%)	1 (0.3%)	0	0	321 (90.9%)
Grade 1	30 (8.3%)	6 (1.7%)	3 (0.8%)	1 (0.3%)	0	40 (11.0%)	23 (6.5%)	6 (1.7%)	0	0	0	29 (8.2%)
Grade 2	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	3 (0.8%)	0	0	2 (0.6%)	0	0	2 (0.6%)
Grade 3	0	0	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	327 (90.3%)	29 (8.0%)	4 (1.1%)	2 (0.6%)	0	362 (100%)	317 (89.8%)	33 (9.3%)	3 (0.8%)	0	0	353 (100%)
Sodium (mmol/L) (hyper grade) Baseline												
Grade 0	309 (85.4%)	31 (8.6%)	0	1 (0.3%)	0	341 (94.2%)	295 (83.6%)	35 (9.9%)	1 (0.3%)	0	0	331 (93.8%)
Grade 1	7 (1.9%)	13 (3.6%)	1 (0.3%)	0	0	21 (5.8%)	8 (2.3%)	14 (4.0%)	0	0	0	22 (6.2%)
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	316 (87.3%)	44 (12.2%)	1 (0.3%)	1 (0.3%)	0	362 (100%)	303 (85.8%)	49 (13.9%)	1 (0.3%)	0	0	353 (100%)

	Doripenem (N=376) Maximum Post-baseline Grade						Levofloxacin (N=372) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	ade 2 Grad	Grade 4	Total	Grade 0	Grade 1	Grade 2 Grade 3	Grade 4	Total		
Total Bilirubin (imol/L) Baseline												
Grade 0	321 (88.7%)	9 (2.5%)	0	0	0	330 (91.2%)	302 (85.6%)	9 (2.5%)	2 (0.6%)	0	0	313 (88.7%)
Grade 1	12 (3.3%)	5 (1.4%)	3 (0.8%)	1 (0.3%)	0	21 (5.8%)	19 (5.4%)	5 (1.4%)	2 (0.6%)	0	0	26 (7.4%)
Grade 2	5 (1.4%)	3 (0.8%)	0	0	0	8 (2.2%)	5 (1.4%)	4 (1.1%)	2 (0.6%)	1 (0.3%)	0	12 (3.4%)
Grade 3	2 (0.6%)	1 (0.3%)	0	0	0	3 (0.8%)	2 (0.6%)	0	0	0	0	2 (0.6%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	340 (93.9%)	18 (5.0%)	3 (0.8%)	1 (0.3%)	0	362 (100%)	328 (92.9%)	18 (5.1%)	6 (1.7%)	1 (0.3%)	0	353 (100%)
Uric Acid (mmol/L) Baseline												
Grade 0	295 (81.5%)	22 (6.1%)	1 (0.3%)	0	0	318 (87.8%)	283 (80.2%)	22 (6.2%)	1 (0.3%)	0	0	306 (86.7%)
Grade 1	11 (3.0%)	22 (6.1%)	3 (0.8%)	1 (0.3%)	0	37 (10.2%)	7 (2.0%)	28 (7.9%)	4 (1.1%)	1 (0.3%)	0	40 (11.3%)
Grade 2	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	5 (1.4%)	0	1 (0.3%)	4 (1.1%)	0	0	5 (1.4%)
Grade 3	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	0	0	2 (0.6%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	307 (84.8%)	46 (12.7%)	6 (1.7%)	3 (0.8%)	0	362 (100%)	290 (82.2%)	52 (14.7%)	10 (2.8%)	1 (0.3%)	0	353 (100%)

BUN = blood urea nitrogen; GGT = gamma-glutamyltransferase; N = number of patients in the analysis set.
Note: The denominator of the percentage was the number of patients with both a baseline grade and at least 1 post-baseline grade for that laboratory parameter. Toxicity grading was based on the Peninsula Pharmaceutical, Inc. (PPI)-modified NIH Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Grading Scale (PPImDMID). Measured analyte values only were used to calculate grades; clinical signs and symptoms were not applied.

In relation to serum chemistry parameters for subjects participating in study DORI-05, most had Grade 0 baseline chemistry parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade.

The Sponsor reported that five patients (Patients 101/07063, 101/07017, 101/07158, 104/07134, and 104/08015) in the doripenem treatment arm and 1 patient (Patient 109/09036) in the levofloxacin treatment arm had a maximum increase in potassium concentration from Grade 0 at baseline to Grade 4. The maximum shift occurred at the EOT(IV) visit for 3, and at the LFU visit for 2 doripenem-treated patients. For the levofloxacin-treated patient, the maximum shift was noted at the TOC visit. Other than the single timepoint where the maximum shift to Grade 4 occurred, the potassium levels for all 6 patients in both treatment arms were within normal limits at all other time points measured. Because the extreme results appeared spurious, the Sponsor suspected that blood samples were hemolyzed. The maximum shifts in these patients were unlikely related to study drug given the random occurrence for each patient. Furthermore, the timepoint when the maximum shift occurred in 3 of the 6 affected patients (i.e, at the TOC or LFU visits) was several days to weeks after the study drug had already been discontinued.

FDA Medical Officer's Comment: The lack of a temporal relationship between doripenem exposure and the shifts in toxicity grades suggests that the shifts were unlikely to have been related to the drug.

Table 76: Sponsor Shift Table: Shifts from in ALT and AST – Using Sponsor-Defined Ranges (Study DORI-05, ITT, Sponsor Table 34 from Clinical Study Report)

ALT (IU/L)	Doripenem (N=376)					Levofloxacin (N=372)				
	Worst (Maximum) Post-baseline Value					Worst (Maximum) Post-baseline Value				
Baseline	.ULN	(ULN-3xULN]	(3xULN-5xULN]	>5xULN	Total	.ULN	(ULN-3xULN]	(3xULN-5xULN]	>5xULN	Total
.ULN	246 (68.0%)	60 (16.6%)	10 (2.8%)	3 (0.8%)	319 (88.1%)	229 (64.9%)	61 (17.3%)	3 (0.8%)	4 (1.1%)	297 (84.1%)
(ULN-3xULN]	2 (0.6%)	38 (10.5%)	2 (0.6%)	0	42 (11.6%)	7 (2.0%)	35 (9.9%)	9 (2.5%)	2 (0.6%)	53 (15.0%)
(3xULN-5xULN]	0	1 (0.3%)	0	0	1 (0.3%)	0	2 (0.6%)	0	0	2 (0.6%)
>5xULN	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)
Total	248 (68.5%)	99 (27.3%)	12 (3.3%)	3 (0.8%)	362 (100%)	236 (66.9%)	99 (28.0%)	12 (3.4%)	6 (1.7%)	353 (100%)

AST (IU/L)	Doripenem (N=376)					Levofloxacin (N=372)				
	Worst (Maximum) Post-baseline Value					Worst (Maximum) Post-baseline Value				
Baseline	.ULN	(ULN-3xULN]	(3xULN-5xULN]	>5xULN	Total	.ULN	(ULN-3xULN]	(3xULN-5xULN]	>5xULN	Total
.ULN	270 (74.6%)	56 (15.5%)	3 (0.8%)	1 (0.3%)	330 (91.2%)	241 (68.3%)	60 (17.0%)	2 (0.6%)	1 (0.3%)	304 (86.1%)
(ULN-3xULN]	15 (4.1%)	16 (4.4%)	1 (0.3%)	0	32 (8.8%)	20 (5.7%)	23 (6.5%)	1 (0.3%)	3 (0.8%)	47 (13.3%)
(3xULN-5xULN]	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)
>5xULN	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)
Total	285 (78.7%)	72 (19.9%)	4 (1.1%)	1 (0.3%)	362 (100%)	261 (73.9%)	85 (24.1%)	3 (0.8%)	4 (1.1%)	353 (100%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EFU = early follow-up; EOT(IV) = end of intravenous study drug therapy; N = number of patients in the analysis set; TOC = test-of-cure; ULN = upper limit of the normal range for the regional laboratory where the sample was processed. Ranges were ≤ULN, (ULN, 3xULN], (3xULN, 5xULN], and >5xULN, where the bracket notation denoted inclusion of the interval endpoint and the parenthesis notation denoted exclusion of the interval endpoint.
Note: The denominator of the percentage was the number of patients with both baseline and respective post-baseline parameters determined. Source: Table 15.3.2.3

The table above summarizes shifts in Sponsor-defined ranges from baseline to worst (maximum) post-baseline value in ALT and AST. In most cases, the worst (maximum) post-baseline levels remained ≤ ULN (upper limit of normal). There were three doripenem-treated and four levofloxacin-treated patients who had increases in ALT from ≤ ULN to >5x ULN. One doripenem-treated and one levofloxacin-treated subject had AST increases from ≤ ULN at baseline to >5x ULN maximum post-baseline. None of the subjects fulfilled Hy's Rule criteria. Please refer to Section 7.1.7.3.3 for details on specific cases.

Table 77: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Hematology (Study DORI-06, ITT, Sponsor Table 31 from Clinical Study Report)

	Doripenem N=423					
	Maximum Post-Baseline Grade					
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
HAEMOGLOBIN (G/L)						
Grade 0	305 (78.0%)	33 (8.4%)	7 (1.8%)	1 (0.3%)	0	346 (88.5%)
Grade 1	5 (1.3%)	13 (3.3%)	13 (3.3%)	1 (0.3%)	0	32 (8.2%)
Grade 2	0	1 (0.3%)	5 (1.3%)	3 (0.8%)	0	9 (2.3%)
Grade 3	0	1 (0.3%)	1 (0.3%)	2 (0.5%)	0	4 (1.0%)
Grade 4	0	0	0	0	0	0
Total	310 (79.3%)	48 (12.3%)	26 (6.6%)	7 (1.8%)	0	391 (100%)
NEUTROPHILS + BANDS (%)						
Grade 0	234 (63.6%)	15 (4.1%)	3 (0.8%)	0	0	252 (68.5%)
Grade 1	88 (23.9%)	10 (2.7%)	2 (0.5%)	0	0	100 (27.2%)
Grade 2	12 (3.3%)	2 (0.5%)	1 (0.3%)	0	0	15 (4.1%)
Grade 3	0	0	1 (0.3%)	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0
Total	334 (90.8%)	27 (7.3%)	7 (1.9%)	0	0	368 (100%)
NEUTROPHILS, ABS (X109/L)						
Grade 0	354 (96.5%)	8 (2.2%)	3 (0.8%)	0	0	365 (99.5%)
Grade 1	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.5%)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	355 (96.7%)	9 (2.5%)	3 (0.8%)	0	0	367 (100%)
PLATELET COUNT (X109/L)						
Grade 0	376 (99.2%)	0	0	0	0	376 (99.2%)
Grade 1	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.5%)
Grade 2	0	1 (0.3%)	0	0	0	1 (0.3%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	377 (99.5%)	2 (0.5%)	0	0	0	379 (100%)
WBC (X109/L)						
Grade 0	188 (49.2%)	20 (5.2%)	6 (1.6%)	3 (0.8%)	0	217 (56.8%)
Grade 1	34 (8.9%)	7 (1.8%)	6 (1.6%)	4 (1.0%)	0	51 (13.4%)
Grade 2	35 (9.2%)	3 (0.8%)	5 (1.3%)	2 (0.5%)	0	45 (11.8%)
Grade 3	41 (10.7%)	9 (2.4%)	5 (1.3%)	12 (3.1%)	1 (0.3%)	68 (17.8%)
Grade 4	0	0	0	1 (0.3%)	0	1 (0.3%)
Total	298 (78.0%)	39 (10.2%)	22 (5.8%)	22 (5.8%)	1 (0.3%)	382 (100%)

Note: The denominator of the percentage is the number of patients who had the specified laboratory value available at baseline and at least 1 post-baseline time point.
Source: Table 15.3.2.2-1

As evidenced from the tables above, most subjects in DORI-06 had Grade 0 baseline hematology parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade.

The Sponsor reported that no patients had a maximum or last post-baseline Grade 4 hematology parameter except for Patient 453/ 00150 who had a Grade 3 WBC count (24.65 x 10^9/L) at baseline (Screening) and had a Grade 4 value (32.47 x 10^9/L) at the LFU visit.

Table 78: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Chemistry (Study DORI-06, ITT, Sponsor Table 32 from Clinical Study Report)

	Doripenem N=423					
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
ALKALINE PHOSPHATASE (IU/L)						
Grade 0	305 (77.2%)	49 (12.4%)	4 (1.0%)	0	0	358 (90.6%)
Grade 1	7 (1.8%)	17 (4.3%)	4 (1.0%)	1 (0.3%)	0	29 (7.3%)
Grade 2	0	1 (0.3%)	7 (1.8%)	0	0	8 (2.0%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	312 (79.0%)	67 (17.0%)	15 (3.8%)	1 (0.3%)	0	395 (100%)
ALT (SGPT) (IU/L)						
Grade 0	291 (73.9%)	52 (13.2%)	12 (3.0%)	1 (0.3%)	2 (0.5%)	358 (90.9%)
Grade 1	4 (1.0%)	12 (3.0%)	12 (3.0%)	2 (0.5%)	0	30 (7.6%)
Grade 2	0	3 (0.8%)	3 (0.8%)	0	0	6 (1.5%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	295 (74.9%)	67 (17.0%)	27 (6.9%)	3 (0.8%)	2 (0.5%)	394 (100%)
AST (SGOT) (IU/L)						
Grade 0	317 (80.3%)	41 (10.4%)	9 (2.3%)	0	2 (0.5%)	369 (93.4%)
Grade 1	1 (0.3%)	14 (3.5%)	6 (1.5%)	1 (0.3%)	0	22 (5.6%)
Grade 2	0	3 (0.8%)	1 (0.3%)	0	0	4 (1.0%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	318 (80.5%)	58 (14.7%)	16 (4.1%)	1 (0.3%)	2 (0.5%)	395 (100%)
BUN (MMOL/L)						
Grade 0	323 (87.1%)	18 (4.9%)	0	0	0	341 (91.9%)
Grade 1	11 (3.0%)	12 (3.2%)	3 (0.8%)	0	0	26 (7.0%)
Grade 2	0	3 (0.8%)	1 (0.3%)	0	0	4 (1.1%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	334 (90.0%)	33 (8.9%)	4 (1.1%)	0	0	371 (100%)

		Doripenem N=423				
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
CALCIUM (MMOL/L)		(Hypo Grade)				
Grade 0	264 (66.8%)	46 (11.6%)	4 (1.0%)	2 (0.5%)	0	316 (80.0%)
Grade 1	34 (8.6%)	35 (8.9%)	5 (1.3%)	1 (0.3%)	0	75 (19.0%)
Grade 2	1 (0.3%)	2 (0.5%)	1 (0.3%)	0	0	4 (1.0%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	299 (75.7%)	83 (21.0%)	10 (2.5%)	3 (0.8%)	0	395 (100%)
CALCIUM (MMOL/L)		(Hyper Grade)				
Grade 0	374 (94.7%)	18 (4.6%)	0	0	0	392 (99.2%)
Grade 1	0	2 (0.5%)	0	0	0	2 (0.5%)
Grade 2	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	375 (94.9%)	20 (5.1%)	0	0	0	395 (100%)
CREATININE (UMOL/L)						
Grade 0	304 (76.8%)	19 (4.8%)	2 (0.5%)	0	0	325 (82.1%)
Grade 1	22 (5.6%)	25 (6.3%)	4 (1.0%)	1 (0.3%)	0	52 (13.1%)
Grade 2	2 (0.5%)	2 (0.5%)	10 (2.5%)	1 (0.3%)	0	15 (3.8%)
Grade 3	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	4 (1.0%)
Grade 4	0	0	0	0	0	0
Total	328 (82.8%)	47 (11.9%)	17 (4.3%)	3 (0.8%)	1 (0.3%)	396 (100%)
GGT (IU/L)						
Grade 0	240 (60.6%)	43 (10.9%)	10 (2.5%)	6 (1.5%)	0	299 (75.5%)
Grade 1	8 (2.0%)	29 (7.3%)	18 (4.5%)	5 (1.3%)	0	60 (15.2%)
Grade 2	0	2 (0.5%)	12 (3.0%)	7 (1.8%)	1 (0.3%)	22 (5.6%)
Grade 3	0	0	3 (0.8%)	5 (1.3%)	6 (1.5%)	14 (3.5%)
Grade 4	0	0	0	1 (0.3%)	0	1 (0.3%)
Total	248 (62.6%)	74 (18.7%)	43 (10.9%)	24 (6.1%)	7 (1.8%)	396 (100%)
MAGNESIUM (MMOL/L)						
Grade 0	306 (77.3%)	33 (8.3%)	0	0	0	339 (85.6%)
Grade 1	22 (5.6%)	29 (7.3%)	1 (0.3%)	0	0	52 (13.1%)
Grade 2	1 (0.3%)	2 (0.5%)	1 (0.3%)	0	0	4 (1.0%)
Grade 3	1 (0.3%)	0	0	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0
Total	330 (83.3%)	64 (16.2%)	2 (0.5%)	0	0	396 (100%)

			Doripenem N=423			
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
NON-FASTING GLUCOSE (MMOL/L)			(Hypo Grade)			
Grade 0	378 (95.9%)	5 (1.3%)	5 (1.3%)	1 (0.3%)	0	389 (98.7%)
Grade 1	2 (0.5%)	0	1 (0.3%)	0	0	3 (0.8%)
Grade 2	2 (0.5%)	0	0	0	0	2 (0.5%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	382 (97.0%)	5 (1.3%)	6 (1.5%)	1 (0.3%)	0	394 (100%)
NON-FASTING GLUCOSE (MMOL/L)			(Hyper Grade)			
Grade 0	163 (41.4%)	67 (17.0%)	11 (2.8%)	2 (0.5%)	0	243 (61.7%)
Grade 1	61 (15.5%)	36 (9.1%)	13 (3.3%)	1 (0.3%)	0	111 (28.2%)
Grade 2	3 (0.8%)	7 (1.8%)	9 (2.3%)	4 (1.0%)	0	23 (5.8%)
Grade 3	0	2 (0.5%)	7 (1.8%)	8 (2.0%)	0	17 (4.3%)
Grade 4	0	0	0	0	0	0
Total	227 (57.6%)	112 (28.4%)	40 (10.2%)	15 (3.8%)	0	394 (100%)
PHOSPHORUS (MMOL/L)						
Grade 0	320 (80.8%)	30 (7.6%)	5 (1.3%)	0	0	355 (89.6%)
Grade 1	21 (5.3%)	6 (1.5%)	1 (0.3%)	1 (0.3%)	0	29 (7.3%)
Grade 2	10 (2.5%)	0	0	0	0	10 (2.5%)
Grade 3	2 (0.5%)	0	0	0	0	2 (0.5%)
Grade 4	0	0	0	0	0	0
Total	353 (89.1%)	36 (9.1%)	6 (1.5%)	1 (0.3%)	0	396 (100%)
POTASSIUM (MMOL/L)			(Hypo Grade)			
Grade 0	339 (86.0%)	18 (4.6%)	1 (0.3%)	0	0	358 (90.9%)
Grade 1	20 (5.1%)	6 (1.5%)	2 (0.5%)	0	0	28 (7.1%)
Grade 2	3 (0.8%)	3 (0.8%)	2 (0.5%)	0	0	8 (2.0%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	362 (91.9%)	27 (6.9%)	5 (1.3%)	0	0	394 (100%)
POTASSIUM (MMOL/L)			(Hyper Grade)			
Grade 0	373 (94.7%)	14 (3.6%)	2 (0.5%)	1 (0.3%)	1 (0.3%)	391 (99.2%)
Grade 1	2 (0.5%)	1 (0.3%)	0	0	0	3 (0.8%)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

			Doripenem N=423			
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Total	375 (95.2%)	15 (3.8%)	2 (0.5%)	1 (0.3%)	1 (0.3%)	394 (100%)
SODIUM (MMOL/L)		(Hypo Grade)				
Grade 0	297 (75.2%)	41 (10.4%)	2 (0.5%)	0	0	340 (86.1%)
Grade 1	28 (7.1%)	14 (3.5%)	3 (0.8%)	0	0	45 (11.4%)
Grade 2	1 (0.3%)	2 (0.5%)	2 (0.5%)	1 (0.3%)	0	6 (1.5%)
Grade 3	0	0	3 (0.8%)	1 (0.3%)	0	4 (1.0%)
Grade 4	0	0	0	0	0	0
Total	326 (82.5%)	57 (14.4%)	10 (2.5%)	2 (0.5%)	0	395 (100%)
SODIUM (MMOL/L)		(Hyper Grade)				
Grade 0	364 (92.2%)	22 (5.6%)	1 (0.3%)	0	0	387 (98.0%)
Grade 1	5 (1.3%)	2 (0.5%)	0	0	0	7 (1.8%)
Grade 2	0	0	0	0	0	0
Grade 3	0	1 (0.3%)	0	0	0	1 (0.3%)
Grade 4	0	0	0	0	0	0
Total	369 (93.4%)	25 (6.3%)	1 (0.3%)	0	0	395 (100%)
TOTAL BILIRUBIN (UMOL/L)						
Grade 0	351 (88.9%)	5 (1.3%)	2 (0.5%)	0	0	358 (90.6%)
Grade 1	18 (4.6%)	1 (0.3%)	2 (0.5%)	0	1 (0.3%)	22 (5.6%)
Grade 2	6 (1.5%)	4 (1.0%)	2 (0.5%)	1 (0.3%)	0	13 (3.3%)
Grade 3	0	0	2 (0.5%)	0	0	2 (0.5%)
Grade 4	0	0	0	0	0	0
Total	375 (94.9%)	10 (2.5%)	8 (2.0%)	1 (0.3%)	1 (0.3%)	395 (100%)
URIC ACID (MMOL/L)						
Grade 0	332 (83.8%)	25 (6.3%)	3 (0.8%)	2 (0.5%)	0	362 (91.4%)
Grade 1	9 (2.3%)	17 (4.3%)	2 (0.5%)	0	0	28 (7.1%)
Grade 2	0	2 (0.5%)	1 (0.3%)	1 (0.3%)	0	4 (1.0%)
Grade 3	0	0	0	2 (0.5%)	0	2 (0.5%)
Grade 4	0	0	0	0	0	0
Total	341 (86.1%)	44 (11.1%)	6 (1.5%)	5 (1.3%)	0	396 (100%)

In relation to serum chemistry parameters for subjects participating in study DORI-06, most had Grade 0 baseline chemistry parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade. Please refer to Section 7.1.7.3.3 for details regarding specific patients with noteworthy post-baseline shifts in chemistry parameters.

Table 79: Sponsor Shift Table: Shifts from Baseline to Worst (maximum) value at End-of-Therapy (IV) or Day 3 in ALT and AST using Sponsor-Defined Ranges (DORI-06, ITT, Sponsor Table 33 from Clinical Study Report)

		Doripenem N=423a			
ALT (IU/L)		Worst (Maximum) value at EOT(IV) or Day 3			
Baseline	.≤ULN	ULN to 3xULN	3xULN to 5xULN	>5xULN	Total
.≤ULN	253 (66.4%)	65 (17.1%)	3 (0.8%)	2 (0.5%)	323 (84.8%)
(ULN to 3xULN]	11 (2.9%)	35 (9.2%)	7 (1.8%)	2 (0.5%)	55 (14.4%)
(3xULN to 5xULN]	0	2 (0.5%)	1 (0.3%)	0	3 (0.8%)
>5xULN	0	0	0	0	0
Total	264 (69.3%)	102 (26.8%)	11 (2.9%)	4 (1.0%)	381 (100%)

		Doripenem N=423b			
AST (IU/L)		Worst (Maximum) value at EOT(IV) or Day 3			
Baseline	.≤ULN	ULN to 3xULN	3xULN to 5xULN	>5xULN	Total
.≤ULN	289 (75.7%)	47 (12.3%)	4 (1.0%)	1 (0.3%)	341 (89.3%)
(ULN to 3xULN]	10 (2.6%)	24 (6.3%)	4 (1.0%)	2 (0.5%)	40 (10.5%)
(3xULN to 5xULN]	0	1 (0.3%)	0	0	1 (0.3%)
>5xULN	0	0	0	0	0
Total	299 (78.3%)	72 (18.8%)	8 (2.1%)	3 (0.8%)	382 (100%)

EOT = end of therapy
Note: ULN = Upper Limit of the normal range for the regional laboratory where the sample was processed. Ranges are ≤ULN, (ULN, 3xULN], (3xULN, 5xULN], >5xULN, where the bracket notation denoted inclusion of the interval endpoint and the parenthesis notation denoted exclusion of the interval endpoint.
[a] The denominators of the percentages are the number of patients for whom the ALT values were available for both the baseline and post-baseline time points; 381 patients.
[b] The denominators of the percentages are the number of patients for whom the AST values were available for both the baseline and post-baseline time points; 382 patients.
Source: Table 15.3.2.3

Table 80: Sponsor Shift Table: Shifts from Baseline to Worst (maximum) value at Test-of-Cure or Last Follow-up Visit in ALT and AST using Sponsor-Defined Ranges (DORI-06, ITT, Sponsor Table 34 from Clinical Study Report)

	Doripenem N=423a				
ALT (IU/L)	Worst (Maximum) value at TOC or LFU				
Baseline	.ULN	ULN to 3xULN	3xULN to 5xULN	>5xULN	Total
.ULN	292 (76.0%)	36 (9.4%)	0	0	328 (85.4%)
(ULN to 3xULN]	29 (7.6%)	20 (5.2%)	3 (0.8%)	1 (0.3%)	53 (13.8%)
(3xULN to 5xULN]	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	3 (0.8%)
>5xULN	0	0	0	0	0
Total	322 (83.9%)	57 (14.8%)	4 (1.0%)	1 (0.3%)	384 (100%)

	Doripenem N=423b				
AST (IU/L)	Worst (Maximum) value at TOC or LFU				
Baseline	.ULN	ULN to 3xULN	3xULN to 5xULN	>5xULN	Total
.ULN	329 (85.5%)	16 (4.2%)	0	0	345 (89.6%)
(ULN to 3xULN]	26 (6.8%)	12 (3.1%)	1 (0.3%)	0	39 (10.1%)
(3xULN to 5xULN]	0	1 (0.3%)	0	0	1 (0.3%)
>5xULN	0	0	0	0	0
Total	355 (92.2%)	29 (7.5%)	1 (0.3%)	0	385 (100%)

The two tables above summarizes shifts in Sponsor-defined ranges from baseline to worst (maximum) post-baseline value at EOT, Day 3, TOC, and LFU for ALT and AST. In most cases, the worst (maximum) post-baseline levels remained ≤ ULN (upper limit of normal). There were two doripenem-treated patients who had increases in ALT from ≤ ULN to >5x ULN at EOT or Day 3. One doripenem-treated subject had an AST increase from ≤ ULN at baseline to >5x ULN maximum post-baseline at EOT or Day 3. No patients had a worst (maximum) post-baseline AST or ALT of >5x ULN at TOC or LFU. Two subjects fulfilled Hy's Rule criteria. Please refer to Sections 7.1.7.3.3 and 7.1.7.5 for details on specific cases.

Table 81: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Hematology (Study DORI-07, ITT, Sponsor Table 30 from Clinical Study Report)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin (g/L)												
Baseline												
Grade 0	130 (61.9%)	31 (14.8%)	14 (6.7%)	3 (1.4%)	0	178 (84.8%)	144 (67.0%)	22 (10.2%)	15 (7.0%)	1 (0.5%)	0	182 (84.7%)
Grade 1	1 (0.5%)	9 (4.3%)	5 (2.4%)	1 (0.5%)	0	16 (7.6%)	4 (1.9%)	7 (3.3%)	6 (2.8%)	0	0	17 (7.9%)
Grade 2	2 (1.0%)	2 (1.0%)	7 (3.3%)	3 (1.4%)	0	14 (6.7%)	0	5 (2.3%)	5 (2.3%)	2 (0.9%)	0	12 (5.6%)
Grade 3	0	0	1 (0.5%)	1 (0.5%)	0	2 (1.0%)	0	0	0	3 (1.4%)	1 (0.5%)	4 (1.9%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	133 (63.3%)	42 (20.0%)	27 (12.9%)	8 (3.8%)	0	210 (100%)	148 (68.8%)	34 (15.8%)	26 (12.1%)	6 (2.8%)	1 (0.5%)	215 (100%)
Neutrophils + Bands (%)												
Baseline												
Grade 0	44 (24.3%)	14 (7.7%)	0	0	0	58 (32.0%)	46 (25.7%)	8 (4.5%)	3 (1.7%)	0	0	57 (31.8%)
Grade 1	39 (21.5%)	44 (24.3%)	4 (2.2%)	0	0	87 (48.1%)	53 (29.6%)	34 (19.0%)	5 (2.8%)	0	0	92 (51.4%)
Grade 2	10 (5.5%)	14 (7.7%)	11 (6.1%)	0	0	35 (19.3%)	13 (7.3%)	13 (7.3%)	3 (1.7%)	1 (0.6%)	0	30 (16.8%)
Grade 3	0	1 (0.6%)	0	0	0	1 (0.6%)	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	93 (51.4%)	73 (40.3%)	15 (8.3%)	0	0	181 (100%)	112 (62.6%)	55 (30.7%)	11 (6.1%)	1 (0.6%)	0	179 (100%)
Abs Neutrophils (x 109/L)												
Baseline												
Grade 0	173 (97.2%)	3 (1.7%)	0	2 (1.1%)	0	178 (100%)	171 (97.7%)	2 (1.1%)	0	1 (0.6%)	0	174 (99.4%)
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	1 (0.6%)	0	0	0	0	1 (0.6%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	173 (97.2%)	3 (1.7%)	0	2 (1.1%)	0	178 (100%)	172 (98.3%)	2 (1.1%)	0	1 (0.6%)	0	175 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Platelet Count (x 109/L)												
Baseline												
Grade 0	202 (99.0%)	1 (0.5%)	0	0	0	203 (99.5%)	204 (97.1%)	0	1 (0.5%)	2 (1.0%)	0	207 (98.6%)
Grade 1	1 (0.5%)	0	0	0	0	1 (0.5%)	1 (0.5%)	0	0	0	0	1 (0.5%)
Grade 2	0	0	0	0	0	0	1 (0.5%)	0	0	1 (0.5%)	0	2 (1.0%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	203 (99.5%)	1 (0.5%)	0	0	0	204 (100%)	206 (98.1%)	0	1 (0.5%)	3 (1.4%)	0	210 (100%)
WBC (x 109/L)												
Baseline												
Grade 0	38 (18.3%)	14 (6.7%)	6 (2.9%)	3 (1.4%)	0	61 (29.3%)	47 (22.2%)	8 (3.8%)	9 (4.2%)	11 (5.2%)	2 (0.9%)	77 (36.3%)
Grade 1	16 (7.7%)	5 (2.4%)	3 (1.4%)	5 (2.4%)	0	29 (13.9%)	17 (8.0%)	6 (2.8%)	5 (2.4%)	6 (2.8%)	1 (0.5%)	35 (16.5%)
Grade 2	14 (6.7%)	12 (5.8%)	10 (4.8%)	7 (3.4%)	0	43 (20.7%)	19 (9.0%)	9 (4.2%)	6 (2.8%)	7 (3.3%)	0	41 (19.3%)
Grade 3	16 (7.7%)	12 (5.8%)	14 (6.7%)	28 (13.5%)	1 (0.5%)	71 (34.1%)	18 (8.5%)	10 (4.7%)	12 (5.7%)	18 (8.5%)	0	58 (27.4%)
Grade 4	0	0	1 (0.5%)	0	3 (1.4%)	4 (1.9%)	0	0	0	1 (0.5%)	0	1 (0.5%)
Total	84 (40.4%)	43 (20.7%)	34 (16.3%)	43 (20.7%)	4 (1.9%)	208 (100%)	101 (47.6%)	33 (15.6%)	32 (15.1%)	43 (20.3%)	3 (1.4%)	212 (100%)

Abs = absolute; N = number of patients in the analysis set; WBC = white blood cell.
Note: The denominator of the percentage is the number of patients with both a baseline grade and at least 1 post-baseline grade for that laboratory parameter. Toxicity grading was based on the Peninsula Pharmaceuticals, Inc. (PPI)-modified NIH Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Grading Scale (PPImDMID). Measured analyte values only were used to calculate grades; clinical signs and symptoms were not applied.
Source: Table 15.3.2.2-1

As evidenced from the tables above, most subjects in Study DORI-07 had Grade 0 baseline hematology parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade.

The Sponsor reported that one doripenem-treated patient (Patient 016/11018) was discontinued from study drug therapy on Day 3 due to an adverse event of elevated WBC count (values not reported), which the investigator considered unlikely to be related to study drug therapy. No meropenem-treated patient was discontinued as a result of a hematology laboratory abnormality. In addition, no doripenem-treated patient had Grade 4 shifts in hematology parameters compared with 2 meropenem-treated patients. There were no Grade 0 to 4 hematology shifts noted except for WBC shifts, which were considered by the Sponsor to be related to the disease process in this study. Two patients in each treatment arm had maximum increases from baseline to Grade 3 or 4 in hematology parameters that remained abnormal (i.e., Grade 3 or 4) at their final study visit. Please refer to Section 7.1.7.3.3 for details on specific cases.

Table 82: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Chemistry (Study DORI-07, ITT, Sponsor Table 31 from Clinical Study Report)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Alkaline Phosphatase (IU/L)												
Baseline												
Grade 0	153 (68.9%)	40 (18.0%)	7 (3.2%)	0	0	200 (90.1%)	169 (75.4%)	31 (13.8%)	4 (1.8%)	0	0	204 (91.1%)
Grade 1	4 (1.8%)	9 (4.1%)	6 (2.7%)	0	0	19 (8.6%)	5 (2.2%)	11 (4.9%)	1 (0.4%)	0	0	17 (7.6%)
Grade 2	0	0	2 (0.9%)	0	0	2 (0.9%)	0	1 (0.4%)	2 (0.9%)	0	0	3 (1.3%)
Grade 3	0	0	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	157 (70.7%)	49 (22.1%)	15 (6.8%)	1 (0.5%)	0	222 (100%)	174 (77.7%)	43 (19.2%)	7 (3.1%)	0	0	224 (100%)
ALT (IU/L)												
Baseline												
Grade 0	126 (57.0%)	41 (18.6%)	14 (6.3%)	3 (1.4%)	0	184 (83.3%)	128 (57.1%)	43 (19.2%)	22 (9.8%)	3 (1.3%)	1 (0.4%)	197 (87.9%)
Grade 1	8 (3.6%)	16 (7.2%)	6 (2.7%)	2 (0.9%)	0	32 (14.5%)	5 (2.2%)	9 (4.0%)	6 (2.7%)	3 (1.3%)	0	23 (10.3%)
Grade 2	0	4 (1.8%)	1 (0.5%)	0	0	5 (2.3%)	0	3 (1.3%)	0	0	0	3 (1.3%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	1 (0.4%)	0	1 (0.4%)
Total	134 (60.6%)	61 (27.6%)	21 (9.5%)	5 (2.3%)	0	221 (100%)	133 (59.4%)	55 (24.6%)	28 (12.5%)	7 (3.1%)	1 (0.4%)	224 (100%)
AST (IU/L)												
Baseline												
Grade 0	134 (60.6%)	44 (19.9%)	6 (2.7%)	3 (1.4%)	0	187 (84.6%)	144 (64.3%)	43 (19.2%)	12 (5.4%)	1 (0.4%)	0	200 (89.3%)
Grade 1	13 (5.9%)	10 (4.5%)	6 (2.7%)	0	0	29 (13.1%)	5 (2.2%)	9 (4.0%)	4 (1.8%)	0	0	18 (8.0%)
Grade 2	1 (0.5%)	3 (1.4%)	0	0	1 (0.5%)	5 (2.3%)	1 (0.4%)	2 (0.9%)	0	2 (0.9%)	0	5 (2.2%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)
Total	148 (67.0%)	57 (25.8%)	12 (5.4%)	3 (1.4%)	1 (0.5%)	221 (100%)	150 (67.0%)	54 (24.1%)	16 (7.1%)	3 (1.3%)	1 (0.4%)	224 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued BUN (mmol/L) Baseline												
Grade 0	189 (85.5%)	11 (5.0%)	3 (1.4%)	0	0	203 (91.9%)	205 (92.3%)	5 (2.3%)	2 (0.9%)	0	0	212 (95.5%)
Grade 1	7 (3.2%)	8 (3.6%)	1 (0.5%)	0	0	16 (7.2%)	3 (1.4%)	5 (2.3%)	2 (0.9%)	0	0	10 (4.5%)
Grade 2	0	1 (0.5%)	1 (0.5%)	0	0	2 (0.9%)	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	196 (88.7%)	20 (9.0%)	5 (2.3%)	0	0	221 (100%)	208 (93.7%)	10 (4.5%)	4 (1.8%)	0	0	222 (100%)
Calcium (mmol/L) (hypo grade) Baseline												
Grade 0	81 (36.5%)	30 (13.5%)	6 (2.7%)	1 (0.5%)	0	118 (53.2%)	84 (37.5%)	26 (11.6%)	2 (0.9%)	0	0	112 (50.0%)
Grade 1	14 (6.3%)	31 (14.0%)	11 (5.0%)	2 (0.9%)	0	58 (26.1%)	18 (8.0%)	41 (18.3%)	10 (4.5%)	1 (0.4%)	0	70 (31.3%)
Grade 2	2 (0.9%)	13 (5.9%)	15 (6.8%)	3 (1.4%)	1 (0.5%)	34 (15.3%)	5 (2.2%)	12 (5.4%)	11 (4.9%)	4 (1.8%)	0	32 (14.3%)
Grade 3	0	2 (0.9%)	2 (0.9%)	4 (1.8%)	0	8 (3.6%)	0	1 (0.4%)	6 (2.7%)	1 (0.4%)	1 (0.4%)	9 (4.0%)
Grade 4	0	2 (0.9%)	0	2 (0.9%)	0	4 (1.8%)	1 (0.4%)	0	0	0	0	1 (0.4%)
Total	97 (43.7%)	78 (35.1%)	34 (15.3%)	12 (5.4%)	1 (0.5%)	222 (100%)	108 (48.2%)	80 (35.7%)	29 (12.9%)	6 (2.7%)	1 (0.4%)	224 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Calcium (mmol/L) (hyper grade) Baseline												
Grade 0	207 (93.2%)	12 (5.4%)	1 (0.5%)	0	0	220 (99.1%)	212 (94.6%)	11 (4.9%)	0	0	0	223 (99.6%)
Grade 1	2 (0.9%)	0	0	0	0	2 (0.9%)	0	1 (0.4%)	0	0	0	1 (0.4%)
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	209 (94.1%)	12 (5.4%)	1 (0.5%)	0	0	222 (100%)	212 (94.6%)	12 (5.4%)	0	0	0	224 (100%)
Creatinine (imol/L) Baseline												
Grade 0	194 (87.4%)	3 (1.4%)	5 (2.3%)	0	0	202 (91.0%)	203 (90.6%)	3 (1.3%)	2 (0.9%)	0	1 (0.4%)	209 (93.3%)
Grade 1	8 (3.6%)	5 (2.3%)	2 (0.9%)	0	0	15 (6.8%)	9 (4.0%)	4 (1.8%)	1 (0.4%)	0	0	14 (6.3%)
Grade 2	1 (0.5%)	1 (0.5%)	2 (0.9%)	1 (0.5%)	0	5 (2.3%)	0	1 (0.4%)	0	0	0	1 (0.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	203 (91.4%)	9 (4.1%)	9 (4.1%)	1 (0.5%)	0	222 (100%)	212 (94.6%)	8 (3.6%)	3 (1.3%)	0	1 (0.4%)	224 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued GGT (IU/L) Baseline												
Grade 0	90 (40.7%)	37 (16.7%)	23 (10.4%)	4 (1.8%)	0	154 (69.7%)	104 (46.4%)	39 (17.4%)	18 (8.0%)	7 (3.1%)	0	168 (75.0%)
Grade 1	1 (0.5%)	18 (8.1%)	14 (6.3%)	4 (1.8%)	0	37 (16.7%)	5 (2.2%)	18 (8.0%)	8 (3.6%)	3 (1.3%)	0	34 (15.2%)
Grade 2	0	2 (0.9%)	12 (5.4%)	5 (2.3%)	1 (0.5%)	20 (9.0%)	0	5 (2.2%)	7 (3.1%)	3 (1.3%)	0	15 (6.7%)
Grade 3	0	0	2 (0.9%)	4 (1.8%)	3 (1.4%)	9 (4.1%)	0	0	1 (0.4%)	5 (2.2%)	0	6 (2.7%)
Grade 4	0	0	0	0	1 (0.5%)	1 (0.5%)	0	0	0	0	1 (0.4%)	1 (0.4%)
Total	91 (41.2%)	57 (25.8%)	51 (23.1%)	17 (7.7%)	5 (2.3%)	221 (100%)	109 (48.7%)	62 (27.7%)	34 (15.2%)	18 (8.0%)	1 (0.4%)	224 (100%)
Magnesium (mmol/L) Baseline												
Grade 0	145 (65.3%)	18 (8.1%)	2 (0.9%)	0	0	165 (74.3%)	159 (71.0%)	25 (11.2%)	1 (0.4%)	0	0	185 (82.6%)
Grade 1	19 (8.6%)	25 (11.3%)	2 (0.9%)	0	0	46 (20.7%)	13 (5.8%)	17 (7.6%)	2 (0.9%)	0	0	32 (14.3%)
Grade 2	3 (1.4%)	2 (0.9%)	5 (2.3%)	0	0	10 (4.5%)	2 (0.9%)	4 (1.8%)	0	0	0	6 (2.7%)
Grade 3	1 (0.5%)	0	0	0	0	1 (0.5%)	0	0	1 (0.4%)	0	0	1 (0.4%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	168 (75.7%)	45 (20.3%)	9 (4.1%)	0	0	222 (100%)	174 (77.7%)	46 (20.5%)	4 (1.8%)	0	0	224 (100%)
Non-fasting Glucose (mmol/L) (hypo grade) Baseline												
Grade 0	203 (91.4%)	9 (4.1%)	6 (2.7%)	1 (0.5%)	0	219 (98.6%)	211 (95.0%)	4 (1.8%)	2 (0.9%)	0	0	217 (97.7%)
Grade 1	3 (1.4%)	0	0	0	0	3 (1.4%)	1 (0.5%)	0	1 (0.5%)	0	0	2 (0.9%)
Grade 2	0	0	0	0	0	0	2 (0.9%)	0	0	0	0	2 (0.9%)
Grade 3	0	0	0	0	0	0	0	1 (0.5%)	0	0	0	1 (0.5%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	206 (92.8%)	9 (4.1%)	6 (2.7%)	1 (0.5%)	0	222 (100%)	214 (96.4%)	5 (2.3%)	3 (1.4%)	0	0	222 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Non-fasting Glucose (mmol/L) (hyper grade) Baseline												
Grade 0	56 (25.2%)	45 (20.3%)	6 (2.7%)	1 (0.5%)	1 (0.5%)	109 (49.1%)	65 (29.3%)	39 (17.6%)	12 (5.4%)	0	0	116 (52.3%)
Grade 1	28 (12.6%)	39 (17.6%)	7 (3.2%)	0	1 (0.5%)	75 (33.8%)	27 (12.2%)	28 (12.6%)	9 (4.1%)	3 (1.4%)	0	67 (30.2%)
Grade 2	9 (4.1%)	10 (4.5%)	12 (5.4%)	1 (0.5%)	1 (0.5%)	33 (14.9%)	7 (3.2%)	17 (7.7%)	9 (4.1%)	1 (0.5%)	0	34 (15.3%)
Grade 3	1 (0.5%)	0	2 (0.9%)	2 (0.9%)	0	5 (2.3%)	1 (0.5%)	0	2 (0.9%)	2 (0.9%)	0	5 (2.3%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	94 (42.3%)	94 (42.3%)	27 (12.2%)	4 (1.8%)	3 (1.4%)	222 (100%)	100 (45.0%)	84 (37.8%)	32 (14.4%)	6 (2.7%)	0	222 (100%)
Phosphorus (mmol/L) Baseline												
Grade 0	129 (58.1%)	45 (20.3%)	16 (7.2%)	3 (1.4%)	0	193 (86.9%)	121 (54.0%)	39 (17.4%)	18 (8.0%)	5 (2.2%)	1 (0.4%)	184 (82.1%)
Grade 1	10 (4.5%)	5 (2.3%)	4 (1.8%)	1 (0.5%)	0	20 (9.0%)	7 (3.1%)	8 (3.6%)	7 (3.1%)	2 (0.9%)	0	24 (10.7%)
Grade 2	2 (0.9%)	2 (0.9%)	4 (1.8%)	1 (0.5%)	0	9 (4.1%)	5 (2.2%)	0	3 (1.3%)	2 (0.9%)	0	10 (4.5%)
Grade 3	0	0	0	0	0	0	2 (0.9%)	0	2 (0.9%)	1 (0.4%)	1 (0.4%)	6 (2.7%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	141 (63.5%)	52 (23.4%)	24 (10.8%)	5 (2.3%)	0	222 (100%)	135 (60.3%)	47 (21.0%)	30 (13.4%)	10 (4.5%)	2 (0.9%)	224 (100%)

	Doripenem (N=235)						Meropenem (N=236)					
	Maximum Post-baseline Grade						Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Potassium (mmol/L) (hypo grade) Baseline												
Grade 0	170 (76.9%)	28 (12.7%)	4 (1.8%)	1 (0.5%)	0	203 (91.9%)	181 (80.8%)	22 (9.8%)	1 (0.4%)	2 (0.9%)	0	206 (92.0%)
Grade 1	10 (4.5%)	4 (1.8%)	2 (0.9%)	0	0	16 (7.2%)	11 (4.9%)	4 (1.8%)	2 (0.9%)	0	0	17 (7.6%)
Grade 2	2 (0.9%)	0	0	0	0	2 (0.9%)	0	0	1 (0.4%)	0	0	1 (0.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	182 (82.4%)	32 (14.5%)	6 (2.7%)	1 (0.5%)	0	221 (100%)	192 (85.7%)	26 (11.6%)	4 (1.8%)	2 (0.9%)	0	224 (100%)
Potassium (mmol/L (hyper grade) Baseline												
Grade 0	196 (88.7%)	11 (5.0%)	3 (1.4%)	1 (0.5%)	3 (1.4%)	214 (96.8%)	202 (90.2%)	12 (5.4%)	1 (0.4%)	3 (1.3%)	2 (0.9%)	220 (98.2%)
Grade 1	4 (1.8%)	1 (0.5%)	0	0	0	5 (2.3%)	2 (0.9%)	0	0	0	1 (0.4%)	3 (1.3%)
Grade 2	0	0	0	0	0	0	1 (0.4%)	0	0	0	0	1 (0.4%)
Grade 3	1 (0.5%)	0	0	0	0	1 (0.5%)	0	0	0	0	0	0
Grade 4	1 (0.5%)	0	0	0	0	1 (0.5%)	0	0	0	0	0	0
Total	202 (91.4%)	12 (5.4%)	3 (1.4%)	1 (0.5%)	3 (1.4%)	221 (100%)	205 (91.5%)	12 (5.4%)	1 (0.4%)	3 (1.3%)	3 (1.3%)	224 (100%)

	Doripenem (N=235)						Meropenem (N=236)					
	Maximum Post-baseline Grade						Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Sodium (mmol/L) (hypo grade) Baseline												
Grade 0	149 (67.1%)	30 (13.5%)	1 (0.5%)	0	1 (0.5%)	181 (81.5%)	164 (73.2%)	29 (12.9%)	2 (0.9%)	0	0	195 (87.1%)
Grade 1	15 (6.8%)	19 (8.6%)	4 (1.8%)	1 (0.5%)	0	39 (17.6%)	10 (4.5%)	17 (7.6%)	1 (0.4%)	0	0	28 (12.5%)
Grade 2	0	0	0	0	1 (0.5%)	1 (0.5%)	0	0	1 (0.4%)	0	0	1 (0.4%)
Grade 3	0	0	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	164 (73.9%)	49 (22.1%)	5 (2.3%)	2 (0.9%)	2 (0.9%)	222 (100%)	174 (77.7%)	46 (20.5%)	4 (1.8%)	0	0	224 (100%)
Sodium (mmol/L) (hyper grade) Baseline												
Grade 0	184 (82.9%)	27 (12.2%)	1 (0.5%)	1 (0.5%)	0	213 (95.9%)	191 (85.3%)	26 (11.6%)	0	0	0	217 (96.9%)
Grade 1	2 (0.9%)	5 (2.3%)	0	0	0	7 (3.2%)	3 (1.3%)	3 (1.3%)	0	0	0	6 (2.7%)
Grade 2	1 (0.5%)	0	1 (0.5%)	0	0	2 (0.9%)	0	1 (0.4%)	0	0	0	1 (0.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	187 (84.2%)	32 (14.4%)	2 (0.9%)	0	0	222 (100%)	194 (86.6%)	30 (13.4%)	0	0	0	224 (100%)

	Doripenem (N=235) Maximum Post-baseline Grade						Meropenem (N=236) Maximum Post-baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued												
Total Bilirubin (imol/L)												
Baseline												
Grade 0	132 (59.5%)	6 (2.7%)	2 (0.9%)	2 (0.9%)	0	142 (64.0%)	169 (75.4%)	5 (2.2%)	2 (0.9%)	1 (0.4%)	0	177 (79.0%)
Grade 1	29 (13.1%)	4 (1.8%)	3 (1.4%)	2 (0.9%)	0	38 (17.1%)	19 (8.5%)	2 (0.9%)	5 (2.2%)	2 (0.9%)	0	28 (12.5%)
Grade 2	13 (5.9%)	9 (4.1%)	6 (2.7%)	4 (1.8%)	0	32 (14.4%)	6 (2.7%)	1 (0.4%)	2 (0.9%)	4 (1.8%)	0	13 (5.8%)
Grade 3	2 (0.9%)	1 (0.5%)	3 (1.4%)	1 (0.5%)	1 (0.5)	8 (3.6%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	4 (1.8%)
Grade 4	0	0	1 (0.5%)	0	1 (0.5)	2 (0.9%)	0	0	0	2 (0.9%)	0	2 (0.9%)
Total	176 (79.3%)	20 (9.0%)	15 (6.8%)	9 (4.1%)	2 (0.9)	222 (100%)	195 (87.1%)	9 (4.0%)	10 (4.5%)	10 (4.5%)	0	224 (100%)
Uric Acid (mmol/L)												
Baseline												
Grade 0	191 (86.0%)	20 (9.0%)	3 (1.4%)	0	0	214 (96.4%)	204 (91.1%)	12 (5.4%)	0	0	1 (0.4%)	217 (96.9%)
Grade 1	0	7 (3.2%)	0	0	0	7 (3.2%)	1 (0.4%)	5 (2.2%)	0	1 (0.4%)	0	7 (3.1%)
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	191 (86.0%)	28 (12.6%)	3 (1.4%)	0	0	222 (100%)	205 (91.5%)	17 (7.6%)	0	1 (0.4%)	1 (0.4%)	224 (100%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyltransferase; N = number of patients in the analysis set.
Note: The denominator of the percentage was the number of patients with both a baseline grade and at least 1 post-baseline grade for that laboratory parameter. Toxicity grading was based on the Peninsula Pharmaceutical, Inc. (PPI)-modified NIH Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Grading Scale (PPImDMID). Measured analyte values only were used to calculate grades; clinical signs and symptoms were not applied.
Source: Table 15.3.2.2-2

In relation to serum chemistry parameters for subjects participating in study DORI-07, most had Grade 0 baseline chemistry parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade. Four patients in each treatment arm had a shift from Grade 0 at baseline to Grade 4 maximum post-baseline grade: Two doripenem treated subjects had Grade 4 increases in potassium, one had a Grade 4 increase in non-fasting glucose, and one had a Grade 4 increase in sodium and potassium. One meropenem-treated subject had a Grade 4 decrease in phosphorous, two had Grade 4 increases in potassium, and one had a Grade 4 increase in creatinine. Please refer to Section 7.1.7.3.3 for details regarding speficic patients with noteworthy post-baseline shifts in chemistry parameters.

Table 83: Sponsor Shift Table: Shifts from Baseline in ALT and AST using Sponsor-Defined Ranges (DORI-07, ITT, Sponsor Table 32 from Clinical Study Report)

ALT (IU/L):

	Doripenem (N=235) Maximum Post-baseline Value					Meropenem (N=236) Maximum Post-baseline Value				
Baseline	. ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total	. ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total
. ULN	101 (45.7%)	61 (27.6%)	6 (2.7%)	3 (1.4%)	171 (77.4%)	105 (46.9%)	70 (31.3%)	10 (4.5%)	2 (0.9%)	187 (83.5%)
(ULN-3xULN]	9 (4.1%)	32 (14.5%)	5 (2.3%)	2 (0.9%)	48 (21.7%)	3 (1.3%)	22 (9.8%)	4 (1.8%)	5 (2.2%)	34 (15.2%)
(3xULN-5xUL	0	1 (0.5%)	1 (0.5%)	0	2 (0.9%)	0	2 (0.9%)	0	0	2 (0.9%)
> 5xULN	0	0	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)
Total	110 (49.8%)	94 (42.5%)	12 (5.4%)	5 (2.3%)	221 (100%)	108 (48.2%)	94 (42.0%)	14 (6.3%)	8 (3.6%)	224 (100%)

AST (IU/L):

	Doripenem (N=235) Maximum Post-baseline Value					Meropenem (N=236) Maximum Post-baseline Value				
Baseline	. ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total	. ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total
. ULN	111 (50.2%)	61 (27.6%)	3 (1.4%)	2 (0.9%)	177 (80.1%)	115 (51.3%)	62 (27.7%)	6 (2.7%)	1 (0.4%)	184 (82.1%)
(ULN-3xULN]	9 (4.1%)	28 (12.7%)	3 (1.4%)	1 (0.5%)	41 (18.6%)	8 (3.6%)	22 (9.8%)	4 (1.8%)	1 (0.4%)	35 (15.6%)
(3xULN-5xULN]	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	3 (1.4%)	1 (0.4%)	2 (0.9%)	0	1 (0.4%)	4 (1.8%)
> 5xULN	0	0	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)
Total	121 (54.8%)	90 (40.7%)	6 (2.7%)	4 (1.8%)	221 (100%)	124 (55.4%)	86 (38.4%)	10 (4.5%)	4 (1.8%)	224 (100%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EFU = early follow-up; EOT(IV) = end of intravenous study drug therapy; N = number of patients in the analysis set; TOC = test-of-cure; ULN = upper limit of the normal range for the regional laboratory where the sample was processed. Ranges were ≤ ULN, (ULN-3xULN], (3xULN-5xULN], and > 5xULN, where the bracket notation denoted inclusion of the interval endpoint and the parenthesis notation denoted exclusion of the interval endpoint. Note: The denominator of the percentage was the number of patients with both baseline and respective post-baseline parameters determined.
Source: Table 15.3.2.3

The two tables above summarize shifts in Sponsor-defined ranges from baseline to worst (maximum) post-baseline value for ALT and AST. In most cases, the worst (maximum) post-baseline levels remained ≤ ULN (upper limit of normal). There were few subjects with maximum post-baseline elevations of ALT and AST values of >3x ULN. Three doripenem-treated and two meropenem-treated subjects had baseline ALT values of ≤ULN with maximum post-baseline values of >5x ULN. One doripenem-treated and one meropenem-treated subjects had baseline AST values of ≤ULN with maximum post-baseline values of >5x ULN. Two doripenem-treated subjects fulfilled classification for Hy's Rule. There were no meropenem-treated subjects who met the criteria for Hy's Rule in study DORI-07. Please refer to Section 7.1.7.5 for details on specific cases.

Table 84: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Hematology (DORI-08, ITT, Sponsor Table 30 from Clinical Study Report)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=2 33) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin (g/L)												
Baseline												
Grade 0	132 (65.3%)	24 (11.9%)	14 (6.9%)	2 (1.0%)	1 (0.5%)	173 (85.6%)	145 (71.8%)	22 (10.9%)	7 (3.5%)	0	0	174 (86.1%)
Grade 1	1 (0.5%)	5 (2.5%)	6 (3.0%)	1 (0.5%)	0	13 (6.4%)	5 (2.5%)	3 (1.5%)	5 (2.5%)	1 (0.5%)	1 (0.5%)	15 (7.4%)
Grade 2	0	1 (0.5%)	9 (4.5%)	3 (1.5%)	0	13 (6.4%)	1 (0.5%)	3 (1.5%)	3 (1.5%)	1 (0.5%)	0	8 (4.0%)
Grade 3	2 (1.0%)	0	0	1 (0.5%)	0	3 (1.5%)	1 (0.5%)	0	3 (1.5%)	1 (0.5%)	0	5 (2.5%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	135 (66.8%)	30 (14.9%)	29 (14.4%)	7 (3.5%)	1 (0.5%)	202 (100%)	152 (75.2%)	28 (13.9%)	18 (8.9%)	3 (1.5%)	1 (0.5%)	202 (100%)
Neutrophils + Bands (%)												
Baseline												
Grade 0	40 (23.1%)	9 (5.2%)	2 (1.2%)	1 (0.6%)	0	52 (30.1%)	47 (28.3%)	10 (6.0%)	2 (1.2%)	0	0	59 (35.5%)
Grade 1	47 (27.2%)	32 (18.5%)	2 (1.2%)	2 (1.2%)	0	83 (48.0%)	44 (26.5%)	27 (16.3%)	3 (1.8%)	1 (0.6%)	0	75 (45.2%)
Grade 2	21 (12.1%)	9 (5.2%)	5 (2.9%)	1 (0.6%)	0	36 (20.8%)	8 (4.8%)	16 (9.6%)	3 (1.8%)	1 (0.6%)	0	28 (16.9%)
Grade 3	2 (1.2%)	0	0	0	0	2 (1.2%)	0	3 (1.8%)	1 (0.6%)	0	0	4 (2.4%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	110 (63.6%)	50 (28.9%)	9 (5.2%)	4 (2.3%)	0	173 (100%)	99 (59.6%)	56 (33.7%)	9 (5.4%)	2 (1.2%)	0	166 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Abs Neutrophils (x 109/L) Baseline												
Grade 0	166 (97.6%)	1 (0.6%)	0	0	1 (0.6%)	168 (98.8%)	158 (96.9%)	2 (1.2%)	2 (1.2%)	0	0	162 (99.4%)
Grade 1	2 (1.2%)	0	0	0	0	2 (1.2%)	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	1 (0.6%)	0	0	0	0	1 (0.6%)
Total	168 (98.8%)	1 (0.6%)	0	0	1 (0.6%)	170 (100%)	159 (97.5%)	2 (1.2%)	2 (1.2%)	0	0	163 (100%)
Platelet Count (x 109/L) Baseline												
Grade 0	190 (97.9%)	0	2 (1.0%)	0	1 (0.5%)	193 (99.5%)	189 (97.9%)	0	0	1 (0.5%)	1 (0.5%)	191 (99.0%)
Grade 1	0	0	0	0	0	0	2 (1.0%)	0	0	0	0	2 (1.0%)
Grade 2	0	0	1 (0.5%)	0	0	1 (0.5%)	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	190 (97.9%)	0	3 (1.5%)	0	1 (0.5%)	194 (100%)	191 (99.0%)	0	0	1 (0.5%)	1 (0.5%)	193 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued WBC (x 109/L) Baseline												
Grade 0	43 (21.6%)	10 (5.0%)	8 (4.0%)	4 (2.0%)	0	65 (32.7%)	57 (28.6%)	7 (3.5%)	7 (3.5%)	11 (5.5%)	1 (0.5%)	83 (41.7%)
Grade 1	20 (10.1%)	6 (3.0%)	4 (2.0%)	8 (4.0%)	2 (1.0%)	40 (20.1%)	10 (5.0%)	7 (3.5%)	5 (2.5%)	4 (2.0%)	1 (0.5%)	27 (13.6%)
Grade 2	16 (8.0%)	7 (3.5%)	4 (2.0%)	4 (2.0%)	0	31 (15.6%)	12 (6.0%)	6 (3.0%)	3 (1.5%)	6 (3.0%)	0	27 (13.6%)
Grade 3	25 (12.6%)	11 (5.5%)	9 (4.5%)	18 (9.0%)	0	63 (31.7%)	15 (7.5%)	8 (4.0%)	10 (5.0%)	26 (13.1%)	1 (0.5%)	60 (30.2%)
Grade 4	0	0	0	0	0	0	1 (0.5%)	0	0	1 (0.5%)	0	2 (1.0%)
Total	104 (52.3%)	34 (17.1%)	25 (12.6%)	34 (17.1%)	2 (1.0%)	199 (100%)	95 (47.7%)	28 (14.1%)	25 (12.6%)	48 (24.1%)	3 (1.5%)	199 (100%)

Abs = absolute; N = number of patients in the analysis set; WBC = white blood cell.
Note: The denominator of the percentage is the number of patients with both a baselin e grade and at least 1 post -baseline grade for that laboratory parameter. Toxicity grading was based on the Peninsula Pharmaceuticals, Inc. (PPI)-modified NIH Department of Microbiology and Infectious Disease (DMID) Adult Toxicity Grading Scale (PPImDMID).
Measured analyte values only were used to calculate grades; clinical signs and symptoms were not applied.
Source: Table 15.3.2.2-1

As evidenced from the tables above, most subjects in Study DORI-08 had Grade 0 baseline hematology parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade. The Sponsor reported that one doripenem-treated patient (Patient 060/25209) was discontinued from study drug therapy due to an adverse event of low hematocrit, which resolved 2 days later and was not related to study drug therapy. No meropenem-treated patient discontinued study drug therapy due to a laboratory abnormality. Three doripenem-treated patients and 2 meropenem patients had Grade 4 shifts in hematology parameters. Please refer to Section 7.1.7.3.3 for details on specific cases.

Table 85: Sponsor Shift Table: Shifts from Baseline to Maximum Post-Baseline Grade in Chemistry (Study DORI-08, ITT, Sponsor Table 31 from Clinical Study Report)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Alkaline Phosphatase (IU/L)												
Baseline												
Grade 0	155 (73.8%)	29 (13.8%)	3 (1.4%)	0	0	187 (89.0%)	171 (79.2%)	26 (12.0%)	4 (1.9%)	0	0	201 (93.1%)
Grade 1	1 (0.5%)	13 (6.2%)	2 (1.0%)	1 (0.5%)	0	17 (8.1%)	3 (1.4%)	7 (3.2%)	0	1 (0.5%)	0	11 (5.1%)
Grade 2	0	2 (1.0%)	3 (1.4%)	1 (0.5%)	0	6 (2.9%)	0	3 (1.4%)	1 (0.5%)	0	0	4 (1.9%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	156 (74.3%)	44 (21.0%)	8 (3.8%)	2 (1.0%)	0	210 (100%)	174 (80.6%)	36 (16.7%)	5 (2.3%)	1 (0.5%)	0	216 (100%)
ALT (IU/L)												
Baseline												
Grade 0	121 (57.6%)	44 (21.0%)	14 (6.7%)	4 (1.9%)	1 (0.5%)	184 (87.6%)	126 (58.3%)	46 (21.3%)	16 (7.4%)	3 (1.4%)	2 (0.9%)	193 (89.4%)
Grade 1	3 (1.4%)	9 (4.3%)	3 (1.4%)	0	0	15 (7.1%)	6 (2.8%)	11 (5.1%)	0	0	0	17 (7.9%)
Grade 2	0	3 (1.4%)	5 (2.4%)	0	1 (0.5%)	9 (4.3%)	0	2 (0.9%)	2 (0.9%)	0	0	4 (1.9%)
Grade 3	0	0	2 (1.0%)	0	0	2 (1.0%)	0	0	0	1 (0.5%)	0	1 (0.5%)
Grade 4	0	0	0	0	0	0	0	0	0	1 (0.5%)	0	1 (0.5%)
Total	124 (59.0%)	56 (26.7%)	24 (11.4%)	4 (1.9%)	2 (1.0%)	210 (100%)	132 (61.1%)	59 (27.3%)	18 (8.3%)	5 (2.3%)	2 (0.9%)	216 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued AST (IU/L)												
Baseline												
Grade 0	131 (62.4%)	37 (17.6%)	8 (3.8%)	1 (0.5%)	1 (0.5%)	178 (84.8%)	131 (60.6%)	48 (22.2%)	11 (5.1%)	1 (0.5%)	0	191 (88.4%)
Grade 1	9 (4.3%)	11 (5.2%)	3 (1.4%)	0	0	23 (11.0%)	9 (4.2%)	5 (2.3%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	18 (8.3%)
Grade 2	3 -1.40%	2 (1.0%)	1 (0.5%)	0	0	6 (2.9%)	1 (0.5%)	3 (1.4%)	0	0	0	4 (1.9%)
Grade 3	0	1 (0.5%)	0	0	1 (0.5%)	2 (1.0%)	0	1(0.5%)	1 (0.5%)	0	0	2 (0.9%)
Grade 4	1 (0.5%)	0	0	0	0	1 (0.5%)	0	0	0	0	1 (0.5%)	1 (0.5%)
Total	144 (68.6%)	51 (24.3%)	12 (5.7%)	1 (0.5%)	2 (1.0%)	210 (100%)	141 (65.3%)	57 (26.4%)	14 (6.5%)	2 (0.9%)	2 (0.9%)	216 (100%)
BUN (mmol/L)												
Baseline												
Grade 0	173 (87.4%)	8 (4.0%)	1 (0.5%)	0	0	182 (91.9%)	174 (87.9%)	8 (4.0%)	0	0	0	182 (91.9%)
Grade 1	7 (3.5%)	5 (2.5%)	1 (0.5%)	0	0	13 (6.6%)	5 (2.5%)	7 (3.5%)	2 (1.0%)	0	0	14 (7.1%)
Grade 2	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	3 (1.5%)	1 (0.5%)	1 (0.5%)	0	0	0	2 -1.00%
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	181 (91.4%)	14 (7.1%)	3 (1.5%)	0	0	198 (100%)	180 (90.9%)	16 (8.1%)	2 (1.0%)	0	0	198 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Calcium (mmol/L) (hypo grade) Baseline												
Grade 0	76 (36.2%)	32 (15.2%)	2 (1.0%)	0	1 (0.5%)	111 (52.9%)	76 (35.2%)	27 (12.5%)	6 (2.8%)	0	0	109 (50.5%)
Grade 1	18 (8.6%)	30 (14.3%)	13 (6.2%)	1 (0.5%)	1 (0.5%)	63 (30.0%)	22 (10.2%)	36 (16.7%)	6 (2.8%)	3 (1.4%)	0	67 (31.0%)
Grade 2	2 (1.0%)	11 (5.2%)	8 (3.8%)	2 (1.0%)	0	23 (11.0%)	3 (1.4%)	8 (3.7%)	10 (4.6%)	4 (1.9%)	0	25 (11.6%)
Grade 3	0	1 (0.5%)	8 (3.8%)	3 (1.4%)	0	12 (5.7%)	0	2 (0.9%)	4 (1.9%)	5 (2.3%)	1 (0.5%)	12 (5.6%)
Grade 4	1 (0.5%)	0	0	0	0	1 (0.5%)	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (1.4%)
Total	97 (46.2%)	74 (35.2%)	31 (14.8%)	6 (2.9%)	2 (1.0%)	210 (100%)	101 (46.8%)	73 (33.8%)	27 (12.5%)	13 (6.0%)	2 (0.9%)	216 (100%)
Calcium (mmol/L) (hyper grade) Baseline												
Grade 0	200 (95.2%)	9 (4.3%)	1 (0.5%)	0	0	210 (100%)	210 (97.2%)	5 (2.3%)	0	0	0	215 (99.5%)
Grade 1	0	0	0	0	0	0	1 (0.5%)	0	0	0	0	1 (0.5%)
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	200 (95.2%)	9 (4.3%)	1 (0.5%)	0	0	210 (100%)	211 (97.7%)	5 (2.3%)	0	0	0	216 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Creatinine (mmol/L) Baseline												
Grade 0	187 (89.0%)	6 (2.9%)	0	0	0	193 (91.9%)	193 (89.4%)	4 (1.9%)	0	0	0	197 (91.2%)
Grade 1	6 (2.9%)	4 (1.9%)	2 (1.0%)	0	0	12 (5.7%)	5 (2.3%)	2 (0.9%)	2 (0.9%)	0	0	9 (4.2%)
Grade 2	4 (1.9%)	0	1 (0.5%)	0	0	5 (2.4%)	4 (1.9%)	3 (1.4%)	3 (1.4%)	0	0	10 (4.6%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	197 (93.8%)	10 (4.8%)	3 (1.4%)	0	0	210 (100%)	202 (93.5%)	9 (4.2%)	5 (2.3%)	0	0	216 (100%)
GGT (IU/L) Baseline												
Grade 0	88 (41.9%)	40 (19.0%)	21 (10.0%)	6 (2.9%)	0	155 (73.8%)	93 (43.1%)	49 (22.7%)	17 (7.9%)	6 (2.8%)	3 (1.4%)	168 (77.8%)
Grade 1	4 (1.9%)	9 (4.3%)	13 (6.2%)	1 (0.5%)	1 (0.5%)	28 (13.3%)	2 (0.9%)	14 (6.5%)	9 (4.2%)	1 (0.5%)	1 (0.5%)	27 (12.5%)
Grade 2	0	2 (1.0%)	9 (4.3%)	4 (1.9%)	2 (1.0%)	17 (8.1%)	0	1 (0.5%)	8 (3.7%)	2 (0.9%)	1 (0.5%)	12 (5.6%)
Grade 3	0	0	2 (1.0%)	3 (1.4%)	2 (1.0%)	7 (3.3%)	0	0	3 (1.4%)	5 (2.3%)	0	8 (3.7%)
Grade 4	0	0	0	0	3 (1.4%)	3 (1.4%)	0	0	0	1 (0.5%)	0	1 (0.5%)
Total	92 (43.8%)	51 (24.3%)	45 (21.4%)	14 (6.7%)	8 (3.8%)	210 (100%)	95 (44.0%)	64 (29.6%)	37 (17.1%)	15 (6.9%)	5 (2.3%)	216 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Magnesium (mmol/L) Baseline												
Grade 0	123 (58.6%)	24 (11.4%)	3 (1.4%)	0	0	150 (71.4%)	140 (64.8%)	20 (9.3%)	2 (0.9%)	0	0	162 (75.0%)
Grade 1	25 (11.9%)	25 (11.9%)	1 (0.5%)	0	0	51 (24.3%)	24 (11.1%)	14 (6.5%)	3 (1.4%)	1 (0.5%)	0	42 (19.4%)
Grade 2	2 (1.0%)	5 (2.4%)	2 (1.0%)	0	0	9 (4.3%)	4 (1.9%)	4 (1.9%)	2 (0.9%)	0	0	10 (4.6%)
Grade 3	0	0	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	0	2 (0.9%)
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	150 (71.4%)	54 (25.7%)	6 (2.9%)	0	0	210 (100%)	169 (78.2%)	38 (17.6%)	8 (3.7%)	1 (0.5%)	0	216 (100%)
Non-fasting Glucose (mmol/L) (hypo grade) Baseline												
Grade 0	193 (91.9%)	9 (4.3%)	4 (1.9%)	0	0	206 (98.1%)	197 (92.1%)	9 (4.2%)	1 (0.5%)	0	0	207 (96.7%)
Grade 1	2 (1.0%)	1 (0.5%)	0	0	0	3 (1.4%)	2 (0.9%)	0	1 (0.5%)	0	0	3 (1.4%)
Grade 2	1 (0.5%)	0	0	0	0	1 (0.5%)	3 (1.4%)	0	0	0	0	3 (1.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	1 -0.50%	0	0	0	0	1 (0.5%)
Total	196 (93.3%)	10 (4.8%)	4 (1.9%)	0	0	210 (100%)	203 (94.9%)	9 (4.2%)	2 (0.9%)	0	0	214 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Non-fasting Glucose (mmol/L) (hyper grade)												
Baseline												
Grade 0	66 (31.4%)	46 (21.9%)	4 (1.9%)	3 (1.4%)	0	119 (56.7%)	71 (33.2%)	43 (20.1%)	10 (4.7%)	3 (1.4%)	0	127 (59.3%)
Grade 1	20 (9.5%)	30 (14.3%)	13 (6.2%)	2 (1.0%)	1 (0.5%)	66 (31.4%)	24 (11.2%)	31 (14.5%)	12 (5.6%)	1 (0.5%)	0	68 (31.8%)
Grade 2	4 (1.9%)	11 (5.2%)	4 (1.9%)	2 (1.0%)	0	21 (10.0%)	3 (1.4%)	10 (4.7%)	3 (1.4%)	2 (0.9%)	0	18 (8.4%)
Grade 3	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	3 (1.4%)	0	1 (0.5%)	0	0	0	1 (0.5%)
Grade 4	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0	0	0	0
Total	91 (43.3%)	88 (41.9%)	22 (10.5%)	8 (3.8%)	1 (0.5%)	210 (100%)	98 (45.8%)	85 (39.7%)	25 (11.7%)	6 (2.8%)	0	214 (100%)
Phosphorus (mmol/L)												
Baseline												
Grade 0	109 (51.9%)	44 (21.0%)	16 (7.6%)	1 (0.5%)	0	170 (81.0%)	121 (56.0%)	43 (19.9%)	15 (6.9%)	1 (0.5%)	0	180 (83.3%)
Grade 1	15 (7.1%)	5 (2.4%)	6 (2.9%)	2 (1.0%)	0	28 (13.3%)	8 (3.7%)	6 (2.8%)	8 (3.7%)	0	0	22 (10.2%)
Grade 2	4 (1.9%)	2 (1.0%)	3 (1.4%)	1 (0.5%)	0	10 (4.8%)	5 (2.3%)	3 (1.4%)	1 (0.5%)	1 (0.5%)	0	10 (4.6%)
Grade 3	0	1 (0.5%)	0	1 (0.5%)	0	2 (1.0%)	1 (0.5%)	2 (0.9%)	0	0	0	3 (1.4%)
Grade 4	0	0	0	0	0	0	0	1 (0.5%)	0	0	0	1 (0.5%)
Total	128 (61.0%)	52 (24.8%)	25 (11.9%)	5 (2.4%)	0	210 (100%)	135 (62.5%)	55 (25.5%)	24 (11.1%)	2 (0.9%)	0	216 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Potassium (mmol/L) (hypo grade)												
Baseline												
Grade 0	155 (73.8%)	29 (13.8%)	6 (2.9%)	1 (0.5%)	0	191 (91.0%)	161 (75.2%)	29 (13.6%)	6 (2.8%)	2 (0.9%)	0	198 (92.5%)
Grade 1	7 (3.3%)	8 (3.8%)	2 (1.0%)	0	0	17 (8.1%)	4 (1.9%)	6 (2.8%)	4 (1.9%)	0	0	14 (6.5%)
Grade 2	0	2 (1.0%)	0	0	0	2 (1.0%)	0	2 (0.9%)	0	0	0	2 (0.9%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	162 (77.1%)	39 (18.6%)	8 (3.8%)	1 (0.5%)	0	210 (100%)	165 (77.1%)	37 (17.3%)	10 (4.7%)	2 (0.9%)	0	214 (100%)
Potassium (mmol/L (hyper grade)												
Baseline												
Grade 0	192 (91.4%)	9 (4.3%)	1 (0.5%)	0	4 (1.9%)	206 (98.1%)	192 (89.7%)	6 (2.8%)	4 (1.9%)	0	3 (1.4%)	205 (95.8%)
Grade 1	1 (0.5%)	0	0	0	0	1 (0.5%)	2 (0.9%)	0	0	0	1 (0.5%)	3 (1.4%)
Grade 2	3 (1.4%)	0	0	0	0	3 (1.4%)	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)	3 (1.4%)
Grade 4	0	0	0	0	0	0	2 (0.9%)	1 (0.5%)	0	0	0	3 (1.4%)
Total	196 (93.3%)	9 (4.3%)	1 (0.5%)	0	4 (1.9%)	210 (100%)	197 (92.1%)	7 (3.3%)	5 (2.3%)	0	5 (2.3%)	214 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Sodium (mmol/L) (hypo grade) Baseline												
Grade 0	147 (70.0%)	28 (13.3%)	1 (0.5%)	1 (0.5%)	0	177 (84.3%)	147 (68.1%)	36 (16.7%)	1 (0.5%)	0	0	184 (85.2%)
Grade 1	15 (7.1%)	15 (7.1%)	1 (0.5%)	0	0	31 (14.8%)	13 (6.0%)	15 (6.9%)	1 (0.5%)	1 (0.5%)	0	30 (13.9%)
Grade 2	1 (0.5%)	1 (0.5%)	0	0	0	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0	2 (0.9%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	163 (77.6%)	44 (21.0%)	2 (1.0%)	1 (0.5%)	0	210 (100%)	161 (74.5%)	51 (23.6%)	3 (1.4%)	1 (0.5%)	0	216 (100%)
Sodium (mmol/L) (hyper grade) Baseline												
Grade 0	178 (84.8%)	23 (11.0%)	2 (1.0%)	0	0	203 (96.7%)	177 (81.9%)	30 (13.9%)	5 (2.3%)	0	0	212 (98.1%)
Grade 1	4 (1.9%)	3 (1.4%)	0	0	0	7 (3.3%)	0	4 (1.9%)	0	0	0	4 (1.9%)
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Total	182 (86.7%)	26 (12.4%)	2 (1.0%)	0	0	210 (100%)	177 (81.9%)	34 (15.7%)	5 (2.3%)	0	0	216 (100%)

	Doripenem (N=242) Maximum Post-Baseline Grade						Meropenem (N=233) Maximum Post-Baseline Grade					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Continued Total Bilirubin (mmol/L) Baseline												
Grade 0	139 (66.2%)	9 (4.3%)	6 (2.9%)	3 (1.4%)	0	157 (74.8%)	156 (72.2%)	7 (3.2%)	2 (0.9%)	1 (0.5%)	0	166 (76.9%)
Grade 1	18 (8.6%)	7 (3.3%)	1 (0.5%)	1 (0.5%)	0	27 (12.9%)	22 (10.2%)	4 (1.9%)	1 (0.5%)	0	0	27 (12.5%)
Grade 2	6 (2.9%)	5 (2.4%)	6 (2.9%)	1 (0.5%)	0	18 (8.6%)	8 (3.7%)	6 (2.8%)	5 (2.3%)	0	0	19 (8.8%)
Grade 3	1 (0.5%)	1 (0.5%)	3 (1.4%)	2 (1.0%)	0	7 (3.3%)	2 (0.9%)	0	0	1 (0.5%)	1 (0.5%)	4 (1.9%)
Grade 4	0	0	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0	0
Total	164 (78.1%)	22 (10.5%)	16 (7.6%)	8 (3.8%)	0	210 (100%)	188 (87.0%)	17 (7.9%)	8 (3.7%)	2 (0.9%)	1 (0.5%)	216 (100%)
Uric Acid (mmol/L) Baseline												
Grade 0	181 (86.2%)	14 (6.7%)	0	0	0	195 (92.9%)	185 (85.6%)	16 (7.4%)	2 (0.9%)	0	0	203 (94.0%)
Grade 1	8 (3.8%)	5 (2.4%)	1 (0.5%)	0	0	14 (6.7%)	3 (1.4%)	3 (1.4%)	3 (1.4%)	0	0	9 (4.2%)
Grade 2	0	0	1 (0.5%)	0	0	1 (0.5%)	2 (0.9%)	1 (0.5%)	0	0	0	3 (1.4%)
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	1 (0.5%)	0	0	0	0	1 (0.5%)
Total	189 (90.0%)	19 (9.0%)	2 (1.0%)	0	0	210 (100%)	191 (88.4%)	20 (9.3%)	5 (2.3%)	0	0	216 (100%)

In relation to serum chemistry parameters for subjects participating in study DORI-08, most had Grade 0 baseline chemistry parameters, which were maintained during study participation. Most toxicity grade shifts observed involved an increase of only one grade. Five patients in each treatment arm had a shift from Grade 0 at baseline to Grade 4 maximum post-baseline grade: One doripenem-treated subject had Grade 4 increases in ALT and AST levels. One meropenem-treated subject had a Grade 4 decrease in ALT, two had Grade 4 increases in GGT, and one had a Grade 4 increase in ALT and AST. Please refer to Section 7.1.7.3.3 for details regarding specific patients with noteworthy post-baseline shifts in chemistry parameters.

Table 86: Sponsor Shift Table: Shifts from Baseline in ALT and AST using Sponsor-Defined Ranges (DORI-08, ITT, Sponsor Table 32 from Clinical Study Report)

ALT (IU/L)	Doripenem (N=242)					Meropenem (N=233)				
	Maximum Post-Baseline Value					Maximum Post-Baseline Value				
Baseline	≤ ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total	≤ ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total
≤ULN	101 (48.1%)	57 (27.1%)	8 (3.8%)	5 (2.4%)	171 (81.4%)	99 (45.8%)	71 (32.9%)	8 (3.7%)	5 (2.3%)	183 (84.7%)
(ULN-3xULN]	5 (2.4%)	23 (11.0%)	2 (1.0%)	0	30 (14.3%)	9 (4.2%)	18 (8.3%)	1 (0.5%)	0	28 (13.0%)
(3xULN-5xULN]	0	3 (1.4%)	3 (1.4%)	1 (0.5%)	7 (3.3%)	0	2 (0.9%)	1 (0.5%)	0	3 (1.4%)
> 5xULN	0	1 (0.5%)	1 (0.5%)	0	2 (1.0%)	0	0	0	2 (0.9%)	2 (0.9%)
Total	106 (50.5%)	84 (40.0%)	14 (6.7%)	6 (2.9%)	210 (100%)	108 (50.0%)	91 (42.1%)	10 (4.6%)	7 (3.2%)	216 (100%)

AST (IU/L)	Doripenem (N=242)					Meropenem (N=233)				
	Maximum Post-Baseline Value					Maximum Post-Baseline Value				
Baseline	≤ ULN	(ULN-3xULN]	(3xULN-5xULN]	> 5xULN	Total	≤ ULN	(ULN-3xULN]	3xULN-5xULN	> 5xULN	Total
≤ ULN	104 (49.5%)	56 (26.7%)	7 (3.3%)	2 (1.0%)	169 (80.5%)	94 (43.5%)	78 (36.1%)	6 (2.8%)	0	178 (82.4%)
(ULN-3xULN]	6 (2.9%)	25 (11.9%)	3 (1.4%)	0	34 (16.2%)	9 (4.2%)	17 (7.9%)	3 (1.4%)	3 (1.4%)	32 (14.8%)
(3xULN-5xULN]	0	3 (1.4%)	1 (0.5%)	0	4 (1.9%)	0	3 (1.4%)	0	0	3 (1.4%)
> 5xULN	0	2 (1.0%)	0	1 (0.5%)	3 (1.4%)	0	2 (0.9%)	0	1 (0.5%)	3 (1.4%)
Total	110 (52.4%)	86 (41.0%)	11 (5.2%)	3 (1.4%)	210 (100%)	103 (47.7%)	100 (46.3%)	9 (4.2%)	4 (1.9%)	216 (100%)

The table above summarizes shifts in Sponsor-defined ranges from baseline to worst (maximum) post-baseline value for ALT and AST. In most cases, the worst (maximum) post-baseline levels remained ≤ ULN (upper limit of normal). There were few subjects with maximum post-baseline elevations of ALT and AST values of >3x ULN. Five doripenem-treated and four meropenem-treated subjects had baseline ALT values of ≤ULN with maximum post-baseline values of >5x ULN. One doripenem-treated subject had baseline AST levels below ULN at baseline, which increased to >5x ULN at maximum. One doripenem-treated and two meropenem-treated subjects fulfilled classification for Hy's Rule. Please refer to Sections 7.1.7.3.3 and 7.1.7.5 for details on specific cases.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Marker Outliers – Liver Function tests:
Marked outliers for various laboratory abnormalities were identified and pertinent information is summarized. In relation to liver function tests, doripenem-treated subjects with a baseline ALT ≤ULN and maximum post-baseline ALT >5x ULN in the doripenem phase 2 and 3 clinical studies were identified as marked outliers by the FDA Medical Officer.

In DORI-05, there were three patents in the doripenem group (Subject ID# 30404024, 40106187, and 40306177) and four subjects in the levofloxacin group who had ALT increases from ≤ULN at baseline to >5x ULN during the study. None of the patients had concurrent increases in total bilirubin that would fulfill Hy's Rule. In DORI-06, there were two patients who had ALT increases from ≤ULN at baseline to >5x ULN during the study: Subject # 35000106 fulfilled Hy's Rule and is discussed in Section 7.1.7.5 of this report; Subject #35500169 is discussed in this section. In DORI-07, there were two doripenem-treated (Subject ID# 01312512 and 01502045) and one meropenem-treated subjects who had ALT increases from ≤ULN at baseline to >5x ULN during the study. In DORI-08, there were four doripenem-treated (Subject ID# 00302057, 22605036, 38104006, and 38504077) and two meropenem-treated patients with ALT values that increased from <ULN at baseline to >5xULN at EOT or TOC. The following table summarizes details

about each doripenem-treated patient. Subjects who fulfilled Hy's Rule are not included in this table but are discussed separately in Section 7.1.7.5.

Table 87: FDA Medical Officer Summary Table of Doripenem-treated subjects having baseline ALT ≤ULN and maximum post-baseline ALT >5x ULN* in the doripenem phase 2 and 3 clinical trials, ITT population

Study	Subject #	Age/Sex/ Race	Study Drug Duration	Study Time Point/Visit	ALT (IU/L)	AST (IU/L)	ALK PHOS	Prior/Concomitant Medications
DORI-03	09-P0041	50/M/W	7 (IV only)	Baseline	20	20	60	Oxazepram, salbutamol, theophylline, heparin-fraction
				Day 3	22	20	69	
				EOT	252	152	65	
				TOC	67	20	87	
DORI-05	30404024	58/F/W	10 (IV) 1 (PO)	Baseline	15	17	193	Ranitidine, iclofenac, Agarol, Diazepam, Diclofenac, Diptrone, Heparin, Tramadol
				Day 3	16	14	176	
				EOT (IV)	32	21	194	
				TOC	176	148	269	
				LFU	127	41	509	
	40106187	37/F/B	5 (IV) 6 (PO)	Baseline	24	26	176	Ranitidine, Dipyrone, Acetaminophen, Ketoconazole (prior)
				Day 3	37	36	216	
				EOT (IV)	189	150	202	
				TOC	24	16	189	
				LFU	12	15	154	
	40306177	22/F/W	8 (IV) 3 (PO)	Baseline	16	18	211	Dipirone, Escopalamine
				Day 3	149	113	271	
				EOT (IV)	198	184	323	
				TOC	40	28	189	
				LFU	21	21	143	
DORI-06	35500169	25/F/H	5 (IV) 10 (PO)	Baseline	21	20	194	Acetaminophen, Dipirone, Metoclopramide, Ranitidine
				Day 3	419	368	569	
				EOT (IV)	257	82	495	
				TOC	25	22	288	
DORI-07	01312512	86/M/W	14 (IV only)	Baseline	23	45	26	Imdur, Toprol XL, Pepcid, Aspirin, Acyclovir, Morphine, Reglan, Midazolam, Fentanyl, Propofol, Zemuron, Lasix, Heparin, Pepcid, Levonox, Lopressor, Albuterol, Acetaminophen, Insulin, Vasopressin, Nystatin, Phenylephrine, Diflucan, Feosol
				Day 5	25	34	42	
				Day 8	106	97	78	
				Day 11	158	99	94	
				EOT (IV)	400	401	121	
				EFU	192	110	162	
	01502045	76/M/W	11 (IV only)	Baseline	31	27	226	Metoprolol, Insulin, Amiodarone, Heparin, Lasix, Fentanyl, TPN, Coumadin, Lisinopril, Hydrocodone, Hydromorphone, Lansoprazole, Levothyroxine, Zolpidem
				Day 5	67	56	294	
				Day 8	204	181	330	
				Day 11	349	174	394	
				TOC	29	24	142	
				EFU	149	53	379	
DORI-08	00302057	54/M/W	6 (IV) 5 (PO)	Baseline	16	15	52	Dilaudid, Protonix, Lovonox, Versed, Morphine, Zofran, Percocet
				Day 2	25	47	56	
				Day 5	36	47	98	
				EOT (IV)	99	88	161	
				EFU	475	272	381	
	22605036	22/M/W	8 (IV only)	Baseline	5	39	46	Tramadol, heparin-fraction, Hyoscine butylbromide, fentanyl, Barbital, Hydroxyzine, Ketoprofen, Paracetamol
				Day 2	41	46	58	
				Day 5	44	41	47	
				EOT (IV)	107	72	55	
				EFU	211	127	63	
	38104006	32/F/W	4 (IV) 4 (PO)	Baseline	28	46	193	Klosidol, Hyoscine butylbromide
				Day 2	16	21	191	
				EOT (IV)	24	37	183	
				TOC	168	135	575	
				EFU	275	127	544	
	38504077	44/M/W	8 (IV) 3 (PO)	Baseline	9	11	178	Diclofenac, Propofol, Metoclopramide, Ranitidine, D Propoxifen, Fentanyl, Isofluorane
				Day 5	13	21	176	
				EOT (IV)	21	26	176	
				TOC	56	25	245	
				EFU	207	159	285	

*excludes subjects who met Hy's Rule Criteria

DORI-03 Subject 09-P0041: This 50-year-old white man with no previous medical history entered the study with a diagnosis of pyelonephritis. The subject received doripenem 500 mg i.v. infusion q8h for 7 days. No adverse events were reported for this subject. His physical examination findings at baseline were reported as normal and there were no changes at Day 7 (end of i.v. therapy) or Day 16 (test of cure). At baseline, the subject had a fever (temperature, 39°C)(no further temperature readings were reported). The only concomitant medication reported was heparin (given on Days 1 and 2). His measured liver function test (LFT) values were normal at baseline and again on Day 3 (see summary table below for all LFT values). At the end of i.v. treatment on Day 7, the subject's ALT and AST levels were 5 times and 3 times the upper limit of normal (ULN), respectively, while his GGT, alkaline phosphatase, and bilirubin levels were normal and remained normal throughout the study. The elevation in transaminases was not associated with any report of clinical indices of liver dysfunction. By Day 16, the subject's ALT and AST levels had returned to within or near normal limits. The elevation in ALT and AST was not reported as an adverse event and the subject completed the study.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	20	20	13	60	3.4
Day 3	22	20	14	69	5.1
Day 7 (end of i.v.)	252	152	16	65	3.4
Day 16 (TOC)	67	20	21	87	6.8
Normal range	0-50	0-50	0-66	40-129	0-18.8

TOC=test of cure

FDA Medical Officer's Comments: The subject had normal liver function tests at baseline and on Day 3, had substantial elevations of ALT and AST on Day 7 (EOT), and had marked improvement in those test results by Day 16 (TOC). There was no description in the narrative summary above of hepatitis serology or other diagnostic tests to investigate the laboratory abnormalities reported. The marked upward flux in ALT and AST at EOT (IV) without a concurrent increase in ALK PHOS followed by a >50% decrease in the serum transaminase levels at TOC (following discontinuation of study drug) suggests a positive dechallenge. This pattern of hepatic enzyme abnormalities is suspicious for drug-induced hepatocellular injury and, consequently, a contributory role for doripenem cannot be ruled-out.

Patient 304/04024 was a 58-year-old Caucasian female who was enrolled with cLUTI and randomized to the doripenem treatment arm. Laboratory parameters of interest are summarized below. The patient had normal transaminase levels while receiving IV study drug but had an elevated ALT to >5xULN at the TOC assessment. AST, ALK and GGT levels were also elevated at the TOC assessment. Serum chemistry elevations at the LFU assessments demonstrated ALT and AST trending towards normal while alkaline phosphatase and GGT levels continuing to rise. Total bilirubin levels were within normal limits at all timepoints. An evaluation for acute hepatitis was performed between the TOC and

LFU visits and was negative to HBV, HAV, HCV and CMV. Given the resolving ALT and AST, the negative hepatitis work-up and the increasing ALK and GGT at the LFU assessment, it is unlikely that these findings are related to liver injury and more likely reflect effects from ongoing lithotripsy and an evolving obstructive condition.

Patient 30404024: Laboratory Values of Interest					
	ALT	AST	ALK Phos	Total bilirubin	GGT
Visit	(< 31 IU/L)[a]	(< 32 IU/L) [a]	(<240 IU/L) [a]	(6.5-17.1 µmol/L) [a]	(7-32 IU/L) [a]
Screening	15	17	193	6.5	17
Day 3	16	14	176	6.7	16
EOT(IV)	32	21	194	5.6	15
TOC	176*	148	269	5.8	49
LFU	127	41	509	5.3	205

[a] Normal range

FDA Medical Officer's Comments: The increased ALT at TOC was noted after the patient underwent lithotripsy for a kidney stone. The elevated ALK PHOS to greater than 1.5 x ULN in association with elevated GGT levels suggests a hepatic origin for the ALK PHOS, such that biliary obstruction is a consideration in this case. Although transaminasemia has been described following biliary lithotripsy, it is uncertain whether similar laboratory abnormalities occur following lithotripsy for kidney stones.[(11)]

Patient 401/06187 was a 38-year-old black female who was enrolled with pyelonephritis and was randomized to the doripenem treatment arm. Laboratory parameters of interest are summarized below. This patient had normal serum tranasminases levels and elevated ALK at screening and on Day 3 of IV study drug therapy. However, at EOT(IV) visit (Day 5), her ALT value increased to >5xULN. At this visit, elevations in AST (to >4xULN) and GGT (to >5xULN) were also noted. ALK remained elevated at all assessments. By the TOC visit, ALT, AST and GGT values returned to within normal limits without intervention and ALK was trending towards normal. Total bilirubin levels were within normal limits at all timepoints. Given the timing of these laboratory abnormalities relative to IV study drug therapy, a relationship to doripenem treatment could not be ruled out. However, the concurrent elevations in ALT, AST and GGT may be related to an obstructive cause rather than an injury to hepatocytes.

Patient 401/06187: Laboratory Values of Interest					
	ALT	AST	ALK Phos	Total bilirubin	GGT
Visit	(< 31 IU/L)[a]	(< 31 IU/L) [a]	(50-250 IU/L) [a]	(3.4-17.1 µmol/L) [a]	(9-35 IU/L) [a]
Screening	24	26	176	15.7	55
Day 3	37	36	216	8.4	119
EOT(IV)	189*	150	202	6.2	190
TOC	24	16	189	5.3	83
LFU	12	15	154	4.8	28

[a] Normal range

FDA Medical Officer's Comments: The marked upward flux in ALT, AST, and GGT at EOT (IV) without a concurrent increase in ALK PHOS followed by a >50% decrease in the serum transaminase levels at TOC (following discontinuation of study drug) suggests a positive dechallenge. This pattern of hepatic enzyme abnormalities is suspicious for drug-induced hepatocellular injury possibly with a cholestatic component.

Patient 403/06177 was a 38-year-old black female who was enrolled with pyelonephritis and was randomized to the doripenem treatment arm. Laboratory parameters of interest are summarized below. Patient 403/06177 had normal serum tranasminases levels but elevated ALK and GGT levels at screening. While receiving IV study drug therapy, both ALT and AST levels increased to >5xULN as ALK and GGT levels continued to rise. A renal ultrasound demonstrated increased echogenicity of both kidneys but an evaluation for the potential cause for the serum chemistry findings was not pursued. Transaminase levels, ALK and GGT levels all trended towards normal without intervention after IV study drug was discontinued. Total bilirubin levels were within normal limits at all timepoints. Based on the timing of these laboratory abnormalities relative to study drug therapy, a relationship to doripenem treatment could not be ruled out. However, the concurrent elevations in ALT, AST and GGT may also be related to an obstructive cause.

Patient 403/06177: Laboratory Values of Interest					
	ALT	**AST**	**ALK Phos**	**Total bilirubin**	**GGT**
Visit	**(< 31 IU/L)[a]**	**(< 31 IU/L) [a]**	**(50-250 IU/L) [a]**	**(3.4-17.1 µmol/L) [a]**	**(9-35 IU/L) [a]**
Screening	16	18	211	3.6	73
Day 3	149	113	271	5.3	200
EOT(IV)	184*	158*	323	2.9	266
TOC	40	28	189	2.7	172
LFU	21	21	143	5.8	101

[a] Normal range

FDA Medical Officer's Comments: The elevated ALK PHOS in association with elevated GGT levels suggests a hepatic origin for that enzyme. The rapid rise in the ALT, AST, and GGT on Day 3 with further increases noted by EOT (IV) followed by a >50% decrese in the serum transaminase levels at TOC (following discontinuation of study drug) suggests a positive dechallenge. However, as the etiology of the abnormal GGT and ALK PHOS at baseline was not delineated by the investigator, the potential relationship of the hepatic transaminase abnormalities to doripenem administration is uncertain.

Patient 355/00169 was 26-year-old Hispanic female who was enrolled with pyelonephritis. Laboratory parameters of interest are summarized below. She had a prior history of hypokalemia and no prior urologic history. Concomitant medications included: acetaminopen, dipirone, metoclopramide and rantidine. *Escherichia coli* was isolated from her baseline urine culture at $>10^5$ CFU/mL. This patient received doripenem for 5 days followed by oral levofloxacin 500 mg daily for an additional 10 days. Follow-up urine cultures were sterile after she received 2 days of IV study drug therapy. She was clinically

well and had a normal physical examination at the end of IV therapy and at the TOC visit. However, her liver transaminases increased while receiving IV study drug therapy and returned to within normal (ALT) or were returning to within normal (AST) levels without intervention by the TOC visit. Concomitant medications may have contributed to the observed increases in transaminase levels, however the role of doripenem in contributing to these observed findings cannot be ruled out.

Patient 355/00169: Laboratory Values of Interest			
	ALT	**AST**	**Total bilirubin**
Visit	**(< 31 IU/L)[a]**	**(< 32 IU/L) [a]**	**(<17.1 µmol/L)[a]**
Baseline	21	20	13.5
On IV therapy	419	368	7.2
EOT(IV)	257	82	6.2
TOC	25	22	6.0

[a] Normal range

FDA Medical Officer Comments: The marked increase in ALT and AST on IV therapy followed by a >50% decrese in the serum transaminase levels at TOC (following discontinuation of study drug) suggests a positive dechallenge. This pattern of hepatic enzyme abnormalities is suspicious for drug-induced hepatocellular injury, and a contributory role for doripenem cannot be ruled-out. Concomitant medications could have contributed to the findings observed, also.

DORI-07 Subject 01312512: This 86-year-old white man entered the study with a diagnosis of non-appendiceal complicated ("other sites") intra-abdominal infection. He had an extensive medical history including chronic obstructive pulmonary disease, hypoxia, respiratory insufficiency, tachypnea, coronary artery disease, myocardial infarction, premature ventricular contractions, tachycardia, metabolic acidosis, renal insufficiency, right nephrectomy, renal cell carcinoma, diarrhea, hematuria, and anemia. He received renal dose-adjusted doripenem 250 mg as a 60-minute i.v. infusion q12h and meropenem placebo given as a 3- to 5-minute i.v. bolus q8h for 14 days. No oral antibiotic therapy was administered following i.v. treatment. During the course of i.v. study drug therapy, concomitant medications included acyclovir (Day –1 for 17 days), morphine (Day 1 for 11 days), heparin (Day 2 for 10 days), metoprolol (Day 2 for 19 days), albuterol and ipratropium (Day 3, no end date reported), acetaminophen (Day 4 for 7 days, Day 11 for 1 day), insulin (Day 4 for 22 days), vasopressin (Day 9 for 7 days), and propofol (Day 12 for 1 day). The subject's liver function test (LFT) values were within normal limits at baseline and on Days 2 and 5 (see summary table below for all LFT values). On Day 8, the subject's ALT, AST, and GGT levels were more than twice the upper limit of normal (ULN), while his alkaline phosphatase and bilirubin values were normal. On Day 11, the LFT values had not changed significantly, but at the end of i.v. therapy on Day 14, the subject had ALT and AST values that were more than 8 times the ULN, a GGT value that was 3 times the ULN, and normal alkaline phosphatase and bilirubin values. The elevation in LFTs was not associated with any report of clinical indices of liver dysfunction. By Day 26 (12 days after ending i.v. therapy), his ALT, AST, and GGT values had decreased but were still above the ULN and his alkaline phosphatase value was now slightly elevated. The subject's bilirubin values were normal throughout the study. The

elevation in LFT values was not reported as an adverse event. The subject completed the study per protocol through the late follow-up visit. Note that this subject received several concomitant medications, some of which have the potential to raise hepatic enzymes.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	23	45	9	26	10.26
Day 2	20	39	8	34	6.84
Day 5	25	34	15	42	8.55
Day 8	106	97	88	78	15.39
Day 11	158	99	86	94	10.26
Day 14 (end of i.v.)	400	401	127	121	10.26
Day 26 (EFU)	192	110	86	162	6.84
Normal range	6-48	10-45	11-42	45-145	3.42-20.52

EFU=early follow-up

FDA Medical Officer Comments: The subject had normal liver function tests at baseline, Day 2, and on Day 5, had substantial elevations of ALT and AST from Day 8 to Day 14 (EOT), and then had marked improvement in those test results by Day 26 (EFU). There was no description in the narrative summary above of hepatitis serology or other diagnostic tests to investigate the laboratory abnormalities reported. The marked upward flux in ALT and AST at EOT (IV) without a concurrent increase in ALK PHOS followed by a >50% decrese in the serum transaminase levels at EFU (following discontinuation of study drug) suggests a positive dechallenge. This pattern of hepatic enzyme abnormalities is suspicious for drug-induced hepatocellular injury. Although the subject received concomitant medications having the potential for hepatotoxicity, a contributory role for doripenem cannot be ruled-out.

DORI-07 Subject 01502045: This 76-year-old white man entered the study with a diagnosis of nonappendiceal complicated ("other sites") intra-abdominal infection. His medical history included chronic obstructive pulmonary disease, hypoxia, acute inferior and posterior myocardial infarction (past history), atrial fibrillation, atrial flutter, ventricular tachycardia, anastomotic dehiscence, bilious drainage from midline wound, cancerous proximal transverse mass, end ileostomy, fascial closure, and fascial dehiscence. He also required a feeding tube. He received doripenem 500 mg as a 60-minute i.v. infusion q8h and meropenem placebo as a 3- to 5-minute i.v. bolus q8h for 11 days. Concomitant medications received during i.v. therapy included insulin (Day – 16 for 26 days), amiodarone (Day –15, no end date reported), furosemide (Day –15 for 20 days, Day 5 for 3 days), heparin (Day –15 for 26 days), fentanyl (Day –14 for 18 days), lisinopril and warfarin (each on Day –9, no end date), hydrocodone (Day –6 for 13 days), lansoprazole and levothyroxine (each on Day –4, no end date reported), and zolpidem (Day 8 for 3 days). At baseline, the subject had normal ALT, AST, and bilirubin values, but elevated GGT and alkaline phosphatase values (see summary table below for all liver function test [LFT] values). His bilirubin levels remained normal throughout the study, while his GGT levels fluctuated but remained elevated throughout the study. The subject's ALT and AST levels remained normal on Day 2, then progressively increased from Day 5 through Day 8.

On Day 6, increased alkaline phosphatase was reported as an adverse event that was considered moderate in severity and unlikely to be related to study medication. On Day 8, elevated ALT, AST, and GGT were reported as adverse events. The events were considered moderate in severity and not related or unlikely to be related to study medication. On Day 11 (end of i.v. therapy [EOT]), the subject's ALT level was 7 times the upper limit of normal (ULN) and his AST level was greater than 3 times the ULN. By Day 19 (early follow-up visit, 8 days after ending i.v. therapy), his ALT and AST levels had decreased, but were still above the ULN. His alkaline phosphatase level was above the ULN through the early follow-up visit. The central laboratory had requested follow-up tests for hepatitis; however, they were not conducted and by Day 53, his LFT values were within normal limits (ALT, AST, alkaline phosphatase, and bilirubin) or slightly above the ULN (GGT). The subject completed the study through the late follow-up visit.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	31	27	107	226	15.39
Day 2	25	21	85	199	8.55
Day 5	67	56	134	294	6.84
Day 8	204	181	139	330	5.13
Day 11 (end of i.v.)	349	174	190	394	5.13
Day 19 (EFU)	149	53	198	379	6.84
Day 53 (TOC)	29	24	59	142	6.84
Normal range	6-48	10-45	11-42	45-145	3.42-20.52

EFU=early follow-up; TOC=test of cure

In addition, low albumin was reported on Day 4 and increased lactate dehydrogenase was reported on Day 19. This subject, with a complex cardiovascular history (including coronary artery disease) who took multiple concomitant medications, developed increased transaminases related temporally to the administration of doripenem. The LFT's were highest at the EOT visit but had returned to baseline values at the test of cure visit.

FDA Medical Officer Comments: The subject had normal liver transaminases at baseline and Day 2 with elevated GGT and ALK PHOS. The ALT and AST increased from Day 5 to Day 11 (EOT), then declined by Day 19 (EFU) through Day 53(TOC). Hepatitis serology or other diagnostic tests were not performed to investigate the laboratory abnormalities reported. The marked upward flux in ALT and AST at EOT (IV) followed by a >50% decrese in the serum transaminase levels at TOC (following discontinuation of study drug) suggests a positive dechallenge. This pattern of hepatic enzyme abnormalities is suspicious for drug-induced hepatocellular injury. Although the subject received concomitant medications having the potential for hepatotoxicity, a contributory role for doripenem cannot be ruled-out.

Patient 003/02057: This doripenem-treated patient had AST values that increased from a value below the ULN at baseline to greater than 5xULN at the EFU or TOC visit. This patient had AST and ALT values within normal ranges at screening and while on study drug therapy as follows: AST values of 15 IU/L (Day -1), and 47 IU/L (Day 2 and Day 5); ALT values of 16 IU/L (Day -1), 25 IU/L (Day 2), and 36 IU/L (Day 5). On Day 7 at the

EOT(IV) visit, the patient had Grade 1 levels in both AST (99 IU/L) and ALT (88 IU/L). At the EFU visit (Day 11), Grade 3 levels were seen in AST (475 IU/L) and ALT (272 IU/L). No treatment-emergent adverse events associated with these laboratory abnormalities were reported for this patient.

FDA Medical Officer Comments: The liver function test abnormalities developed after doripenem had been discontinued. In view of the short half-life of the drug and the lack of a close temporal association with doripenem exposure, it is unlikely that doripenem had a contributory role in the subject's abnormal liver function test abnormalities.

DORI-08 Subject 22605036: This 22-year-old white man with no prior medical history entered the study with a diagnosis of complicated appendicitis. He received doripenem 500 mg as a 60-minute infusion q8h and meropenem placebo as a 3- to 5-minute i.v. bolus q8h for 8 days. No oral antibiotic therapy was administered following i.v. treatment. Concomitant medications received included heparin (Day –1 for 8 days), acetaminophen (Day 2 for 2 days), tramadol (Day 2 for 2 days, Day 3 for 6 days), and ketoprofen (Day 2 for 7 days, Day 8 for 10 days). At baseline and on Days 3 and 6, all liver function test (LFT) values (except AST that was borderline high at baseline - see following summary table for all LFT values) for this subject were within normal limits. By the end of i.v. therapy on Day 8, the subject's ALT level had increased to more than 2 times the upper limit of normal (ULN) and his AST level was more than 1.5 times the ULN, while other LFTs were within normal limits. On Day 17 (early followup visit; 9 days after ending i.v. therapy), the subject's ALT value had nearly doubled since the end of i.v. therapy and his AST value had risen to greater than 3 times the upper limit of normal. His GGT, alkaline phosphatase, and bilirubin values were normal throughout the study. The elevations in ALT and AST on Days 8 and 17 were not reported as adverse events, were not associated with any reports of clinical liver disease, and the subject completed the study per protocol through the late follow-up visit. Following the discontinuation of doripenem, the subject's ALT level remained elevated at the early follow-up visit; however, there were no subsequent values reported (e.g., none were reported at the test of cure visit). Note that this subject received an NSAID (ketoprofen), which has the potential to cause liver toxicity, on Days 2 through 17.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	5	39	22	46	12.141
Day 3	41	46	27	58	15.39
Day 6	44	41	33	47	6.156
Day 8 (end of i.v.)	107	72	39	55	5.814
Day 17 (EFU)	211	127	47	63	9.918
Normal range	NR-41	NR-38	15-75	40-129	3.42-17.10

EFU=early follow-up; NR=none reported.

FDA Medical Officer Comments: Elevations in ALT and AST became evident by Day 8 (EOT) and increased further by Day 17 (EFU). There was no concomitant rise in ALK PHOS, GGT, or bilirubin. No subsequent hepatic enzyme tests were reported, and there

were no hepatitis serologies r other diagnostic tests performed. Although the subject received concomitant medications having the potential for hepatotoxicity, a contributory role for doripenem cannot be ruled-out.

DORI-08 Subject 38104006: This 32-year-old white woman with no relevant past medical history entered the study with a diagnosis of non-appendiceal complicated ("other sites") intra-abdominal infection. The subject received doripenem 500 mg as a 60-minute infusion q8h and meropenem placebo as a 3- to 5-minute i.v. bolus q8h for 4 days followed by oral amoxicillin/clavulanate tablets (1000 mg once or twice daily) for 4 days. No concomitant medications were reported after Day 1 (baseline) of the study. On Day 1, the subject experienced myocardial ischemia; the event was considered moderate in severity and not related to i.v. study medication. It resolved in 2 days. No other adverse events were reported during the study. The subject's liver function tests (LFTs) were normal during her 4 days of i.v. therapy and 4 days of oral antibiotic therapy (see summary table below for all LFT values). On Day 14 (early follow-up visit; 10 days after ending i.v. doripenem treatment), the subject's ALT, AST, GGT, and alkaline phosphatase levels were greater than 2 times to 8 times the upper limit of normal (ULN); her bilirubin level was also above the ULN. By Day 42 (test of cure visit), the subject's ALT, AST, and GGT had decreased but were still more than 3 times the ULN and her alkaline phosphatase level had risen further since the Day 14 visit. The subject completed the study per the protocol through the late follow-up visit. The elevation in LFT's in this subject occurred more than 1 week after discontinuation of doripenem therapy.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	28	46	30	193	6.84
Day 2	16	21	24	191	6.669
Day 4 (end of i.v.)	24	37	32	183	4.617
Day 14 (EFU)	275	127	119	544	20.007
Day 42 (TOC)	168	135	103	575	17.1
Normal range	NR-31	NR-32	7-32	NR-240	NR-17.10

EFU=early follow-up; NR=none reported; TOC=test of cure

FDA Medical Officer Comments: The patient had elevations in ALT, AST, GGT, ALK PHOS, and bilirubin at Day 14 (EFU visit), about 10 days after discontinuation of doripenem. By Day 42 (TOC), she had decreases in ALT and AST, but persistent increases in ALK PHOS and bilirubin. She had been treated with doripenem for only four days followed by oral switch (amoxicillin/clavulanate) for another four days. As doripenem has a short half-life and the LFT elevation were reported after discontinuation of the drug, there is not temporal association of exposure with the onset of the event. Thus, it is unlikely that the hepatic enzyme elevations were related to doripenem administration.

DORI-08 Subject 38504077: This 44-year-old white man entered the study with a diagnosis of non-appendiceal complicated ("other sites") intra-abdominal infection. The only reported medical history for this subject was biliary colic and double

urinary excretory system. The subject received doripenem 500 mg as a 60-minute infusion q8h and meropenem placebo as a 3- to 5-minute i.v. bolus q8h for 8 days followed by oral amoxicillin/clavulanate tablets (1000 mg once daily) for 3 days. Concomitant medications included metoclopramide (Day 1 for 8 days), ranitidine (Day 1 for 8 days, Day 8 for 1 day), dextropropoxyphene (Day 4 for 1 day), and diclofenac (Day 6 for 3 days, Day 8 for 2 days). The subject experienced vomiting on Day 3 and diarrhea on Day 5; each lasted 1 day and was considered mild and not related to study medication. No other adverse events were reported during the study. The subject's liver function tests (LFTs) were normal throughout i.v. doripenem treatment (see summary table below for all LFT values). On Day 18 (early follow-up visit; 10 days after ending i.v. treatment), the subject's ALT and AST values rose to 4 to 5 times the upper limit of normal (ULN), while the subject's GGT, alkaline phosphatase and bilirubin levels remained normal or were near normal levels. By Day 32 (test of cure), the subject's ALT level had decreased to near the ULN and his AST level was within normal limits. The subject completed the study per protocol through the late follow-up visit.

Day	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Alkaline Phosphatase (IU/L)	Total Bilirubin (µmol/L)
Baseline	9	11	13	178	11.286
Day 4	11	16	23	164	7.182
Day 5	13	21	24	176	9.063
Day 8 (end of i.v.)	21	26	37	176	12.312
Day 18 (EFU)	207	159	33	285	6.156
Day 32 (TOC)	56	25	NR	245	NR
Normal range	NR-41	NR-38	11-49	NR-270	NR-17.10

EFU=early follow-up; NR=none reported; TOC=test of cure

FDA Medical Officer Comments: The subject experienced liver function test abnormalities 10 days following discontinuation of doripenem administration (at EFU visit on Day 18) and five days after discontinuation of the oral switch agent. There is no record of hepatitis serologies. Follow-up testing at Day 32 (TOC) revealed substantial improvements in the ALT and AST levels. As doripenem has a short half-life and the LFT elevations were reported after discontinuation of the drug, there is not temporal evidence to associate doripenem exposure with the onset of the event. Thus, it is unlikely that the hepatic enzyme elevations were related to doripenem administration. There is no record of any concomitant medications following study Day 8 that overlapped with the Day 18 (EFU) visit.

DORI-07: Liver function test parameters that remained abnormal at the final study visit

Two patients in the doripenem treatment arm had maximum increases from baseline to Grade 3 or 4 in serum chemistry parameters that remained abnormal (i.e., Grade 3 or 4) at their final study visit:

Doripenem-treated Patient 201/06049 had a screening GGT value of 315 IU/L (normal range: 15 to 75 IU/L). On Days 3 and 6, while on IV study drug therapy, the patient's GGT

value decreased to 115 and 157 IU/L, respectively. On Day 9, the patient had a Grade 3 increase in GGT to 398 IU/L, and at the EOT(IV) visit on Day 10, the patient's GGT value had increased further to 432 IU/L, which was still considered a Grade 3 abnormality.

Doripenem-treated Patient 372/04111 had a screening GGT value of 460 IU/L (normal range: 11 to 49 IU/L), which was considered a Grade 3 abnormality. On Days 3 and 6, while on IV study drug therapy, the patient's GGT values continued to be considered Grade 3 abnormalities at 248 and 409 IU/L, respectively. At the EOT(IV) visit on Day 8, the patient had a Grade 4 increase in GGT to 581 IU/L. Twelve days later at the EFU visit, the patient's GGT value had decreased to 254 IU/L, which was still considered a Grade 3 abnormality.

FDA Medical Officer Comments: Both subjects had elevated GGT values at baseline and during study drug treatment at a Grade 3 level. One subject had a transient increase to a Grade 4 abnormality followed by a decrease back to a Grade 3 abnormality. It is unlikely that the liver test abnormalities were related to doripenem treatment.

Marker Outliers – Other serum chemistry tests
The following narratives refer to other chemistry laboratory abnormalities that were marked outliers in the analysis:

DORI-05:
As described in the Sponsor's Clinical Study Report DORI-05, five patients (Patients 101/07063, 101/07017, 101/07158, 104/07134, and 104/08015) in the doripenem treatment arm and 1 patient (Patient 109/09036) in the levofloxacin treatment arm had a maximum increase in potassium concentration from Grade 0 at baseline to Grade 4. The maximum shift occurred at the EOT(IV) visit for 3, and at the LFU visit for 2 doripenem-treated patients. For the levofloxacin-treated patient, the maximum shift was noted at the TOC visit. Other than the single timepoint where the maximum shift to Grade 4 occurred, the potassium levels for all 6 patients in both treatment arms were within normal limits at all other time points measured. Because the extreme results appear spurious, it is suspected that blood samples were hemolyzed. The maximum shifts in these patients were unlikely related to study drug given the random occurrence for each patient. Furthermore, the timepoint when the maximum shift occurred in 3 of the 6 affected patients (i.e, at the TOC or LFU visits) was several days to weeks after the study drug had already been discontinued.

DORI-06:
Patient 359/00350 was a 78-year-old Caucasian female with pyelonephritis who received doripenem IV for 10 days. Follow-up urine cultures were sterile and the patient did clinically well. At the TOC visit, the patient was clinically cured, however she had asymptomatic bacteriuria with *P. mirabilis*. Potassium levels were 5.4 mmol/L (normal 3.5-5.5) at baseline, 4.9 while receiving IV study drug, 5.1 at EOT(IV) and 7.1 the TOC visit. It is doubtful that the hyperkalemia at the TOC visit was related to IV study drug given the patient's potassium level was within normal limits while receiving IV study drug therapy. It is probable that this finding is secondary to hemolysis of the sample since this was an

isolated event that occurred after the patient was removed from study drug therapy.

FDA Medical Officer's Comments: The patient's serum potassium at LFU visit was 5.0 mmol/L, which was within the normal range. The Sponsor's assessment of the event appears reasonable.

Patient 45100077: This 84-year-old white man entered the study with a diagnosis of symptomatic complicated lower urinary tract infection. His medical history included bronchopneumonia, chronic obstructive pulmonary disease, arterial systemic hypertension, cardiac arrhythmia, left branch block, dysuria, and renal impairment. The diagnosis of renal impairment was made approximately 9 months before entry into the study. At baseline, the subject had elevated blood urea nitrogen (23.57 mmol/L; normal range, 3.57-16.07 mmol/L), creatinine (132.6 μmol/L; normal range, 70.72-106.8 μmol/L), and uric acid (0.4403 mmol/L; normal range; 0.2-0.42 mmol/L) levels. These clinical laboratory analytes remained elevated in this subject through the test of cure visit (Day 20). The subject's calculated creatinine clearance at baseline (using the Cockcroft and Gault equation) was 31.1 mL/min. The subject received renal dose-adjusted doripenem 250 mg as a 60-minute infusion q8h for 11 days. No oral antibiotic therapy was administered following i.v. treatment. His potassium level was normal at baseline and on Day 4. At the end of i.v. therapy on Day 11, his potassium level was above the upper limit of normal (ULN) (5.8 mmol/L; normal range, 3.6-5.0 mmol/L). Hyperkalemia and syncope were reported as adverse events on Day 15 (4 days after doripenem was discontinued), which were considered severe and life threatening, respectively (narrative details as provided in the DORI-06 clinical study report are repeated below). He also experienced peripheral edema on Day 20 (which was mild and not related) and hypotension on Day 22; both events were considered mild or moderate and not related to study medication. The subject completed the study per protocol through the late follow-up visit.
The following was extracted from the DORI-06 Clinical Study Report, Section 15.3:
On Day 15, the subject was hospitalized after he reported experiencing 3 episodes of brief loss of consciousness causing him to fall. The probable diagnosis was that the syncope was caused by cardiac arrhythmia and atrioventricular block was confirmed by an electrocardiogram. His cardiac enzymes were within normal range, but he had a potassium level of 6.9 mEq/L (normal range not reported). For treatment of the hyperkalemia, the subject received sodium chloride with calcium gluconate, glucose, regular insulin, and furosemide. A pacemaker was implanted on Day 21 for treatment of sick sinus syndrome, which was the final diagnosis. The investigator considered the syncope resolved on Day 23 and the subject was discharged from the hospital on the same day. The investigator assessed the event as severe, serious because it was life threatening and led to hospitalization, and unlikely unrelated to treatment with study drug therapy.

FDA Medical Officer's Comments: Hyperkalemia and syncope were noted four days following discontinuation of doripenem. In view of the short half-life of the drug, it is unlikely that either event was related to administration of the drug.

DORI-07:

Doripenem-treated patient 015/02045 had a normal screening potassium value of 5.0 mmol/L (normal range: 3.6 to 5.5 mmol/L). On Days 2, 5, 8, and 11, while on IV study drug therapy, the patient's potassium levels were 4.9, 5.2, 4.4, and 5.0 mmol/L (i.e., within the normal range). On Day 19, at the EFU visit, the patient had a Grade 4 increase in potassium to 7.4 mmol/L, which was confirmed by repeat analysis. Thirty-four days later at the TOC visit, the patient's potassium value had returned to within the normal range (5.2 mmol/L).

Doripenem-treated patient 204/06005 had screening potassium and sodium values of 5.1 mmol/L (normal range: 3.5 to 5.1 mmol/L) and 137 mmol/L (normal range: 136 to 146 mmol/L), respectively. On Day 3, while on IV study drug therapy, the patient had a Grade 4 increase in potassium to 11.8 mmol/L and a Grade 4 decrease in sodium to 112 mmol/L. At the EOT(IV) visit on Day 6, the patient's potassium value had decreased to 5.2 mmol/L and his sodium value had increased to 140 mmol/L (i.e., within the normal range). On Day 8, an unscheduled laboratory assessment showed a potassium value of 5.3 mmol/L and a normal sodium value (140 mmol/L). His sodium value remained within the normal range (141 mmol/L) and his potassium value decreased to 4.2 mmol/L (i.e., within the normal range) at the EFU visit 7 days later. The abnormal findings on Day 3 were probably related to an issue with sample collection and analysis as neither the hyperkalemia nor hyponatremia were considered related to study drug therapy by the investigator nor did they require any treatment to correct the abnormalities. In addition, results from samples taken before and after these abnormal values were within the normal ranges.

Doripenem-treated patient 372/04079 had a screening non-fasting glucose value of 6.33 mmol/L (normal range: 3.89 to 5.83 mmol/L). On Day 3, the patient had a Grade 4 increase in non-fasting glucose to 30.86 mmol/L. At the EOT(IV) visit on Day 5, the patient's non-fasting glucose value had decreased to 9.93 mmol/L, and 18 days later, at the EFU visit, it was within the normal range (4.44 mmol/L).

Doripenem-treated patient 373/04005 had a screening potassium value of 4.0 mmol/L (normal range: 3.5 to 5.5 mmol/L). On Days 3, 5, 7, and 11, while on IV study drug therapy, the patient's potassium values were 4.5, 4.4, 4.5, and 4.7 mmol/L, respectively. At the EOT(IV) visit on Day 15, the patient had a Grade 4 increase in potassium to 10.4 mmol/L. Eleven and 31 days later, at the EFU and TOC visits, respectively, the patient's potassium values had returned to the normal range (4.6 and 4.8 mmol/L, respectively).

Marker Outliers – Hematology tests:
The following narratives refer to hematology laboratory abnormalities that were marked outliers in the analysis:

DORI-05:
As described in the Sponsor's Clinical Study Report DORI-05, one patient (Patient 201/07094) in the doripenem treatment arm and 2 patients (Patients 203/07105 and 204/09082) in the levofloxacin treatment arm had maximum shifts in absolute neutrophil count from Grade 0 at baseline to Grade 4. For all 3 patients, the maximum shift to Grade 4 occurred by Day 3 but returned to Grade 0 by the EOT(IV) assessment. All patients

continued to have Grade 0 absolute neutrophil counts at the TOC and LFU visits. Given that the Grade 4 absolute neutrophil count returned to Grade 0 while the patients continued to receive IV study drug therapy, it is unlikely that these shifts were caused by IV study drug administration. Instead the observed decreases in absolute neutrophil count probably reflect the patients' underlying infectious process.

DORI-06:
No patients had a maximum or last post-baseline Grade 4 hematology parameter except for Patient 453/ 00150 who had a Grade 3 WBC count (24.65 x 109/L) at baseline (Screening) and had a Grade 4 value (32.47 x 109/L) at the LFU visit.

DORI-07:
No doripenem-treated patient had Grade 4 shifts in hematology parameters compared with 2 meropenem-treated patients as follows:

– Meropenem-treated Patient 040/02073 had a normal WBC count at screening and during IV study drug therapy (range: 6.6 to 8.8 x 10^9/L; normal range: 4.1 to 12.3 x 10^9/L). The patient completed the study. On Day 31, 23 days after the last meropenem dose and at the EFU visit, the patient had a Grade 4 increase in WBC count to 40.9 x 10^9/L, which the investigator considered clinically significant. No further relevant hematology values were reported for this patient.

– Meropenem-treated Patient 402/04519 had a normal screening WBC count of 6.08 x 10^9/L (normal range: 3.5 to 10.5 x 10^9/L). On Day 8, while receiving IV study drug therapy, the patient had a Grade 4 increase in WBC count to 38.2 x 10^9/L. The patient was also reported to have concurrent worsening anemia (hemoglobin of 82 g/L, normal range: 135 to 175 g/L; hematocrit of 26%, normal range: 39 to 50%; RBC value of 2.6 x 1012/L, normal range: 4.3 to 5.7 x 1012/L). On Day 10, the patient died due to sepsis.

There were no Grade 0 to 4 hematology shifts noted except for WBC shifts, which were considered by the Sponsor to be related to the disease process in this study. Two patients in each treatment arm had maximum increases from baseline to Grade 3 or 4 in hematology parameters that remained abnormal (i.e., Grade 3 or 4) at their final study visit:

– Doripenem-treated Patient 013/02016 had a normal screening WBC count of 12.1 x 10^9/L (normal range: 4.1 to 12.3 x 10^9/L). On Day 2, while on IV study drug therapy, the patient had a Grade 3 increase in WBC count to 18.1 x 10^9/L. On Day 5 and at the EOT(IV) visit on Day 8, the patient's WBC count decreased to 9.9 and 9.0 x 10^9/L, respectively (i.e., within the normal range). However, 12 days later at the EFU visit, the patient had a Grade 3 increase in WBC count to 20.2 x 10^9/L.

– Doripenem-treated Patient 018/01504 had a high normal screening WBC count of 12.3 x 109/L (normal range: 4.1 to 12.3 x 10^9/L). On Day 3, while on IV study

drug therapy, the patient had a Grade 3 increase in WBC count to 24.1 x 10^9/L. At the EOT(IV) visit on Day 8, the patient's WBC count decreased to 18.9 x 10^9/L, which was still considered to be a Grade 3 abnormality.

– Meropenem-treated Patient 040/02515 had a low screening WBC count of 2.3 x 10^9/L (normal range: 4.1 to 12.3 x 10^9/L). On Days 2 and 5, while on IV study drug therapy, the patient's WBC count was 10.6 and 12.8 x 10^9/L, respectively. On Day 8, the patient had a Grade 3 increase in WBC to 18.6 x 10^9/L. At the EOT(IV) visit on Day 11, the patient's WBC count decreased to 14.8 x 10^9/L, which was considered a Grade 2 abnormality. However, 10 days later at the EFU visit, the patient's WBC count had returned to a Grade 3 abnormal value of 15.6 x 10^9/L.

– Meropenem-treated Patient 200/06022 had a normal screening WBC count of 6.1 x 10^9/L (normal range: 1.5 to 11.0 x 10^9/L). On Day 2, while on IV study drug therapy, the patient had a Grade 3 increase in WBC count to 18.1 x 10^9/L. The patient's WBC count returned to within the normal range on Day 5 and on Day 8 at the EOT(IV) visit (8.8 and 10.2 x 10^9/L, respectively). At the EFU visit, 11 days later, the patient's WBC count had returned to a Grade 3 abnormal value (20.4 x 10^9/L).

FDA Medical Officer Comments: None of the individual subjects described above was discontinued as a result of a study drug-related hematology laboratory abnormality.

DORI-08:
The following provides a listing of subjects had Grade 4 toxicity grade shifts in hematology parameters along with Sponsor's narratives:

On Day 1, doripenem-treated Patient 048/02026 had a normal neutrophil count of 2.71 x 10^9/L (normal range: 2.03 to 8.36 x 10^9/L). On Day 18 at the EFU visit, the patient had a Grade 4 decrease in neutrophil count to 0.07 x 10^9/L. No immediate retest was performed and no outcome was given.

On Day 1, doripenem-treated Patient 232/05038 had a normal platelet count of 271 x 10^9/L (normal range: 150 to 450 x 10^9/L). On Day 2, the patient had a Grade 4 decrease in platelet count to 11 x 10^9/L. This event was resolved by Day 4, with a platelet count of 433 x 10^9/L and remained within the normal range thereafter.

On Day 1, doripenem-treated Patient 428/04062 had a normal hemoglobin level of 163 g/L (normal range: 135 to 175 g/L). On Day 2, the patient had a Grade 4 decrease to 52 g/L. The event resolved with a hemoglobin level of 148 g/L and remained within the normal range thereafter.

On Day 1, meropenem-treated Patient 385/04047 had a normal platelet count of 383 x 10^9/L (normal range: 140 to 400 x 10^9/L). On Day 23, the patient had a

Grade 4 decrease in platelet count to 19 x 10^9/L. This event was resolved by Day 26 with a platelet count of 317 x 10^9/L.

On Day 1, meropenem-treated Patient 430/04512 had a normal WBC count of 4.53 x 10^9/L (normal range: 3.5 to 10.5 x 10^9/L). On Day 2, the patient had a Grade 3 increase to 23.47 x 10^9/L, and by Day 8, the count had increased to a Grade 4 level of 36.75 x 10^9/L. One day prior, the patient presented with septic shock. The WBC count attenuated to a Grade 3 level of 19.07 x 10^9/L on Day 11. No further hematology values were reported for this patient.

FDA Medical Officer Comments: None of the five subjects described above was discontinued as a result of a study dryg-related hematology laboratory abnormality.

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

Special assessments were conducted with respect to hematology laboratory test abnormalities, liver function laboratory test abnormalities, subjects who fulfilled Hy's Rule, renal failure/impairment-related adverse events, anemia (Coombs testing), *Clostridium difficile* colitis, hypersensitivity reactions, and valproic acid drug-drug interactions in relation to the phase 3 clinical trials. In addition, special procedures that were required due to an adverse event are detailed. A Hematology consultataion was obtained to assess anemia as a treatment-emeregent adverse event and to evaluate doripenem as a potential cause for drug-induced hemolytic anemia.

Hematology Laboratory Test Abnormalities
Phase 2 Study:
A high incidence of increased eosinophil counts and eosinophila was observed at both dosing regimens among the doripenem-treated subjects (16/121, 13.2%) in DORI-03. The investigators assessed 14 of the cases (88%) as being related or possibly related to the study drug. Although none of the cases was associated with rash concomitantly, the hematologic findings suggest possible hypersensitivity reactions to the study drug. In the doripenem phase 3 studies in cUTI and cIAI, in contrast, increased eosinophil counts and eosinophilia were not observed as treatment-emergent adverse events. This striking difference in incidence between the phase 2 and phase 3 trials raises concern that there may have been differences in the drug substance formulation between the phase 2 and phase 3 batches that could have contributed to the problem. According to the FDA Chemistry Reviewer, there were changes to drug substance synthesis methods and drug product manufacturing over the preclinical, clinical, and proposed commercial phases of development. Phase 2 batches had [redacted] n the formulation, and the drug product was manufactured [redacted] The phase 3 formulation had no excipients in drug substance, and drug product was made by [redacted]

Phase 3 Studies:
The comparative number of subjects with hematology test abnormalities in the doripenem

phase 3 clinical studies that were assessed as treatment-emergent adverse events is summarized in the following table:

Table 88: FDA Medical Officer Summary of hematology laboratory test abnormalities as treatment-emergent adverse events (n, %) in subjects in the doripenem phase 3 clinical studies, ITT population

Parameter	Total # of subjects, n	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem N=376	Levofloxacin N=372	Doripenem N=423	Doripenen N=235	Meropenem N=236	Doripenem N=242	Meropenem N=233
WBC increased	10	0	0	0	5 (2.13)	4 (1.69)	0	1 (0.43)
Platelets increased	9	1 (0.27)	1 (0.27)	0	5 (2.13)	1 (0.42)	1 (0.41)	0
Neutrophils increased	5	0	0	0	3 (1.28)	1 (0.42)	0	1(0.43)
Hematocrit decreased	3	0	0	0	1 (0.43)	1 (0.42)	1 (0.41)	0
Platelet count decreased	3	0	0	1 (0.24)	0	0	1 (0.41)	1 (0.43)
Toxic granulation	3	0	0	0	1 (0.43)	1 (0.42)	1 (0.41)	0
White blood cell count increased	2	0	1 (0.27)	0	0	1 (0.42)	0	0
Band neutrophil count increased	1	0	0	0	1 (0.43)	0	0	0
Band neutrophil percentage increased	1	0	0	0	1 (0.43)	0	0	0
Coagulation time increased	1	0	0	0	0	0	1 (0.41)	0
Hemoglobin decreased	1	0	0	0	0	1 (0.42)	0	0
INR increased	1	0	0	0	0	0	1 (0.41)	0
Increased platelets	1	0	0	0	0	0	0	1 (0.43)
International normalised ratio abnormal	1	0	0	0	0	0	1 (0.41)	0
Lymphocyte count decreased	1	0	0	0	1 (0.43)	0	0	0
Neutrophil morphology abnormal	1	0	0	0	0	0	1 (0.41)	0
Neutrophil percentage abnormal	1	0	0	0	1 (0.43)	0	0	0
Neutrophil percentage increased	1	0	0	0	1 (0.43)	0	0	0
PT increased	1	0	0	0	0	1 (0.42)	0	0
Prothrombin time decreased	1	0	0	0	0	0	0	1 (0.43)
Prothrombin time prolonged	1	0	0	0	0	0	1 (0.41)	0
Red blood cell count increased	1	0	0	0	0	1 (0.42)	0	0
Thrombocyte count increased	1	0	0	0	0	0	1 (0.41)	0

As depicted in the table above, the most frequently reported abnormal hematology test parameter considered to be a treatment-emergent adverse event was WBC increased. There was some terminology overlap evident, such as "platelets increased," "increased platelets," and "thrombocyte count increased". Most adverse events related to WBC increased were derived from both treatment arms of DORI-07. The total number of hematology test-related adverse events was small across the four phase 3 studies, and there were no marked consistent disparities in the frequency of such adverse events within the comparative treatment groups. In doripenem-treated subjects in DORI-07, there was a higher frequency of WBC increased, platelets increased, and neutrophils increased compared to the comparator arm, but the disparity in frequency of those events was not replicated in the accompanying DORI-08 experience.

Liver Function Laboratory Test Abnormalities

The comparative number of subjects with liver function test abnormalities assessed as treatment-emergent adverse events is summarized in the following table:

Table 89: FDA Medical Officer Summary of liver function laboratory test abnormalities as treatment-emergent adverse events (n, %) in subjects in the doripenem phase 3 clinical studies, ITT population

Parameter	Total # of subjects, n	DORI-05		DORI-06	DORI-07		DORI-08	
		Doripenem N=376	Levofloxacin N=372	Doripenem N=423	Doripenen N=235	Meropenem N=236	Doripenem N=242	Meropenem N=233
GGT increased	32	6 (1.60)	6 (1.61)	1 (0.24)	6 (2.55)	3 (1.27)	5 (2.07)	5 (2.15)
Elevated liver enzymes	27	4 (1.06)	6 (1.61)	5 (1.18)	3 (1.28)	7 (2.97)	1 (0.41)	1 (0.43)
ALT increased	16	2 (0.53)	7 (1.88)	0	2 (0.85)	1 (0.42)	1 (0.41)	3 (1.29)
AST increased	7	2 (0.53)	2 (0.54)	0	1 (0.43)	1 (0.42)	0	1 (0.43)
GGTP increase	3	0	0	0	0	0	1 (0.41)	2 (0.86)
Bilirubin increased	2	0	0	0	0	1 (0.42)	1 (0.41)	0
Bilirubin total increased	2	0	0	0	1 (0.43)	1 (0.42)	0	0
Transaminases increased	2	0	0	0	0	2 (0.85)	0	0
GGTP abnormal	1	0	0	0	1 (0.43)	0	0	0
Gamma glutamyl transpeptidase increased	1	0	0	0	1 (0.43)	0	0	0
Gamma-glutamyltransferase increased	1	0	0	0	0	0	1 (0.41)	0

As depicted in the table above, the most frequently reported abnormal liver function test parameters considered to be a treatment-emergent adverse event were GGT increased and elevated liver enzymes. These adverse events were noted in both treatment arms of all of the doripenem phase 3 clinical trials. There was some terminology overlap evident, such as "GGT increased" and "Gamma-glutamyltransferase increased". The total number of liver function test-related adverse events was small across the four phase 3 studies, and there were no consistent marked disparities in the frequency of such adverse events within the comparative treatment groups. In the doripenem-treated subjects in DORI-07, there was a higher frequency of GGT increased compared to meropenem-treated subjects, but the disparity in frequency of that event was not replicated in the accompanying DORI-08 experience. Subjects who fulfilled Hy's Rule are described below.

Hy's Rule:
The Sponsor defined Hy's High Risk classification (Section 7.1.7.1) as an ALT value greater than 3xULN in combination with a total bilirubin greater than 1.5xULN at a given time point. The following tables summarize the number of subjects who fulfilled Hy's Rule in the doripenem Phase 3 clinical studies, detailed information on each doripenem-treated case, and laboratory parameter values at various study visits.

There were eleven subjects in the pooled doripenem Phase 3 studies who fulfilled Hy's Rule as depicted in Table 90 below. Five subjects fulfilled Hy's Rule at screening (Baseline): one levofloxacin-treated patient in DORI-05 (subject #03103074), one doripenem-treated patient in DORI-07 (subject # 03502005), two doripenem-treated patients in DORI-08 (subjects 04302050 and 38504049), and one meropenem-treated patient in DORI-08 (subject # 38103013). One of the five subjects withdrew consent (subject #03103074 after receiving four days of levofloxacin). The other four subjects successfully completed study drug and study participation.

Table 90: FDA Medical Officer List of all Study Subjects who fulfilled Hy's Rule in the doripenem Phase 3 Clinical Trials, ITT population

Study	Subject#	Treatment	Lab Test	Lab Value	Units	Visit	Window*	Study Day
DORI-05	03103074	Levo	ALT (SGPT)	123	U/L	SCREENING	Baseline	1
			TOTAL BILIRUBIN	2.8	MG/DL			
DORI-06	35000106	Dori	ALT (SGPT)	486	U/L	END IV THERAPY	EOT(IV)	3
			TOTAL BILIRUBIN	1.45	MG/DL			
			ALT (SGPT)	379	U/L	RP/UNS SFTY LAB ASMT	EFU	8
			TOTAL BILIRUBIN	1.63	MG/DL		EFU, MAXIMUM#	
	45000084	Dori	ALT (SGPT)	178	U/L	ON STUDY DRUG	MAXIMUM#	4
			TOTAL BILIRUBIN	2.4	MG/DL			
DORI-07	03502005	Dori	ALT (SGPT)	225	U/L	SCREENING	Baseline	1
			TOTAL BILIRUBIN	3.3	MG/DL			
			ALT (SGPT)	145	U/L	ON STUDY DRUG	MAXIMUM#	2
			TOTAL BILIRUBIN	2.5	MG/DL			
	40104517	Dori	ALT (SGPT)	137	U/L	EARLY FOLLOW-UP	EFU	23
			TOTAL BILIRUBIN	1.71	MG/DL		EFU, MAXIMUM#	
DORI-08	04302050	Dori	ALT (SGPT)	214	U/L	SCREENING	Baseline	1
			TOTAL BILIRUBIN	2.1	MG/DL			
	38504049	Dori	ALT (SGPT)	130	U/L	SCREENING	Baseline	1
			TOTAL BILIRUBIN	5.47	MG/DL			
	43104023	Dori	ALT (SGPT)	150	U/L	ON STUDY DRUG	EOT(IV)	12
			TOTAL BILIRUBIN	2.31	MG/DL		EOT(IV), MAXIMUM#	
	38103013	Mero	ALT (SGPT)	160	U/L	SCREENING	Baseline	1
			TOTAL BILIRUBIN	1.93	MG/DL			
	00302056	Mero	ALT (SGPT)	169	U/L	ON STUDY DRUG	MAXIMUM#(IV)	11
			TOTAL BILIRUBIN	3.4	MG/DL			
			ALT (SGPT)	186	U/L	END IV THERAPY	EOT(IV), MAXIMUM#	14
			TOTAL BILIRUBIN	4.8	MG/DL		EOT(IV)	
			ALT (SGPT)	146	U/L	EARLY FOLLOW-UP	EFU	27
			TOTAL BILIRUBIN	8.9	MG/DL		EFU, MAXIMUM#	
	04502513	Mero	ALT (SGPT)	520	U/L	EARLY FOLLOW-UP	EFU, MAXIMUM#	15
			TOTAL BILIRUBIN	3	MG/DL			

EOT(IV)=End of IV Therapy; EFU=Early Followup; *visit and window(s) at which subject met HHR Criteria
MAXIMUM# refers to maximum ALT or total bilirubin levels observed during the study (excluding Baseline)

At end of i.v. therapy, two doripenem-treated, no levofloxacin-treated, and one meropenem-treated patient fulfilled Hy's Rule. One of the doripenem-treated patients had an elevated serum alkaline phosphatase level concurrent with abnormalities in ALT and total bilirubin, a finding that is suggestive of a hepatobiliary (rather than an hepatocellular) disorder.

Based on the maximum ALT and total bilirubin levels (MAXIMUM#) observed during the study, there were a total of seven subjects who fulfilled Hy's Rule: five doripenem-treated, no levofloxacin-treated, and 2 meropenem-treated subjects. Of the five doripenem-treated subjects, two had elevated serum alkaline phosphatase levels concurrently suggestive of a hepatobiliary disorder. Table 91 summarizes pertinent demographic, clinical, and laboratory data regarding all subjects who fulfilled Hy's Rule for hepatotoxicity followed by narrative summaries from the Sponsor.

Table 91: FDA Medical Officer's Information Summary for all Phase 3 Study Subjects who fulfilled Hy's Rule for Hepatotoxicity

Study	Subject ID#	Study Drug Duration	Age/Sex/ Race	Concomitant/Prior Medications	Concurrent/Prior Medical Illnesses	Lab test results that fulfill Hy's Rule
DORI-05	03103074	Levofloxacin IV: 3 days Withdrew consent; started on non-study Levoflox	37/F/H	Enoxaoparin sodium, Potassium, Acetaminophen, Promethazine, Fentanyl, Ibuprofen, Pantoprazole sodium, Phosphorous, Folic acid, Thiamine, Multivitamin, Lorazepan	Bipolar disease, alcoholism, hypokalemia, headache, dizziness, visual changes	Baseline: T. Bili=2.8; ALT=123
DORI-06	350/00106	Doripenem IV: 3 days PO: none	37/M/W	Ranitidine, Diclophenac, spironolactone, Enalapril, Dopamine, Heparin, Sucralafate, Lorazepan, Dipirone, Metoclopramide, Digoxin, Nubain, Hyoscyamine/dipirone, Amoxicillin/clavulanate, levofloxacin, doxycycline	History of gallstones, choledochal syndrome, chest pain	Day 3 (EOT): T. Bili=1.45; ALT 486; AST 724; Alk Phos 608
	450/00084	Doripenem IV: 7 days PO: none	81/M/W	Furosemide, amiodarone, Metoclopramide, Omeprazole, Midazolam, Atropine, Epinephrine, Norepinephrine, Fentanyl, Heparin, Insulin, Dobutamine, Warfarin, Levothyroxine, Hydralazine, Isosorbide monohydrate, Enoxaparin, Captopril, Carvedilol	History of Chagas myocardiopathy, CHF, ventricular thrombus, cardiac pacemaker, pulmonary edema, hepatomegaly, chronic severe renal impairment, lower extremity edema, and hypothyroidism.	Day 3: T. Bili=2.40; ALT 178; AST 233; Alk Phos 363
DORI-07	401/04517	Doripenem IV: 11 days PO: 5 days	42/M/W	Hioscine, Dipirone, Heparin, Lasix, Metoclopramide, Ipratropium, albuterol, Paracetamol, Codeine, Acetaminophen, Dimeticone, Metoclopramide, Heparin, Corticotrophin, Hydrocortisone, Prednisone, ciprofloxacin, metronidazole	Acute cholecystitis, Addison's Disease	EFU: T. Bili=1.71; ALT 137; AST 48; Alk Phos 290

	035/02005	Doripenem IV: 8 days PO: 8 days	84/M/W	Unasyn, Levofloxacin, Vancomycin, Aspirin, Acetaminophen, Atenolol, Donepizil, Atorvastatin, Morphine, Ketorolac, Hydrocodone, Glimepiride, Ondansetron, Codeine sulfate, Famotidine, Senna, Psyllium	Cholecytectomy just prior to enrollment; renal impairment	Baseline: T. Bili=3.3; ALT 225; AST 144; Alk Phos 1360
DORI-08	04302050	Doripenem IV: 4 days PO: 6 days	39/M/H	Acetaminophen, prevacid, morphine, Pepcid, Benadryl, Colace, Ibuprofen	Substance abuse (alcohol, cocaine, marijuana), diverticulitis, nicotine use, post-cholecystectomy (one year prior to study)	Baseline: T. Bili=2.1; ALT=214
	38504049	Doripenem IV: 4 days PO: 7 days	54/M/W	Ranitidine, Fentanyl, Metoclopramide, Amlodipine, Carvedilol, Heparin, Salbutamol, Diclofenac, Clorthalidone, Amlodipine/Hydro-chlorthiazide, Clotrimazole/Beta-methasone	Hypertension, cholelithiasis (post-cholecystectomy 2 months prior to study), nicotine use	Baseline: T. Bili=5.47; ALT=130
	38103013	Meropenem IV: 5 days PO: 9 days	40/M/W	Diclofenac, Ranitidine, Dextropropoxifene	Obesity, nicotine use	Baseline: T. Bili=1.93; ALT=160
	00302056	Meropenem	53/M/W	Ranitidine, Potassium, Morphine, Pantoprazole, Heparin, Hydralazine, Labetolol, Lorazepam, Insulin, albuterol, Midazolam, Metoprolol, Ipratropium, Haloperidol, Loperamide, Hydromorphone, acetaminophen, Oxycodone/Aceta-minophen, Diphenoxylate, Cyclobenzaprine, electrolyte supplements	Elevated liver function tests, diverticular disease, melanoma	Day 11: T. Bili=3.4; ALT=169
	04502513	Meropenem	70/M/W	Zocor, Prilosec, Xanax, Aceon, Pepcid, Darvocet, Heparin, Morphine, Protonix, Combivent, Dexamethasone, Famotidine, Insulin, Hydrocortisone, Cardizem, Solucortef, ASA, Lopressor, Albuterol, Lasix, Compazine, Dilaudid, Bumex, amiodarone, Reglan, Diflucan, electrolyte supplements	Colon surgery (sigmoid cancer), hypertensionm, emphysema, ascites	Early Follow-up: T. Bili=3; ALT=520

	431/04023	Doripenem IV:12 days PO: none	80/F/H	Captopril, Metoclopramide, Hyocin, Ranitidine, Morphine, Tramadol, Amiodarone, Fentanyl, Propofol, Isofluorane, Insulin, Midazolam, Etomidate, Lasix, Combivent, Epoetin, Heparin, Haloperidol, Dobutamine, Nitroprussiate, Tropine, Terbutaline, Fluconazole, Noradrenaline, Mefoxin, Polymixin B, Vancomycin, Imipenem	Generalized peritonitis following perforated appendix	Day 11: T. Bili=2.31; ALT 150; AST 46; Alk Phos 112

Patient Narratives (from Sponsor's report):
Patient 350/00106 was a 37-year-old Caucasian male who was enrolled in DORI-06 with a diagnosis of cLUTI. His past medical history was significant for gallbladder stones, choledochal syndrome and chest pain. Medications at the time of study entry were ranitidine and metoclopramide. Screening laboratory values for serum chemistries were remarkable for ALT and AST at the ULN, and GGT>ULN. The patient received a total of six 500-mg doses of doripenem over 2 days and was discontinued on Day 3 due to the lack of a qualifying pretreatment urine culture. No oral study drug therapy was administered. The patient was assessed as clinically improved at EOT(IV); the physical examination at EOT was significant for mild hypogastric pain only. Safety labs obtained at EOT(IV) on Day 3 met the criteria to fulfill Hy's rule: ALT and AST>10xULN with concurrent elevation in total bilirubin to approximately 1.5xULN. However GGT was also elevated to >5xULN and ALP>2xULN. Repeat labs performed on Day 8 demonstrated decreasing ALT and AST to levels to >5xULN, a persistently elevated total bilirubin to approximately 1.5xULN and increasing GGT to >5xULN and ALP to >4xULN. On Day 10, the patient was diagnosed with a deep vein thrombosis via ultrasound after developing significant dyspnea and left lower limb edema. A chest radiograph performed the same day showed cardiac enlargement. An ECHO was performed, and the patient was diagnosed with acute myocarditis. The myocarditis was considered to be caused by Mycoplasma pneumoniae (IgM 1/1024; positive >1/16) and/or coxsackie A virus (IgM positive). Serology for hepatitis B, HIV, and Coxsackie B were negative. The patient was managed medically. LFU assessments occurred on Day 31 at which time the ALT, AST and total bilirubin levles had returned to WNL and GGT remained >5xULN and ALP decreased to >2xULN. This patient's physical findings and laboratory values are consistent with acute myocarditis and hepatitis due to mycoplasma and/or viral infections and concurrent development of obstructive jaundice in a patient with a history of biliary obstruction.

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-06	350/00106	Baseline	0.81	41	39	227
		Day 3 (EOT)	1.45	486	724	608
		EFU	1.63	379	NA	NA
		LFU	0.84	32	27	748

EOT=end of IV therapy, TOC= test of cure, LFU= late follow-up; NA=not available

FDA Medical Officer Comments: The elevated alkaline phosphatase in association with the elevations in ALT and AST is suggestive of a hepatobiliary disorder. This is further supported by the subject's history of gallstones and choledochal syndrome. However, the positive serology for mycoplasma and Coxsackie B confound assessment of the cause of the laboratory test elevations. In addition, serologies for hepatitis A and C viruses were not performed. Due to the temporal association of the peak in liver function test abnormalities coinciding with the three day duration of doripenem administration followed by an abrupt decline in AST and ALT abnormalities following discontinuation of the drug, it is not possible to definitively exclude doripenem as a contributory factor in this case.

Patient 450/00084 was an 81-year-old Caucasian male who was enrolled in DORI-06 with a diagnosis of cLUTI. His past medical history was significant for ongoing Chagas myocardiopathy, congestive heart failure, ventricular thrombus, regurgitant systolic murmur, cardiac pacemaker, tachypnea, pulmonary edema, hepatomegaly, chronic severe renal impairment, lower extremity edema, hypothyroidism and body petechiae. Recent past medical history was significant for sustained ventricular tachycardia leading to cardiogenic shock which was treated with electrocardioversion, amiodarone and life support measures including assisted ventilation and inotropic agents within the 2 weeks prior to study enrollment. Medications at the time of study entry were amiodaraone, furosemide, omeprazole, dobutamine, mirtazapine, levothyroxine, warfarin, domperidone and metoclopramide. Screening laboratory values for serum chemistries wre remarkable for hypoalbuminemia, elevated ALT and AST to >2xULN, total bilirubin at the ULN, elevated GGT to >2xULN, and ALP>ULN. The patient's calculated creatinine clearance at study entry was 14.5 mL/min. He initially received 500-mg doses of doripenem q8h for a total of 5 doses. On Day 2, the dose of doripenem was adjusted for the patient's renal function and he received a total of 9 doses of 250 mg q12h to complete a total of 6 days of therapy. The last dose of doripenem was administered on Day 7. Safety labs obtained on Day 3 met the criteria to fulfill Hy's rule: ALT >4xULN, AST >6xULN, total bilirubin 1.8xULN, GGT>3xULN and ALP approximately 1.5xULN. Follow-up serum chemistries were not obtained. On Day 7, the patient experienced ventricular tachycardia which was treated with electrocardioverion, intubaton and assisted ventilation, and intropic support. However, the patient developed intermittent arrhythmias and cardiac arrest and died the same day. The investigator confirmed that the event of cardiogenic shock was probably related to Chagas cardiomyopathy and assessed the cardiac arrythmia as related to the Chagas disease. This patient's physical findings and laboratory values are consistent with liver congestion due to the patient's right-sided heart failure.

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-06	450/00084	Baseline	1.44	96	82	282
		Day 3	2.40	178	233	363

FDA Medical Officer Comments: The patient received doripenem for seven days prior to his death. The marked elevations in his liver function tests were noted on Day 3, but there are no laboratory results after Day 3 to allow assessment of their trend between Days 3 and 7. Due to the temporal association of the peak in liver function test abnormalities coinciding with the first three days of doripenem administration, it is not possible to

definitively exclude doripenem as a contributory factor in this case. However, the assessment of causality is confounded by the recent episode of cardiogenic shock and congestive heart failure with hepatic congestion.

Subject 40104517: This doripenem-treated patient with elevated ALT values met the definition of Hy's High Risk (HHR) classification (i.e., ALT greater than 3xULN and bilirubin greater than 1.5xULN) at the EFU visit, 15 days after discontinuing IV doripenem study drug therapy. At screening, the patient had a normal ALT value of 29 IU/L (normal: less than or equal to 41 IU/L), and an elevated AST value of 52 IU/L (normal: less than or equal to 37 IU/L). Screening indirect bilirubin was elevated at 18 µmol/L (normal range: 3.42 to 13.68 µmol/L), and the patient had a Grade 4 elevated total bilirubin of 95.25 µmol/L (normal range: 3.42 to 17.1 µmol/L). The dosage of IV study drug therapy was adjusted on Days 1 through 7 due to renal impairment. During IV study drug therapy, the patient had ALT values of 42, 31, and 54 IU/L, and AST values of 108, 61, 63, and 87 IU/L. The patient completed 11 days of IV study drug therapy, and then switched to oral study drug therapy with amoxicillin/clavulanate (875/125 mg), which was completed on Day 15. That same day, the patient's ALT was 59 IU/L, AST was 110 IU/L, and total bilirubin was 44.97 µmol/L. On Day 23, the patient's laboratory values included ALT of 137 IU/L, AST of 48 IU/L, and total bilirubin of 29.24 µmol/L. On Day 46, the patient's ALT was 227 IU/L, AST was 102 IU/L, and total bilirubin was 11.63 µmol/L. This laboratory finding represented a combination of mild hyperbilirubinemia due to acute cholecystitis, which continued to improve after baseline, and a seemingly independent elevation in ALT, which coincided with the diagnosis of Addison's disease and the introduction of steroid therapy. Incidentally, the hyperbilirubinemia had already declined from baseline levels when the patient met the criteria for Hy's rule. The investigator considered this event unlikely to be related to study drug therapy.

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-07	401/04517	Baseline	5.57	29	52	122
		Day 2	7.39	42	108	140
		Day 5	6.45	31	61	181
		Day 8	2.51	31	63	491
		EOT	2.38	54	87	586
		Day 11	2.16	47	59	520
		Day 14	2.63	59	110	627
		EFU	1.71	137	48	290

EOT=end of IV therapy, EFU= early follow-up

FDA Medical Officer Comments: In view of the lack of a close temporal association with doripenem exposure, it is unlikely that doripenem had a contributory role in the subject's abnormal liver function test abnormalities.

Subject 03502005: This doripenem-treated patient had a screening ALT value of 225 IU/L (normal range: 6 to 48 IU/L) and a total bilirubin value of 56.43 µmol/L (normal range: 3.42 to 20.52 µmol/L), thus meeting the HHR classification. The patient also had an AST value of 144 IU/L (normal range: 10 to 45 IU/L), alkaline phosphatase value of 1360 IU/L (normal range: 45 to 145 IU/L), and GGT value of 982 IU/L (normal range: 11 to 42 IU/L). The patient's medical history included a cholecystectomy just prior to enrollment in the study. The dosage of IV study drug

therapy was adjusted on Days 1 through 8 due to renal impairment. During IV study drug therapy, the patient had ALT values of 145 and 53 IU/L and total bilirubin values of 42.75 and 18.81 µmol/L. The patient completed 8 days of IV study drug therapy, and then switched to oral study drug therapy with amoxicillin/clavulanate (875/125 mg), which was completed on Day 15. On Day 22, the patient's laboratory values included ALT of 23 IU/L, total bilirubin of 11.97 µmol/L, AST of 17 IU/L, alkaline phosphatase of 349 IU/L, and GGT of 214 IU/L. None of these elevated laboratory values was reported as an adverse event by the investigator.

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-07	035/02005	Baseline	3.3	225	144	1360
		Day 2	2.5	145	59	1140
		Day 5	1.1	53	26	669
		EOT	1.0	38	31	682
		TOC	0.5	63	44	293
		EFU	0.7	23	17	349

EOT=end of IV therapy, TOC= test of cure, EFU= early follow-up

FDA Medical Officer Comments: The abnormal liver function tests and alkaline phosphatase levels at baseline are likely related to his recent cholecystectomy. As those laboratory test abnormalities declined substantially in the subsequent days despite continuation of doripenem therapy, the drug does not appear to have a contributory role in causing the elevated test values.

Subject 43104023: This doripenem-treated patient was an 80-year-old Hispanic female who was enrolled with generalized peritonitis following a perforated appendix. Baseline bilirubin and LFT values were normal. Study drug therapy was discontinued due to lack of efficacy. The patient subsequently developed septic shock and was treated with multiple antibacterial and cardiotonic therapies (including dobutamine). Liver function tests (LFTs) were elevated and a hepatitis serology was performed but was negative. By the EFU visit, the LFTs had decreased and the patient no longer met Hy's rule.

Study	Subject ID#	Study Time Point/ Study Visit	Total bilirubin (mg/dl)	ALT (IU/L)	AST (IU/L)	Alk phos (IU/L)
DORI-08	431/04023	Baseline	0.47	25	23	69
		Day 2	0.47	26	23	68
		Day 5	0.96	1759	950	92
		Day 8	1.62	267	43	76
		Day 11	2.31	150	46	112

FDA Medical Officer Comments: The patient was treated with doripenem until Day 12, when it was discontinued due to lack of efficacy. Prior to that time, the patient experienced septic shock with possible shock liver on Day 5, which likely accounted for the marked liver function tests elevations noted on that day. At the time that doripenem was discontinued, the ALT and AST had declined to near normal range, although the bilirubin remained elevated. The improvement in liver function tests despite continued exposure to doripenem suggests that the drug did not have a contributory role in causing the elevated test values.

Subject 00302056 (DORI-08), a 53-year-old White man, had a complex medical history

including a history of chronic abdominal pain, elevated liver enzymes, melanoma, and diverticular disease. He was enrolled with generalized peritonitis underwent a partial colectomy and small bowel resection. Serum bilirubin was abnormal at screening (63 µmol/L); ALT was normal (23 IU/L). Following treatment, his bilirubin initially decreased to 31 µmol/L before increasing to a last post-baseline value of 152 µmol/L. At the same time, the subject experienced a modest increase in serum ALT from normal baseline values to a maximum post baseline value of 186 IU/L. Following this, the ALT trended downwards with a last post-baseline measurement of 146 IU/L. There were no reports of clinical liver disease and neither the elevated bilirubin nor the increased ALT was reported as an AE. The subject completed the study but was considered a treatment failure. He was not classified as HHR at baseline but shifted to HHR at end of i.v. therapy

FDA Medical Officer Comments: The patient's serum ALT and total bilirubin levels remained elevated during treatment and post-therapy (see Table 90). By the early follow-up visit, the serum ALT had decreased but the total bilirubin was at its maximum level. The changes in liver function tests did not appear to correlate with meropenem treatment.

Subject 04502513, a 69-year-old White man, had a complex medical history including colon surgery for sigmoid cancer, hypertension, emphysema and ascites. Baseline bilirubin was 43 µmol/L and ALT was normal (17 IU/L). During the course of the study, the subject developed CHF necessitating treatment with several concomitant medications including stress steroids and additional antibiotics for infection of an ostomy wound. Prior to this, bilirubin values had trended downward to 17 µmol/L along with an increase in ALT to 75 IU/L. Following treatment for CHF, the subject developed a sharp sudden increase in ALT from 75 IU/L to 520 IU/L and bilirubin from 17 µmol/L to 51 µmol/L. The increased liver function tests and serum bilirubin were not reported as AEs by the investigator. The subject completed the study through the LFU visit. In the opinion of the Sponsor's medical monitor, plausible explanations for the increased liver function test results include congestive hepatopathy and/or steroid therapy.

FDA Medical Officer Comments: The patient's serum ALT and total bilirubin levels reached their maximum levels at the time of the early follow-up visit (see Table 90). The etiology of the elevated liver function tests is uncertain, but may be multifactorial related to hepatic congestion secondary to heart failure, concomitant medications, and poor clinical response to study drug.

Subject 04302050: This was a 39-year-old Hispanic male with a medical history including substance abuse (alcohol, cocaine and marijuana), diverticulitis, nicotine use and a history of cholecystectomy 1-year prior to participation in the study. He was enrolled into the study following a diagnosis of diverticular abscess involving the proximal sigmoid colon requiring CT-guided drainage. Following screening, the subject was randomized to doripenem 500 mg i.v. q8h. Baseline laboratory values included a total bilirubin value of 2.1 mg/dL (>1.5xULN), ALP of 269 IU/L (>1.5xULN) and ALT of 214 IU/L (>4xULN). The subject was classified as meeting the HHR criteria at baseline. He received i.v. study therapy from Day 1 to 4 before switching to oral

Augmentin from Day 4 to 10. While on i.v. therapy, his liver function test values decreased progressively. At the EOT (i.v.), the total bilirubin level was 0.5 mg/dL, ALP was 186 IU/L and ALT was 74 IU/L. The subject did not meet biochemical criteria consistent with HHR classification at any other time post baseline. He eventually completed the study per protocol and was classified as a clinical cure. A table showing this subject's liver function test values from baseline through to EFU is shown below.

Day	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)	Alkaline Phosphatase (IU/L)
Baseline (Day 1)	2.1	214	213	269
Day 2	1.7	151	52	255
Day 4 (EOT i.v.)	0.5	74	15	186
Day 19 (EFU)	1.2	35	30	94
Normal range	0.2-1.2	6-48	10-45	45-145

EFU=early follow-up

No liver related adverse events were reported during the course of the subject's participation in the study. Prior antibiotic medications included metronidazole and piperacillin-tazobactam. Prior and concomitant nonantibiotic medications included morphine sulphate and acetaminophen administered on an as needed basis for pain and fever, respectively.

FDA Medical Officer Comments: The subject had maximal serum ALT and total bilirubin levels at baseline, and they decreased progressively while he was receiving doripenem. This pattern of negative dechallenge characterized by declining liver function test abnormalities despite ongoing treatment with study drug indicates that doripenem did not have a contributory role in causing the elevated laboratory test values.

Subject 38504049: This was a 54-year-old white male with a past medical history of hypertension, cholelithiasis (status post cholecystectomy 2 months prior to entering study) and nicotine use. He was enrolled into the study following a diagnosis of a colonic abscess requiring open surgery (Hartmann's procedure). Following screening, he was randomized to doripenem 500 mg i.v. q8h. i.v. Study drug was adjusted during the course of treatment because of renal impairment (dosage administered was at various times either 250 or 500 mg i.v. q8h on Days 2-4 of i.v. therapy). At baseline, laboratory values included a total bilirubin value of 5.47 mg/dL (>5xULN), ALT of 130 IU/L (>3xULN) and ALP of 814 IU/L (>3xULN). The subject was classified as meeting the biochemical criteria for HHR at baseline. Following randomization, he received i.v. doripenem from Day 1 to 4 before switching to oral Augmentin from Day 4 until Day 11. While on i.v. study therapy, the liver function test values decreased progressively towards normal values. At the EOT (i.v.), the ALT level was 58 IU/L, total bilirubin was 2.21 mg/dL and ALP was 587 IU/L. The subject did not meet the biochemical criteria consistent with HHR classification at any other time during the study. He completed the study per protocol and was classified as a clinical cure. The following table summarizes this subject's liver function test values from baseline through to the last visit.

Day	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)	Alkaline Phosphatase (IU/L)
Baseline (Day 1)	5.47	130	110	814
Day 3	2.83	61	31	564
Day 4 (EOT i.v.)	2.21	58	40	587
Day 24 (EFU)	0.45	87	34	658
Day 40 (TOC)	N	179	N	1541
Day 59 (UNV)	0.36	14	19	364
Normal range	0-1	0-41	0-38	0-270

EFU=early follow-up; EOT i.v.=end of i.v. therapy; N=no data available; TOC=test of cure; UNV=unscheduled visit

No liver related adverse events were reported during study drug therapy (i.v. and oral). On Day 40, hepatitis was reported (no etiology was provided by the investigator, diagnosis followed increased liver function tests). This event was considered by the investigator to be non-serious, moderate and not related to study drug therapy. The event was considered resolved by Day 60.

FDA Medical Officer Comments: The subject had maximal serum ALT and total bilirubin levels at baseline, and they decreased progressively while he was receiving doripenem through EOT. The concurrent elevation in serum alkaline phosphatase levels suggested a cholestatic component. This patient exhibited negative dechallenge characterized by declining liver function test abnormalities despite ongoing treatment with study drug indicating that doripenem did not have a contributory role in causing the elevated laboratory test values. The laboratory test abnormalities noted at TOC (36 days after doripenem had been discontinued) resolved by the time of the Day 59 visit.

Subject 38103013: This was a 40-year-old white male with a history of obesity (130 kg, 190 cm) and nicotine use. He was enrolled in the study following a diagnosis of gangrenous appendicitis with perforation and peritonitis. Prior to surgery he received i.v. ampicillin, gentamicin and metronidazole prophylaxis. Following screening, he was randomly assigned to meropenem 1 g given as a bolus over 3-5 minutes q8h. At baseline his bilirubin level was elevated at 1.93 mg/dL (>1.5xULN) with indirect bilirubin only slightly elevated; his ALT was 160 IU/L (>3xULN) and ALP was 290 IU/L (just above the ULN). Other significant abnormalities were an albumin just below normal of 35 g/L; AST 2xULN; GGT 272 IU/L (3xULN); and nonfasting glucose of 9.213 mmol/L (<2xULN). The subject received i.v. meropenem from Day 1 to 5 followed by oral Augmentin until Day 14, with a good clinical response. His course was complicated by an external wound infection on Day 3 that resolved in 19 days. This was associated with a transient fever on Day 4 for 2 days. His bilirubin level decreased on Day 2 to <1.5 ULN and was normal on Day 5 at the end of i.v. therapy through early follow up on Day 21. His ALT level also decreased to <3xULN by Day 2 but rose on Day 5 to 5xULN, was >3xULN on Day 10 and then decreased to <3xULN on Day 21 through 45.

His ALP decreased to within the normal range on Day 2, rose modestly to 385 IU/L on Day 5 to <1.5xULN and remained slightly elevated through Day 21 (<1.5xULN) and was just

above normal on Day 45. He had improvement in his serum albumin and no further abnormal glucoses were reported. He only met the criteria for HHR at baseline prior to the administration of study medication and did not meet the criteria on study drug or through the follow-up period as he improved clinically. The following table summarizes this subject's liver function test values from baseline through to the last visit.

Day	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)	Alkaline Phosphatase (IU/L)
Baseline (Day 1)	1.93	160	86	290
Day 2	1.13	90	37	254
Day 5 (EOT i.v.)	0.99	204	155	385
Day 10 (UNV)	N	154	67	338
Day 21 (EFU)	0.56	113	54	302
Day 45 (TOC)	N	61	31	278
Normal range	0-1	0-41	0-38	0-270

EFU=early follow-up; EOT i.v.=end of i.v. therapy; N=no data available;
TOC=test of cure; UNV=unscheduled visit

The timing of his elevated ALT is co-incident with acute infection at baseline and the wound infection that developed on Day 3 and lasted through Day 22.

FDA Medical Officer Comments: The subject had elevated serum ALT and total bilirubin levels at baseline. The total bilirubin level decreased progressively while he was receiving meropenem, whereas the ALT level declined and then increased at the time of a wound infection. By the TOC visit, both serum liver function test levels were within normal range. It is unlikely that meropenem contributed to the liver test abnormalities observed.

Subject 03103074 was a 37-year-old Hispanic female with a history of bipolar disease, alcoholism, hypokalemia, headaches, dizziness and visual changes who was enrolled in DORI-05 with *E. coli* pyelonephritis and bacteremia and randomized to receive levofloxacin 500 mg q12h. Her baseline laboratory values met the criteria for HHR classification and included total bilirubin 2.8 mg/dL (>2xULN), ALT 123 IU/L (>3xULN), AST 70 IU/L (~2xULN), GGT 554 IU/L (>10xULN; normal range, 5-49 IU/L), and ALP 88 IU/L (<ULN). The subject received i.v. study drug for 3 days during which time her urine obtained on Days 2 and 3 was without growth and her blood obtained on study Day 2 grew *E. coli*. A retroperitoneal ultrasound performed on Day 2 was normal. The subject withdrew consent on Day 4 and she was switched to non-study oral levofloxacin 500 mg qd on the same day. The following table summarizes this subject's liver function test values measured at baseline.

Day	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)	Alkaline Phosphatase (IU/L)
Baseline (Day 1)	2.8	123	70	88
Normal range	0.2-1.2	6-37	10-36	40-100

Additional liver function test values from blood samples taken post-baseline at unscheduled visits were analyzed at a local laboratory (and therefore are not in the study database).

These values indicated improvement in liver function over the course of i.v. study therapy as shown in the table below.

Day	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)	Alkaline Phosphatase (IU/L)
Day 2	N	92	42	N
Day 3	1.0	53	28	80
Normal range	0.2-1.3	0-40	0-37	20-125

FDA Medical Officer Comments: The subject had elevated serum ALT and total bilirubin levels at baseline. She received i.v. levofloxacin for four days, withdrew consent, and was then changed to oral levofloxacin. This patient exhibited negative dechallenge characterized by declining liver function test abnormalities despite ongoing treatment with study drug indicating that levofloxacin did not have a contributory role in causing the elevated laboratory test values.

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Renal Failure/Renal Impairment treatment-emergent Adverse Events:

Table 92: FDA Medical Officer Summary of Subjects with Renal Failure and Renal Impairment treatment-emergent adverse events

Event Term	Combined Doripenem (DORI-05, -06,-07, -08)	Levofloxacin (DORI-05)	Combined Meropenem (DORI-07 and -08)
Renal failure	5	0	1
Renal failure acute	8	0	0
Renal impairment	4	0	0

As depicted in the table above, there were 17 subjects who had a total of 19 renal failure or renal impairment-related TEAEs observed in the phase 3 clinical studies: 16 were doripenem-treated, one was meropenem-treated, and none were levofloxacin-treated subjects. Nine of the adverse events were assessed as serious by study investigators, and all of the serious AEs occurred in doripenem-treated subjects. One subject in DORI-06 (ID# 64300217) had two separate episodes of renal failure and renal failure acute, and one subject in DORI-07 (ID #10006028) had two separate episodes of renal failure acute (one serious and one non-serious). The adverse events were considered related to study drug by the investigator in only two of the 17 cases (both in DORI-06). The following tables summarize additional information on the 17 affected subjects:

Table 93: FDA Medical Officer Summary of subjects with renal failure or renal impairment-related, treatment-emergent adverse events observed in the pooled phase 3 clinical studies, ITT Population

Study	Subject ID#	Study Drug	Age	Race	Sex	BLCRCL ml/min	Medical History and Concurent suspect medications
DORI-05	01303031	Doripenem	40	W	F	57.9	Hypotension, vulvar cancer
	30306011	Doripenem	69	W	M	69.1	obstructive uropathy, prostatic adenoma, CHF
	30704002	Doripenem	82	H	F	34.8	Cardiac failure, HPT, pericarditis, furosemide
DORI-06	35100066	Doripenem	73	H	F	36	uropathy (radiation fibrosis), Left nephrectomy, contrast media
	35700366	Doripenem	81	H	F	12	chronic renal failure, bladder cancer, obstructive uropathy
	63000035	Doripenem	71	W	F	30.3	sepsis, dehydration, DM, HPT, furosemide
	63300108	Doripenem	61	W	M	50.6	DM, PVD, spina bifida
	63300210	Doripenem	62	W	F	40.3	intermittent nausea, diarrhea, vomiting
	64300217[a]	Doripenem	63	W	M	53.5	Cardiomyopathy, CHF, DM
	64300217[a]	Doripenem	63	W	M	53.5	hypovolemia, medications
DORI-07	04102020	Doripenem	66	W	M	91.1	dehydration, alcohol withdrawal
	04602510	Doripenem	61	W	F	120.2	CHF, DM, CAD, bacteremia, pneumonia, pancreatitis
	10006028[b]	Doripenem	61	W	M	111.9	CAD, cirrhosis, DM, furosemide
	10006028[b]	Doripenem	61	W	M	111.9	as above
	40103049	Meropenem	34	W	F	48	renal insufficiency, sepsis, furosemide
DORI-08	02902030	Doripenem	71	W	M	61.2	HPT, kidney stones
	12606026	Doripenem	69	W	F	82.6	CAD PAD, post-MI
	12806502	Doripenem	51	W	M	48.8	sepsis, organ failure, post-op cardiac insufficiency
	38304104	Doripenem	69	H	F	59.4	HPT, pre-renal insufficiency, furosemide

BLCRCL=baseline creatinine clearance; W=white, H=Hispanic; F=female, M=male; CHF=congestive heart failure, DM=diabetes mellitus, HPT=hypertension, CAD=coronary artery disease, PVD=peripheral vascular disease, PAD=peripheral artery disease
[a,b] Patients who had multiple renal failure or renal impairment-related TEAEs

Table 94: FDA Medical Officer Summary of subjects with renal failure- or renal impairment-related, treatment-emergent adverse events observed in the pooled phase 3 clinical studies, ITT Population

Study	Subject ID#	Study Drug	Serious AE	Adverse event Term	Study Day of Onset	Relationship	Study Drug Duration		VA/AG	Negative rechallenge	Post-Treatment renal failure*	Study Drug Withdrawn	Deaths
							IV	PO					
DORI-05	01303031	Dori		Renal impairment	3	Not related	10	5	No	X			
	30306011	Dori	X	Renal failure acute	4	Not related	5	5	No				
	30704002	Dori		Renal impairment	11	Not related	5	7	No	X			
DORI-06	35100066	Dori	X	Renal failure acute	12	Not related	5	5	No		X (6 days)		
	35700366	Dori	X	Renal failure	11	Not related	11	0	No		X (6 days)	X	
	63000035	Dori	X	Renal impairment	3	Possible	2	7	GENT			X	
	63300108	Dori		Renal failure acute	4	Possible	15	0	VANCO	X			
	63300210	Dori		Renal failure acute	3	Unlikely	12	0	No	X			
	64300217[a]	Dori		Renal failure	1	Not related	2	0	VANCO				
	64300217[a]	Dori	X	Renal failure acute	13	Not related	2	0	VANCO				
DORI-07	04102020	Dori	X	Renal failure acute	23	Not related	4	0	No		X (19 days)		
	04602510	Dori		Renal failure	14	Not related	6	0	AMIK				X
	10006028[b]	Dori		Renal failure acute	18	Not related	7	0	No		X (11 days)		
	10006028[b]	Dori	X	Renal failure acute	18	Not related	7	0	No				
	40103049	Mero		Renal failure	2	Not related	15	0	No	X			
DORI-08	02902030	Dori		Renal failure acute	30	Not related	8	0	No		X (22 days)		
	12606026	Dori	X	Renal failure	32	Not related	6	0	BOTH		X (26 days)		X
	12806502	Dori		Renal failure	10	Not related	11	0	VANCO				
	38304104	Dori	X	Renal impairment	16	Unlikely	9	0	No		X (7 days)		

*number of days post-treatment indicated in parentheses; VANCO and VA=vancomyicn; AG=aminoglycoside; GENT=gentamicin, AMIK=amikacin; AE=adverse event; IV=intravenous, PO=oral switch; [a,b] Patients who had multiple renal failure or renal impairment-related TEAEs

Table 95: FDA Medical Officer Summary of selected Laboratory Test Results for subjects with renal failure- or renal impairment-related, treatment-emergent adverse events observed in the pooled phase 3 clinical studies, ITT Population

Study	Subject ID#	Study Drug	Study Day of Onset	Study Drug Duration		BL CREAT† mg/dl	CREAT ON STUDY DRUG† mg/dl	EOT(IV) CREAT† mg/dl	EFU/TOC CREAT† mg/dl	LFU CREAT† mg/dl
				IV	PO					
DORI-05	01303031	Doripenem	3	10	5	1.3 (1)	2.7 (3)	0.9 (10)	0.7 (TOC, 22)	NR
	30306011	Doripenem	4	5	5	1 (1)	4.2 (4)	4.9 (6)	1.1 (TOC, 19)	NR
	30704002	Doripenem	11	5	7	2.2 (1)	1.8 (4)	1.4 (5)	5.2 (TOC, 11)	0.7 (LFU, 45)
DORI-06	35100066	Doripenem	12	5	5	1.1 (1)	0.7 (3)	1.1 (6)	0.8 (TOC, 17)	0.8 (LFU, 35)
	35700366	Doripenem	11	11	0	3.9 (1)	4.1 (4)	6.7 (11)	8.1 (TOC, 19)	3.3 (LFU, 40)
	63000035	Doripenem	3	2	7	2.3 (1)	NR	3.6 (4)	1.1 (TOC, 14)	1.2 (LFU, 36)
	63300108	Doripenem	4	15	0	2.1 (1)	3.4 (3)	1.1 (15)	1.6 (TOC, 22)	1.3 (LFU, 50)
	63300210	Doripenem	3	12	0	1.4 (1)	4.2 (4)	1.4 (14)	1.3 (TOC, 20)	1 (LFU, 40)
	64300217[a]	Doripenem	1	2	0	2.2 (1)	NR	1.4 (2)	NR	1.1 (LFU, 25)
	64300217[a]	Doripenem	13	2	0	as above				
DORI-07	04102020	Doripenem	23	4	0	1.1 (1)	1.1 (2)	1 (5)	1.5 (EFU, 12)	NR
	04602510	Doripenem	14	6	0	1.2 (1)	1.9 (3)	1.6 (6)	1.0 (EFU, 17)	NR
	10006028[b]	Doripenem	18	7	0	0.9 (-1)	2.7 (5)	2.5 (7)	3.5 (EFU 14))	NR
	10006028[b]	Doripenem	18	7	0	as above				
	40103049	Meropenem	2	15	0	2.8 (1)	6.3 (6)	NR	0.9 (EFU, 25)	NR
DORI-08	02902030	Doripenem	30	8	0	0.9 (1)	0.8 (3)	0.7 (EOT, 8)	0.8 (EFU, 17)	NR
	12606026	Doripenem	32	6	0	0.8 (1)	0.6 (3)	0.6 (EOT, 6)	1.3 (TOC, 35)	NR
	12806502	Doripenem	10	11	0	1.5 (1)	0.7 (3)	2.7 (EOT, 9)	1.4 (EFU, 21)	NR
	38304104	Doripenem	16	9	0	NR	0.6 (6)	0.7 (EOT, 9)	1.5 (EFU, 19)	0.9 (TOC, 48)

†Study day indicated in parentheses; IV=intravenous, PO=oral switch; BL=baseline, EOT=end of IV therapy, EFU=early follow-up, TOC=test of cure, LFU=late follow-up; NR=not reported (missing); CREAT=serum creatinine
[a,b] Patients who had multiple renal failure or renal impairment-related TEAEs

At baseline, four subjects had a normal creatinine clearance (≥80 ml/min), 12 subjects had mild to moderate renal impairment (>30 to <80 ml/min), and one subject had severe renal impairment (≤30 ml/min). Eleven of the 17 subjects (65%) had pre-renal azotemia that was likely related to dehydration, hypovolemia, diuretic use, or congestive heart failure. Nine of the events were considered serious by the reporting investigators. Doripenem was withdrawn in two subjects (one each with moderate and severe renal impairment at baseline). One subject in DORI-07 died 47 days after the last dose of doripenem due to complications of sepsis (including renal insufficiency), pancreatitis, and gall bladder necrosis. Six subjects had received concomitant vancomycin, aminoglycosides (gentamicin or amikacin), or both agents, all of which are potentially nephrotoxic. Five subjects had negative rechallenge in that their serum creatinine levels were markedly abnormal at baseline or during the course of study drug, but then declined to normal or near normal values by EOT. In contrast, seven subjects had post-treatment renal failure in which elevations in serum creatinine levels were noted at EFU or at later time points after study drug treatment had already been completed.

The Sponsor provided the following narratives on the subjects with renal failure- or renal

impairment-related, serious treatment-emergent adverse events:

Subject 30306011 (Doripenem 500 mg IV infusion q8h): This 69-year-old Caucasian man had a history of chronic heart failure, chronic anemia, monoclonal gammopathy, and asthma. His urological history included incontinence, prostate adenoma, and pyelonephritis. Concomitant medications included heparin and salbutamol. Antibacterial medications included ciprofloxacin and piperacillin with tazobactam. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and levofloxacin placebo as a 60-minute IV infusion q24h for 6 days (Days 1 through 6) followed by oral levofloxacin tablets (250 mg once daily) for 6 days (Days 6 through 11) for the treatment of complicated pyelonephritis. The subject received study drug therapy for a total of 11 days (Days 1 through 11). The baseline pathogen isolated from a clean-catch urine specimen was *Pseudomonas aeruginosa*. The subject initially presented with a progressive urinary tract obstruction due to benign prostate hypertrophy. His serum creatinine at screening on Day 1 was 1 mg/dL. On Day 4, the subject had acute renal failure. His serum creatinine on that day was 4.2 mg/dL, 4.9 mg/dL on Day 6, and 4.1 mg/dL on Day 8. On Day 7, the subject also experienced worsening of prostate adenoma, which the investigator assessed as unrelated to treatment with study drug therapy. A urinary catheter was placed on the same day. On Day 12, the serum creatinine was 1 mg/dL again and the investigator considered the acute renal failure resolved. The investigator assessed the event to be severe in severity, serious due to prolongation of hospitalization, associated with the subject's underlying illness of prostate adenoma, and unrelated to treatment with study drug therapy.

FDA Medical Officer Comments: Based on the narrative summary, it appears likely that the subject's renal failure was probably related to obstructive uropathy from underlying prostatic hypertrophy/adenoma and was not related to doripenem exposure.

Subject 35100066 (Doripenem 500 mg IV infusion q8h): This 73-year-old Hispanic woman had a medical history of bowel obstruction, colon adenocarcinoma, Hartman's surgery, right hemicolectomy, suspected candidemia, sepsis due to *Klebsiella pneumoniae*, coagulase-negative *Staphylococcus* infection, and ventilator-associated pneumonia and ongoing cholestasis, and chronic anemia. Her urological history included obstructive uropathy due to fibrosis (secondary to radiotherapy) and left nephrectomy. Concomitant medications included ranitidine, paracetamol, heparin calcium, potassium gluconate, fluconazole, and multivitamins with iron. Antibacterial medication included cefepime. The subject was scheduled to receive doripenem 500 mg as a 60-minute IV infusion q8h for Days 1 through 6 followed by oral levofloxacin for Days 6 through 11 for the treatment of complicated pyelonephritis. Intravenous study drug therapy was adjusted for renal impairment for the fourth through seventh doses of doripenem and oral levofloxacin was adjusted on Days 6 through 11. Calculated creatinine clearance on Days 2 and 3 was 49.4 mL/min. The baseline pathogen isolated from urine was *Citrobacter koseri (diversus)*. On Day 3, *Candida parapsilosis* was isolated from the indwelling catheter urine and on Day 6, from the clean-catch urine specimen. On Day 11, the subject developed pyrexia that, although mild in severity, prolonged her hospitalization. At that time, she had a concurrent mild candiduria infection and mild nausea and had already undergone fluconazole and metoclopramide treatment and abdominal ultrasound, computed

tomography and magnetic resonance imaging scans, cystoscopy, and urinary catheter insertions to determine the causes of fever and right flank pain. Findings included dilated pelvic calyceal system, an enlarged right kidney with a cystic image near the pelvis, ureteral dilatation, and free liquid in the subphrenic area. There were no intraabdominal collections noted and acute renal failure was diagnosed on Day 12. Treatment included hydration. Her calculated creatinine clearance was decreased at 15.3 mL/min (normal range not provided), but improved to 54 mL/min on Day 15, at which time the pyrexia resolved. A cystoscopy on Day 16 showed mild bladder congestion. No cause for the renal failure was determined. The acute renal failure was considered resolved on Day 27 and the subject was discharged from the hospital. The investigator assessed the pyrexia mild in severity, serious because it prolonged hospitalization, and unrelated to treatment with study drug therapy. The investigator assessed the acute renal failure mild in severity, related to the condition under study, serious because it prolonged hospitalization, and unrelated to treatment with study drug therapy.

FDA Medical Officer Coments: There are multiple confounding issues affecting assessment of causality for this patient, including underlying obstructive uropathy due to radiation-induced fibrosis, abnormal urologic anatomy with previous left nephrectomy, fungal UTI, and dehydration. Doripenem had been discontinued six days prior to the diagnosis of acute renal failure.

Subject 35700366 (Doripenem 500 mg IV infusion q8h): This 81-year-old Hispanic woman had a history of acute auricular fibrillation, acute pulmonary edema, aortic stenosis, arterial hypertension, atrio-ventricular block (primary grade), chronic heart failure, ischemic heart disease, myocardial infarction, left ventricular hypertrophy, anemia, hypercholesterolemia, and tobacco use. Her urological history included bladder papilloma, prior lower urinary tract infections, and chronic renal failure. Concomitant medications included atenolol, simvastatin, acetylsalicylic acid, furosemide, isosorbide mononitrate, and omeprazole. Antibacterial medications included cephalothin. The subject was assigned to receive doripenem 500 mg as a 60-minute IV infusion q8h for the treatment of symptomatic complicated lower urinary tract infection. She received study drug therapy adjusted for renal impairment, for a total of 11 days (Days 1 through 11). Calculated creatinine clearance at screening was 12.0 mL/min and ranged from 6.9 mL/min to 12.0 mL/min on Days 1 through11. The baseline pathogen isolated from a clean-catch urine specimen was *Klebsiella pneumoniae*. Her screening (Day -1) and Day 1 serum creatinine levels were 3.6 mg/mL and her creatinine was grade 3 with a value of 344.76 µmol/L (normal range: 44.2 to 79.56 µmol/L). On Day 5, her serum creatinine was 4.3 mg/dL. On Day 7, a renal and bladder ultrasound performed to evaluate worsening creatinine levels detected bilateral pyelocaliceal ectasia and thickening of bladder mucosa. On Day 11, the subject was diagnosed with severe renal insufficiency, indicated by a grade 4 creatinine level of 592.28 µmol/L and a serum creatinine level of 6.7 mg/dL (normal value <1.1 mg/dL). Treatment with study drug therapy was permanently discontinued due to this event. On Day 12, a cystoscopy disclosed an infiltrating formation on the trigone and left lateral bladder and a right nephrostomy was performed on Day 22. By Day 27, her creatinine value had decreased to 291.72 µmol/L and her corresponding serum creatinine had decreased to 4 mg/dL, which were similar to her study entry values. The investigator

considered the renal insufficiency resolved on Day 27. The investigator assessed the event to be severe in severity, serious due to prolongation of hospitalization and medical importance, associated with the subject's underlying illness of bladder carcinoma, and unrelated to treatment with study drug therapy.

FDA Medical Officer Comments: The patient appeared to have developed acute on underlying chronic renal failure that was likely due to obstructive uropathy from progressive bladder cancer.However, in view of the temporal association of progressive renal dysfunction coinciding with the 12 day course of doripenem therapy, it is not possible to definitvely exclude doripenem exposure as having a contributory role.

Subject 63000035 (Doripenem 500 mg IV infusion q8h): This 71-year-old Caucasian woman had a history of hypertension, diabetes mellitus, and renal failure. Her urological history included recurrent urinary tract infections. Concomitant medications included metformin, nifedipine, insulin, paracetamol, glipizide, gabapentin, multivitamins, acetylsalicylic acid, zolpidem tartrate, carvedilol, pantoprazole, heparin-fraction sodium salt, digoxin, potassium chloride, and metoprolol tartrate. Antibacterial medications included gentamicin, imipenem with cilastatin, metronidazole, cefepime, and meropenem. The subject was scheduled to receive doripenem 500 mg as a 60-minute IV infusion q8h for the treatment of uncomplicated pyelonephritis. The subject received treatment with IV study drug therapy for 2 days (Days 1 through 2) after which IV study drug therapy was permanently discontinued due to the events of atrial fibrillation and renal impairment. Study drug therapy was adjusted for renal impairment on Days 1 and 2. Calculated creatinine clearance was 30.3 mL/min on Day 1 and 23.0 mL/min on Day 2. Twelve 12 days later, when the subject met the criteria set in the protocol for the switch to oral therapy, the subject received oral levofloxacin (250 mg once daily) for 7 days (Days 14 through 20). The subject received study drug therapy for a total of 9 days (Days 1, 2, and 14 through 20). The baseline pathogen isolated from blood and urine was *Klebsiella pneumoniae*. On Day 2, the subject had a temperature of 102.8° F, chills, weakness, abdominal and back pain, dysuria, urinary frequency, nausea, and loss of appetite. Intravenous hydration was started for dehydration secondary to presumed sepsis and volume depletion. Her fever subsided over the next few days. On Day 3, the subject showed signs and symptoms of renal impairment (unspecified), became diaphoretic, hypotensive, and had respiratory distress. Her arterial blood gas, while on 2 liters of oxygen, showed a markedly decreased PO2 of 54 mmHg. A 2-D echocardiogram, thyroid function tests, and a renal ultrasound were unremarkable. An electrocardiogram showed atrial fibrillation with rapid ventricular rate. Treatment with IV imipenem with cilastatin and gentamicin was started. On Day 4, the subject's heart rate was controlled after starting digoxin therapy. On Day 9, the subject was noted to have increased hepatic enzymes (laboratory test results not reported). The investigator assessed the increased hepatic enzyme moderate in severity, resolved on Day 13, and probably related to treatment with study drug therapy. According to the study records, treatment with study drug therapy was permanently discontinued; however, the subject was not taking any study drug medication at the time of the event. The renal impairment resolved on Day 14 and the subject was discharged from the hospital that same day with instructions to take a 7-day course of oral study drug levofloxacin. The atrial fibrillation was not considered resolved until Day 157

as determined at a follow-up visit. The investigator assessed the event of renal impairment severe in severity, serious due to prolongation of hospitalization, probably related to sepsis and dehydration, and possibly related to treatment with study drug therapy. The investigator assessed the event of atrial fibrillation severe in severity, serious due to prolongation of hospitalization, and possibly related to treatment with study drug therapy.

FDA Medical Officer Comments: The patient had multiple issues confounding causality assessment, including underlying renal failure and diabetes mellitus, sepsis, dehydration, and gram-negative bacteremia. She had received doripenem for a very brief time period (only two days) when study drug was discontinued; subsequently, she received gentamicin, a potentially nephrotoxic drug, which could also have contributed to the renal impairment observed.

Subject 64300217 (Doripenem 500 mg IV infusion q8h): This 63-year-old Caucasian man had a history of occasional reflux, mild diabetes, arthritis of the right knee, aortic valve replacement and mitral and tricuspid valves annuloplasties with the complication of pericardial effusion that required drainage, hypotension, atrial fibrillation, severe decreased left ventricular function, bundle branch blocks, cardiomyopathy, congestive heart failure, insomnia, and low electrolyte values. His urological history included benign prostatic hypertrophy. Concomitant medications included enalapril maleate, spironolactone, carvedilol, furosemide, colchicine, amiodarone, and warfarin sodium. Antibacterial medications included gatifloxacin, vancomycin, and sulfamethoxazole with trimethoprim. The subject received doripenem 500 mg as a 60-minute IV infusion q8h for the treatment of asymptomatic complicated lower urinary tract infection for a total of 2 days (Days 1 to 2). The subject did not have a study-qualifying baseline urine culture and, therefore, was discontinued from the study on Day 2. The baseline pathogen isolated from a urine sample was *Escherichia coli*. On Day 13, the subject, who had nonserious worsening renal failure on Day 1 and nonserious episodes of edema peripheral, nausea, vomiting, and diarrhea on Day 6, was hospitalized with complaints of lightheadedness. The investigator considered all of these events unrelated to treatment with study drug therapy. The subject's cardiac history and surgery as well as the history of hypotension all had started within the month of study participation. His systolic blood pressure was measured in the 70s and admission laboratory results revealed a blood urea nitrogen level of 44 and creatinine of 4.2, which improved to 26 and 1.6, respectively (units and ranges not reported). Diagnoses of acute renal failure and hypotension were made. Treatment details were not reported. The investigator considered both events resolved on Day 15 and the subject was discharged from the hospital on the same day. The investigator assessed the events to be caused by hypovolemia and hypovolemia medications including enalapril maleate, carvedilol, furosemide, and spironolactone, and unrelated to treatment with study drug therapy.

FDA Medical Officer Comments: The patient received doripenem for a very brief time period (only two days) when study drug was discontinued. He experienced multiple medical problems following discontinuation of the drug that likely contributed to worsening of his renal function, including hypotension (decreased renal perfusion), dehydration, and exposure to potentially nephrotoxic medications (vancomycin). It appears unlikely that his renal failure was related to doripenem exposure

Subject 04102020 (Doripenem 500 mg IV infusion q8h): This 66-year-old Caucasian man had a history of cardiac insufficiency, hypertension, alcoholism, chronic renal insufficiency, dyslipidemia, gout, renal carcinoma and nephrectomy, and type 2 diabetes mellitus. In addition, ventricular arrhythmia, cholecystitis, partial small bowel resection, anemia, hypoalbuminemia, hypocalcemia, anxiety, edema of the ankles, and bilateral vascular pulmonary murmur occurred just before study entry. Concomitant medications included carvedilol, atorvastatin, ramipril, glibenclamide, clotrimazole, thiamine, folic acid, heparin, pantoprazole, paracetamol, furosemide, insulin, and acetylsalicylic acid. Antibacterial medications included cefazolin, ciprofloxacin, ertapenem, bacitracin, and mupirocin. The subject enrolled in the study following a cholecystectomy. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and meropenem placebo as a 3- to 5-minute IV bolus q8h for the treatment of a complicated intra-abdominal infection for a total of 4 days (Days 1 through 4). No baseline pathogen was reported. Between Days 1 and 23, the subject experienced several adverse events that were all deemed unrelated to treatment with study drug therapy as determined by the investigator. These events included ventricular extrasystoles (Day 1), supraventricular tachycardia (Day 2), postprocedural discharge (Day 3), thrombophlebitis superficial (Day 8), edema peripheral (Day 12), urinary tract infection (Day 20), wound infection staphylococcal (Day 23), dehydration (Day 23), and confusional state (Day 23). On Day 23, *Staphylococcus* species was isolated (source not reported). On Day 27, *Staphylococcus aureus* was identified as a new intra-abdominal organism. The source of the pathogen was not reported. On Day 23, the subject was hospitalized for severe renal failure acute and moderate confusion, which were secondary to alcohol withdrawal and dehydration. On admission, the subject's creatinine level was 358 mmol/L and blood urea nitrogen (BUN) was 22.7 mmol/L (normal ranges not provided). Two days later, the creatinine level and BUN decreased to 109 mmol/L and 15.3 mmol/L, respectively. On Day 27, an abdominal ultrasound showed inflammation that was reported as "normal" and the subject's creatinine had improved to 115 mmol/L and the BUN remained the same at 15.3 mmol/L. The investigator considered the renal failure acute resolved on Day 27 and the subject was discharged from the hospital on Day 36. While hospitalized, the subject also experienced skin candida (Day 24), and postprocedural discharge, conjunctivitis, balanitis, and wound infection on Day 27. All of these events were considered unrelated to treatment with study drug therapy by the investigator. The investigator assessed the renal failure acute as severe in intensity, serious due to hospitalization, attributed to alcohol withdrawal and dehydration, and unrelated to treatment with study drug therapy.

FDA Medical Officer Comments: The patient developed acute on chronic renal failure about 19 days after discontinuing doripenem in the setting of alcohol withdrawal and dehydration. There was not a close temporal association of the event with doripenem exposure, but underlying pre-renal azotemia secondary to dehydration may have enhanced the subject's susceptibility to develop acute renal failure following drug exposure.

Subject 10006028 (Doripenem 500 mg IV infusion q8h): This 61-year-old Caucasian man had a history of arterial hypertension, coronary heart disease due to posterior wall infarction, ICD implantation, grade 1 mitral valve insufficiency, grade 1 tricuspid valve

insufficiency grade 1, acute cholecystitis, cirrhosis hepatis, diabetes mellitus, and hypercholesterolemia. Concomitant medications included glibenclamide, acetylsalicylic acid, atorvastatin, carvedilol, digoxin, prinzide, furosemide, and potassium canrenoate. Antibacterial medications included mezlocillin, metronidazole, and imipenem. The subject received doripenem 500 mg 60-minute IV infusion q8h and meropenem placebo 3- to 5-minute IV bolus q8h for the treatment of a complicated intra-abdominal infection for a total of 7 days (Days 1 through 7). Study drug therapy was adjusted for renal impairment on Days 5, 6, and 7. Calculated creatinine clearance on these days ranged from 42.7 mL/min to 49.6 mL/min. No baseline pathogen was reported. While on treatment with study drug therapy, the subject had several adverse events including high loss of drainage fluid (intra-abdominal), high loss of ileostoma, hypocalcemia, wound dehiscence (with secretion), and back pain. The investigator considered none of these events to be serious or related to treatment with study drug therapy. The subject received his last dose of study drug therapy on Day 7. On Day 18, the subject was hospitalized due to acute renal failure, hyperkalemia, and cardiac decompensation. On admission, the subject's poor condition and low blood pressure (60/40 mm Hg) were noted, together with increased bowel activity. Abnormal laboratory results during the subject's hospitalization included creatinine 2.24 mg/dL (normal range: <1.3 mg/dL), calcium 1.92 mmol/L (normal range: 2.1 mmol/L to 2.65 mmol/L), alkaline phosphatase 213 U/L (normal range: 38 to 126 U/L), lactic dehydrogenase 323 U/L (normal range: <248 U/L), and gammaglutamyl transferase 428 U/L (normal range: <55 U/L). The subject was treated aggressively with the diuretics including oral furosemide, potassium canrenoate, and spironolactone from Day 18 (ongoing). Following volume replacement and catecholamine infusions, the subject's renal function improved rapidly. On Day 23, the subject's creatinine was within the normal range with 1.29 mg/dL and the investigator considered the acute renal failure resolved. The subject's creatinine continued to improve and was 1.12 mg/dL on Day 25. The subject was discharged from the hospital on Day 35. The investigator assessed the acute renal failure to be severe in severity, serious as it required prolonged hospitalization, related to the subject's cardiac insufficiency, and unrelated to treatment with study drug therapy.

FDA Medical Officer's Comments: The patient was diagnosed with acute renal failure 11 days after completion of doripenem therapy. He had developed cardiac decompensation, hypotension, and dehydration concurrent with the onset of the renal dysfunction; treatment of those medical problems resulted in resolution of the acute renal failure. There was not a close temporal association of the event with doripenem exposure, but underlying pre-renal azotemia secondary to hypotension and dehydration may have enhanced the subject's susceptibility to develop acute renal failure following drug exposure.

Subject 12606026 (Doripenem 500 mg IV infusion q8h): This 69-year-old Caucasian woman had a history of coronary heart disease, peripheral artery disease, hyperlipoproteinemia, and chronic obstructive pulmonary disease. In addition, the subject experienced a myocardial infarction in the month prior to study entry. Concomitant medications included bisoprolol, ramipril, galenic/fluticasone/salmeterol, insulin, dobutamine, furosemide, norepinephrine, metamizole, propofol, acetylcysteine, ranitidine, theoadrenaline/cafedrine, desflurane, heparin-fraction sodium salt, digitoxin, piritramide, midazolam, hydrocortisone, epinephrine, omeprazole, metoclopramide, salbutamol, and

fluconazole. Antibacterial medications included mezlocillin, sulbactam, gentamicin, ceftazidime, vancomycin, metronidazole, cefotaxime, linezolid, and imipenem/cilastatin. On Day –1, the subject was hospitalized for an acute abdomen and severe sepsis. On Day 1, the subject underwent an open sigmoid resection, abdominal lavage, temporary abdominal wall closure, intraoperative washout, and appendectomy. A diagnosis of perforated sigmoid colon with peritonitis was made. Peritoneal fluid was sent for culture, and the subject was enrolled in the study. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and meropenem placebo as a 3- to 5-minute IV bolus q8h for a total of 6 days (Days 1 through 6) for the treatment of a complicated intra-abdominal infection. Baseline pathogens isolated from the peritoneal fluid were *Bacteroides thetaiotamicron*, *Enterococcus faecium*, and *Klebsiella pneumoniae*. While in the hospital, the subject returned to surgery on 4 consecutive days (Days 2 through 5) for repeat laparotomies for the following procedures: lavage, temporary abdominal wall closure, resection of the necrotic omentum major with placement of 3 drains, monitoring of the anastomosis, omphalectomy due to umbilical necrosis, and protective loop ileostomy. On Day 6, diagnoses of bacteremia and pneumonia were made. Intravenous study drug therapy was permanently discontinued on Day 6 because of these events, and the subject was withdrawn from the study. Treatment for the events included ceftazidime, gentamicin, vancomycin, and metronidazole. On Day 8, a tracheotomy was performed and mechanical ventilation was initiated. On Day 15, a severe anastomotic leak was noted. A repeat laparotomy was performed, and the leakage was considered resolved with sequelae that same day. On Day 16, IV cefotaxime was initiated for sepsis. On Day 27, linezolid was added for the pneumonia, and imipenem/cilastatin was initiated for the intra-abdominal infection. The bacteremia was eventually considered resolved on Day 37 but the pneumonia persisted. On Day 32, the subject again underwent laparoscopic surgery for repair of an anastomotic leak. Also on Day 32, the subject was noted to have sepsis-induced renal insufficiency, reported by the investigator as kidney failure. The subject received continuous venous hemodiafiltration for 3 days followed by dialysis at regular intervals. On Day 34, a diagnosis of pancreatitis was made, and on Day 40, a diagnosis of gallbladder necrosis was made. On Day 53, the subject died as a result of the renal insufficiency; no autopsy was performed. The pneumonia was considered resolved on Day 53 at the subject's death. The investigator assessed the bacteremia and pneumonia as severe, serious because they were life threatening, and secondary to the disease under study. The renal insufficiency was assessed as life threatening, serious as it led to death, and secondary to the disease under study. The investigator considered all 3 events unrelated to treatment with study drug therapy.

FDA Medical Officer Comments: The patient developed renal failure 26 days after discontinuing doripenem therapy. There were identifiable aggravating factors noted in association with the deterioration of renal function, including sepsis (from pulmonary and intra-abdominal sources) and exposure to potentially nephrotoxic drugs (vancomycin and gentamicin). In view of the lack of a close temporal association with doripenem exposure and the existence of identifiable aggravating factors, it unlikely that doripenem had a substantial contributory role in the subject's development of acute renal failure.

Subject 38304104 (Doripenem 500 mg IV infusion q8h): This 69-year-old Hispanic woman had a history of hypertension, cholecystectomy, hysterectomy, neurosurgery (stroke),

eventroplasty, and prerenal failure. Concomitant medications included amlodipine, ranitidine, tramadol, heparin, metoclopramide, and furosemide. Antibacterial medication included cefazolin. On Day –2, the subject was hospitalized with abdominal pain and vomiting. Emergency laparotomy disclosed umbilical eventration. After surgery, the subject had persistent fever and paralytic ileum. On Day 1, a second laparotomy disclosed bowel perforation and diffuse peritonitis, a partial enterectomy was performed, and the subject was enrolled in the study. The subject received doripenem 500 mg as a 60-minute IV infusion q8h and meropenem placebo as a 3- to 5-minute IV bolus q8h for the treatment of complicated intra-abdominal infection for a total of 9 days (Days 1 through 9). Baseline pathogens isolated from the peritoneal fluid were *Bacteroides thetaiotaomicron*, *Escherichia coli, Klebsiella pneumoniae*, *Peptostreptococcus micros, Porphyromonas gingivalis,* and *Streptococcus bovis.* On Day 8, the subject started oral food intake for the first time after surgery. On Day 9, the subject experienced dyspepsia. Treatments included metoclopramide, ranitidine, and parenteral nutrition. The investigator considered the event resolved on Day 15. The investigator assessed the dyspepsia to be moderate in severity, serious because it prolonged hospitalization, related to the subject's age and postoperative status, and unlikely related to treatment with study drug therapy. On Day 16, the subject experienced renal impairment (laboratory data not reported). Her serum creatinine was 132.6 µmol/L (normal range: 44.2 to 79.56 µmol/L) on Day 19. The subject was considered well enough for discharge from the hospital on Day 21. The investigator considered the renal impairment resolved on Day 48 at which time the serum creatinine was in the normal range (79.56 µmol/L). The investigator assessed the renal impairment mild in severity, serious because it prolonged hospitalization, related to the prerenal failure and unspecified drug-induced nephrotoxicity, and unlikely related to treatment with study drug therapy.

FDA Medical Officer's Comments: The patient developed renal impairment seven days after discontinuing doripenem. There was not a close temporal association of the event with doripenem exposure, but underlying pre-renal azotemia secondary to diuretic use may have enhanced the subject's susceptibility to develop acute renal failure following exposure to the drug.

The Sponsor provided the following narratives on the subjects with renal failure- or renal impairment-related, non-serious treatment-emergent adverse events:

DORI-05 Subject 01303031 (Doripenem 500 mg IV infusion q8h):
This 40-year-old Caucasian woman entered the study with a diagnosis of uncomplicated pyelonephritis. The subject had a history of multiple medical problems including hypotension, diarrhea, and cancer of the labia/vulva. The subject received doripenem 500 mg as a 60-minute IV infusion q24h and q8h for 10 days (Days 1 to 10) followed by oral levofloxacin tablets (500 mg once daily) for 5 days (Days 10 to 14). The subject's serum creatinine level was above the upper limit of normal (ULN) at baseline (114.92 µmol/L; ULN=106.08 µmol/L). On Day 3, her serum creatinine level rose to 238.68 µmol/L and renal impairment was reported as an adverse event that was judged by the investigator as mild in severity and not related to study medication. No action was taken in response to the event. Subsequently, the creatinine level continued to