

Clinical Efficacy of Doripenem in Nosocomial Pneumonia

Thomas Smith, M.D.

Division of Anti-Infective and Ophthalmology Products

July 16, 2008



Nosocomial Pneumonia Studies

- DORI-09
 - Open-label; nosocomial pneumonia or early-onset (<5 d) ventilator-associated pneumonia
 - Doripenem 500 mg iv q8h (1 h infusion) vs piperacillin/tazobactam 4.5 g iv q6h
 - Option to switch to oral levofloxacin after day 3
 - Total duration of therapy 7 to 14 days
- DORI-10
 - Open-label; ventilator-associated pneumonia
 - Doripenem 500 mg q8h (4 h infusion) vs imipenem/cilastatin 500 mg q6h (30 m infusion) or 1000 mg q8h (60 m infusion)
 - No oral switch
 - Total duration of therapy 7 to 14 days

DORI-09: Inclusion Criteria

- Hospitalization ≥ 48 h or prior admission with discharge within last 7d
- Clinical Pulmonary Infection Score (CPIS) ≥ 5 (intubated patients only)
- New or progressive infiltrate on chest radiograph
- Fever or WBC abnormalities (leukocytosis, increased bands, leukopenia)
- Respiratory failure requiring mechanical ventilation or at least two of: cough, sputum change, auscultatory findings, dyspnea/tachypnea, hypoxemia on room air

DORI-09: Microbiology

- Lower respiratory tract cultures to be obtained before enrollment
 - Non-intubated patients: sputum by deep expectoration or tracheal aspiration; sputum adequate if <10 squamous epithelial cells and >25 polymorphonuclear leukocytes per low power field
 - Intubated patients: endotracheal aspiration or bronchoscopy (bronchoalveolar lavage or protected-specimen brush); acceptability according to local guidelines
- Blood cultures

DORI-09: Study Treatments

- Doripenem 500 mg q8h vs piperacillin/tazobactam 4.5 g q6h; open-label
- Randomization stratified by geographic region, APACHE II score, ventilator status
- Adjunctive therapy
 - Amikacin 7.5 mg/kg q12h for potential *Pseudomonas aeruginosa* infection
 - Vancomycin permitted if methicillin-resistant *Staphylococcus aureus* (MRSA) isolated or suspected
- Option for oral switch
 - Investigators encouraged to continue iv study drug for entire duration of treatment
 - Oral levofloxacin 750 mg qd permitted after at least 72 hours of iv study drug if criteria for improvement met
- Total duration of therapy 7 to 14 days

DORI-09: Primary Endpoint

- Primary endpoint: clinical cure rate at test of cure visit 7 to 14 days following completion of all therapy
- Final clinical outcome determined by blinded evaluation committee of 10 physicians
 - Outcomes determined based on data summarized from case report forms from which references to study drug therapy received were removed
 - Committee members aware of investigators' unblinded determinations of clinical outcome

DORI-09: Statistical Considerations

- Clinically evaluable and clinical modified intent-to-treat (cMITT) populations co-primary for analysis of efficacy
 - cMITT: all randomized patients who received any amount of study drug and met “minimal definition” for pneumonia (presence of infiltrate on chest x-ray and either fever or WBC abnormalities)
 - Clinically evaluable: all randomized patients who met protocol-specified definition of nosocomial pneumonia, received adequate study therapy, had a valid test-of-cure assessment, and had no confounding factors; if baseline pathogens isolated, at least one susceptible to study drug received
- Noninferiority if lower bound of 95% confidence interval of difference in clinical success rates (doripenem minus piperacillin/tazobactam) greater than -20%

DORI-09: Demographic and Baseline Characteristics

	Doripenem (N=225)		Pip/tazo (N=223)	
Gender				
Male	159	(71)	153	(69)
Female	66	(29)	70	(31)
Age				
Median	59		63	
Range	19-94		18-97	
Race				
White	167	(74)	173	(78)
Hispanic/Latino	37	(16)	36	(16)
Black	14	(6)	13	(6)

DORI-09: Demographic and Baseline Characteristics

	Doripenem (N=225)		Pip/tazo (N=223)	
Region				
Europe (Eastern)	97	(43)	100	(45)
South America	72	(32)	71	(32)
North America	46	(20)	47	(21)
Other	10	(4)	5	(2)
Ventilator-associated				
No	161	(72)	161	(72)
Yes	64	(28)	62	(28)
Baseline APACHE II				
≤15	166	(74)	166	(74)
>15	59	(26)	57	(26)

DORI-09: Evaluability

	Doripenem (N=225)	Pip/tazo (N=223)
cMITT	217 (96)	212 (95)
Not cMITT evaluable	8 (4)	11 (5)
Clinically evaluable (CE)	134 (60)	119 (53)
Not CE	91 (40)	104 (47)
Microbiologically evaluable	84 (37)	83 (37)

Issues

- Diagnosis of pneumonia
 - CPIS
 - CXR
- Gram stain data to support adequacy of lower respiratory tract cultures
- Determination of effect of doripenem in nosocomial pneumonia
 - Adjunctive therapy
 - Oral switch

Clinical Pulmonary Infection Score

CPIS Points	0	1	2
Tracheal secretions*	Few	Moderate	Large
Chest x-ray infiltrates	None	Patchy or diffuse	Localized
Core/rectal temperature (°C)	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Leukocytes (per mm ³)	≥ 4000 and ≤ 11000	< 4000 or > 11000	
PaO ₂ /FiO ₂ (mmHg)	> 240 or ARDS		≤ 240 and no evidence of ARDS

* If purulent: +1

Ref: Appendix DORI-09.5, from Luna et al. Crit Care Med 2003;31:676

DORI-09: CPIS and VAP

	Doripenem	Pip/tazo
cMITT	62	61
CPIS \leq 6	31 (50)	25 (41)
CPIS $>$ 6	31 (50)	36 (59)
Clinically evaluable (CE)	29	26
CPIS \leq 6	14 (48)	7 (27)
CPIS $>$ 6	15 (52)	19 (73)

DORI-09: Chest Radiographs

- “Radiologists were generally not part of the study personnel and were likely to have evaluated the radiographic findings objectively, in isolation from detailed information on the clinical status of the patient. In cases where the radiology report and the investigator’s description in the CRF differed, the investigator’s interpretation was generally regarded as more definitive.” (S-015, 1/14/08)
- Subsequent identification of patients who did not have new or progressive infiltrates consistent with pneumonia; based only on radiologist’s report and included patients with missing reports
 - cMITT: 18 patients (9 with no formal report): 11 doripenem, 7 pip/tazo
 - CE: 6 patients (3 with no formal report): 3 doripenem, 3 pip/tazo

DORI-09: Gram Stains

- Results of Gram stain examinations of screening lower respiratory tract specimens not recorded on case report forms and not included in datasets
- Applicant subsequently obtained Gram stain reports from local laboratories for expectorated sputum specimens from 129 patients; 100 (77.5%) adequate by semiquantitative criteria
- cMITT analysis set
 - Cultures obtained from 294 patients with NP not ventilator-associated; most common specimen expectorated sputum (222/294; 76%)
 - Cultures obtained from 129 patients with VAP; most common specimen endotracheal aspirate (103/129); no supporting Gram stain data

DORI-09: Adjunctive Therapy for *Pseudomonas aeruginosa*

- Upon enrollment, patients in both arms treated with amikacin
- If *P. aeruginosa* not confirmed by culture, “amikacin should be discontinued, at the discretion of the investigator.”
- If *P. aeruginosa* confirmed:
 - Pip/tazo arm: continue amikacin for approximately 5 days (as in label)
 - Doripenem arm: “amikacin can be discontinued, at the discretion of the investigator, if the patient has improved clinically and the *P. aeruginosa* isolate is susceptible to meropenem (surrogate for doripenem).”

DORI-09: Adjunctive Therapy for *Pseudomonas aeruginosa*

Clinically evaluable	Doripenem (N=134)			Pip/tazo (N=119)		
Adjunct. therapy	Total n (%)	Baseline <i>P. aeruginosa</i> n (%)		Total n (%)	Baseline <i>P. aeruginosa</i> n (%)	
		Yes	No		Yes	No
No	29 (22)	2 (7)	26 (90)	18 (15)	2 (11)	15 (83)
Yes	105 (78)	16 (15)	88 (84)	101 (85)	17 (17)	83 (82)
<2d	10 (7)	1 (10)	9 (90)	11 (9)	0	10 (91)
3-5d	52 (39)	5 (10)	47 (90)	50 (42)	2 (4)	48 (96)
>5d	43 (32)	10 (23)	32 (74)	40 (34)	15 (38)	25 (63)

DORI-09: Adjunctive Therapy for *Pseudomonas aeruginosa*

- In doripenem clinically evaluable group, 95 of 134 patients (71%) treated with adjunctive anti-pseudomonal therapy for 3 days or more; 43 patients (32%) treated for >5 days
- 18 patients with *P. aeruginosa* isolated at baseline; no isolates resistant to meropenem or doripenem

DORI-09: Adjunctive Therapy for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

- If MRSA isolated or suspected, use of vancomycin permitted at discretion of investigator
- Vancomycin should be discontinued within 48 hours if the respiratory specimen and blood culture are negative for MRSA.

DORI-09: Adjunctive Therapy for MRSA

Clinically evaluable	Doripenem (N=134)			Pip/tazo (N=119)		
Adjunct. therapy	Total n (%)	Baseline MRSA, n (%)		Total n (%)	Baseline MRSA, n (%)	
		Yes	No		Yes	No
No	117 (87)	3 (3)	109 (93)	98 (82)	0	97 (99)
Yes	17 (13)	2 (12)	15 (88)	21 (18)	4 (19)	16 (76)
<2d	3 (2)	0	3 (100)	2 (2)	0	2 (100)
3-5d	7 (5)	0	3 (100)	9 (8)	1 (11)	8 (89)
>5d	7 (5)	2 (29)	5 (71)	10 (8)	3 (30)	6 (60)

DORI-09: Adjunctive Therapy for MRSA

- In doripenem clinically evaluable group, 14 of 134 patients (10%) treated with adjunctive vancomycin therapy for 3 days or more; 7 patients (5%) treated for >5 days
- 2 patients (1%) with MRSA isolated at baseline

DORI-09: Oral Switch

- In doripenem clinically evaluable group, 60 of 134 patients (45%) received combined iv and oral therapy; median duration of iv therapy 7 days, of oral therapy 5 days
- 74 of 134 patients (55%) received iv therapy only; median duration 10 days

DORI-09: Exposure to Doripenem as Single Agent

109 clinically evaluable cures in doripenem arm

<u>Days of single-agent therapy</u>	<u>Number of patients, (%)</u>
0	19 (17%)
1	11 (10%)
2	9 (8%)

DORI-09: Clinical Outcomes at Test of Cure

Analysis set	Doripenem n/N (%)	Pip/tazo n/N (%)	Difference % (95% CI)
Clinically evaluatable	109/134 (81.3)	95/119 (79.8)	1.5 (-9.1, 12.1)
Clinical MITT	148/213 (69.5)	134/209 (64.1)	5.4 (-4.1, 14.8)

DORI-09: Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

Region	Doripenem n/N (%)	Pip/tazo n/N (%)	Difference %
North America	14/19 (74)	14/17 (82)	-8.7
US	8/13 (62)	10/13 (77)	-15.4
South America	28/41 (68)	25/37 (68)	0.7
Europe	64/70 (91)	54/62 (87)	4.3
Other	3/4 (75)	2/3 (67)	8.3

DORI-09: Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

	Doripenem n/N (%)	Pip/tazo n/N (%)	Difference %
Ventilator-associated			
No	89/105 (85)	80/93 (86)	-1.3
Yes	20/29 (69)	15/26 (58)	11.3
Baseline APACHE II			
≤15	89/99 (90)	76/91 (84)	6.4
>15	20/35 (57)	19/28 (68)	-10.7

DORI-09: All-Cause Mortality (Intent-to-Treat)

Study period	Doripenem (N=223)	Pip/tazo (N=221)	Difference (Dori-P/T) (95% CI)*	Rel. Risk (Dori/P/T) (95% CI)
During iv	21 (9.4)	9 (4.1)	5.3 (0.3, 10.4)	2.3 (1.1, 4.9)
Days 1-28	34 (15.2)	31 (14.0)	1.2 (-5.8, 8.2)	1.1 (0.7, 1.7)
During therapy + 30 days	43 (19.3)	38 (17.2)	2.1 (-5.5, 9.7)	1.1 (0.8, 1.7)

* Confidence interval using a continuity correction

DORI-10: Inclusion Criteria

- Mechanical ventilation for >24 hours or weaned within preceding 72 hours
- Clinical Pulmonary Infection Score (CPIS) ≥ 5
- New or progressive infiltrate on chest radiograph
- Fever or WBC abnormalities (leukocytosis, increased bands, leukopenia)

DORI-10: Microbiology

- Lower respiratory tract cultures to be obtained before enrollment
 - Intubated patients: endotracheal aspiration or bronchoscopy (bronchoalveolar lavage or protected-specimen brush); acceptability according to local guidelines
 - Non-intubated patients: sputum by deep expectoration or tracheal aspiration; sputum adequate if <10 squamous epithelial cells and >25 polymorphonuclear leukocytes per low power field
- Blood cultures

DORI-10: Study Treatments

- Doripenem 500 mg infused over 4h q8h vs imipenem/cilastatin 500 mg infused over 30 min q6h or 1000 mg infused over 60 min q8h; open-label
- Randomization stratified by geographic region, duration of ventilation, APACHE II score
- Adjunctive therapy
 - Amikacin 7.5 mg/kg q12h
 - Doripenem: permitted at discretion of investigator for potential carbapenem-resistant *P. aeruginosa*
 - Imipenem: recommended if *P. aeruginosa* suspected
 - Vancomycin permitted if MRSA isolated or suspected
- No option for oral switch
- Total duration of therapy 7 to 14 days

DORI-10: Primary Endpoint

- Primary endpoint: clinical cure rate at test of cure visit 7 to 14 days following completion of all therapy
- No blinded evaluator or evaluation committee

DORI-10: Statistical Considerations

- Clinically evaluable and clinical modified intent-to-treat (cMITT) co-primary populations for analysis of efficacy
 - cMITT: all randomized patients who received any amount of study drug and met “minimal definition” for VAP (presence of infiltrate on chest x-ray and either fever or WBC abnormalities)
 - Clinically evaluable: all randomized patients who met protocol-specified definition of VAP, received adequate study therapy, had a valid test-of-cure assessment, and had no confounding factors; if baseline pathogens isolated, at least one susceptible to study drug received
- Noninferiority if lower bound of 95% confidence interval of difference in clinical success rates (doripenem minus imipenem) greater than -20%

DORI-10: Demographic and Baseline Characteristics

	Doripenem (N=264)	Imipenem (N=267)
Gender		
Male	208 (79)	204 (76)
Female	56 (21)	63 (24)
Age		
Median	51	53
Range	18-93	18-86
Race		
White	229 (87)	218 (82)
Black	23 (9)	31 (12)
Other	12 (5)	18 (7)

DORI-10: Demographic and Baseline Characteristics

	Doripenem (N=264)		Imipenem (N=267)	
Region				
North America	126	(48)	129	(48)
Europe (Western)	92	(35)	93	(35)
Other	46	(17)	45	(17)
Ventilator-associated status				
Early-onset (<5d)	105	(40)	106	(40)
Late-onset (≥5d)	159	(60)	161	(60)
Baseline APACHE II				
≤15	122	(46)	129	(48)
>15	142	(54)	138	(52)

DORI-10: Evaluability

	Doripenem (N=264)	Imipenem (N=267)
cMITT	249 (94)	252 (94)
Not cMITT evaluable	15 (6)	15 (6)
Clinically evaluable (CE)	126 (48)	122 (46)
Not CE	138 (52)	145 (54)
Microbiologically evaluable	116 (44)	110 (41)

DORI-10: Clinical Pulmonary Infection Scores

	Doripenem	Imipenem
cMITT	248	252
CPIS \leq 6	86 (35)	103 (41)
CPIS >6	162 (65)	149 (59)
Clinically evaluable (CE)	126	122
CPIS \leq 6	49 (39)	44 (36)
CPIS >6	77 (61)	78 (64)

DORI-10: Chest Radiographs

- Radiologists generally not part of the study personnel
- Subsequent identification of patients who did not have new or progressive infiltrates consistent with pneumonia; based only on radiologist's report and excluded patients with missing reports
 - cMITT: 68 patients (14%): 32 doripenem, 36 imipenem
 - CE: 38 patients (15%): 18 doripenem, 20 imipenem

DORI-10: Chest Radiographs

- Many sites in Europe did not have formal radiology reports of chest x-rays; investigators' interpretations of films entered on worksheets
- For some patients, a “note to file” was provided and information entered directly into case report form rather than on worksheet
- Worksheet interpretations considered equivalent to x-ray reports, part of source documentation, and “the only documented interpretation at those sites.” (S-024, 2/22/08)
- Identification of all patients with no formal radiology report (not available, worksheet, or note to file)
 - cMITT: 133 patients (27%): 62 doripenem, 71 imipenem
 - CE: 76 patients (31%): 36 doripenem, 40 imipenem

DORI-10: Chest Radiographs

- Applicant contacted sites and requested review of original films by independent radiologist, who provided summary form or formal report (S-037, 6/30/08)
 - 122 replies, nearly all on summary sheets (3 reports)
 - 118/122 (97%) with infiltrate(s) that could be pneumonia
 - Compared with films ≥ 24 hours earlier, 2 improved, 15 no change, 61 worsened or new infiltrate, 38 no previous film available, 2 no comment

DORI-10: Chest Radiographs

- Patients who did not meet strict radiologic criteria for pneumonia or who did not have formal radiology reports of screening chest films
 - cMITT: 60 patients (12%): 31 doripenem, 29 imipenem
 - CE: 35 patients (14%): 20 doripenem, 15 imipenem

DORI-10: Gram Stains

- Results of Gram stain examinations of screening lower respiratory tract specimens not recorded on case report forms and not included in datasets
- Applicant subsequently obtained Gram stain reports from local laboratories for expectorated sputum specimens from 6 nonintubated patients; 1 adequate by semiquantitative criteria
- No supporting Gram stain data for other specimens
- cMITT analysis set
 - Cultures obtained from 488 patients with VAP; most common specimens endotracheal aspirate (305/488; 63%)

DORI-10: Adjunctive Therapy for *Pseudomonas aeruginosa*

- If *P. aeruginosa* suspected (e.g., patient hospitalized >7 days or prior broad spectrum antibacterial therapy), adjunctive amikacin permitted
 - Doripenem arm: amikacin should only be added at discretion of investigator, if carbapenem-resistant *P. aeruginosa* is concern (e.g., previous carbapenem therapy or ICU carbapenem resistance rate >15%)
 - Imipenem arm: amikacin recommended if *P. aeruginosa* suspected, regardless of susceptibility
- If *P. aeruginosa* not confirmed by culture (generally, within 48 hours), amikacin should be discontinued
- If *P. aeruginosa* confirmed:
 - Imipenem arm: continue amikacin for total of 5 to 7 days
 - Doripenem arm: discontinue if isolate not resistant to meropenem and patient stable or improving

DORI-10: Adjunctive Therapy for *Pseudomonas aeruginosa*

Clinically evaluable	Doripenem (N=126)			Imipenem (N=122)		
Adjunct. therapy	Total n (%)	Baseline <i>P. aeruginosa</i> n (%)		Total n (%)	Baseline <i>P. aeruginosa</i> n (%)	
		Yes	No		Yes	No
No	101 (80)	12 (12)	88 (87)	92 (75)	5 (5)	86 (93)
Yes	25 (20)	8 (32)	17 (68)	30 (25)	9 (30)	21 (70)
<2d	9 (7)	1 (11)	8 (89)	11 (9)	3 (27)	8 (73)
3-5d	7 (6)	2 (29)	5 (71)	12 (10)	2 (17)	10 (83)
>5d	9 (7)	5 (56)	4 (44)	7 (6)	4 (57)	3 (43)

DORI-10: Adjunctive Therapy for *Pseudomonas aeruginosa*

- In doripenem clinically evaluable group, 16 of 126 patients (13%) treated with adjunctive anti-pseudomonal therapy for 3 days or more; 9 patients (7%) treated for >5 days
- 20 patients with *P. aeruginosa* isolated at baseline; no isolates resistant to doripenem (based on tentative breakpoints)

DORI-10: Adjunctive Therapy for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

- If MRSA isolated or suspected, use of vancomycin permitted at discretion of investigator
- Vancomycin should be discontinued within 48 hours if the respiratory specimen and blood culture are negative for MRSA.

DORI-10: Adjunctive Therapy for MRSA

Clinically evaluable	Doripenem (N=126)			Imipenem (N=122)		
Adjunct. therapy	Total n (%)	Baseline MRSA, n (%)		Total n (%)	Baseline MRSA, n (%)	
		Yes	No		Yes	No
No	89 (71)	0	84 (94)	88 (72)	1 (1)	84 (95)
Yes	37 (29)	11 (30)	24 (65)	34 (28)	6 (18)	27 (79)
<2d	10 (8)	0	9 (90)	7 (6)	0	7 (100)
3-5d	12 (10)	1 (8)	10 (83)	18 (15)	1 (6)	16 (89)
>5d	15 (12)	10 (67)	5 (33)	9 (7)	5 (56)	4 (44)

DORI-10: Adjunctive Therapy for MRSA

- In doripenem clinically evaluable group, 27 of 126 patients (21%) treated with adjunctive vancomycin therapy for 3 days or more; 15 patients (12%) treated for >5 days
- 11 patients (9%) with MRSA isolated at baseline

DORI-10: Clinical Outcomes at Test of Cure

Analysis set	Doripenem n/N (%)	Imipenem n/N (%)	Difference % (95% CI)
Clinically evaluatable	86/126 (68.3)	79/122 (64.8)	3.5 (-9.1, 16.1)
Clinical MITT	144/244 (59.0)	144/249 (57.8)	1.2 (-7.9, 10.3)

DORI-10: Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

Region	Doripenem n/N (%)	Imipenem n/N (%)	Difference %
North America	40/53 (75)	29/50 (58)	17.5
Europe	31/47 (66)	34/47 (72)	-6.4
Other	15/26 (58)	16/25 (64)	-6.3

DORI-10: Clinical Outcomes at Test of Cure (Clinically Evaluable Subgroups)

	Doripenem n/N (%)	Imipenem n/N (%)	Difference %
Days ventilation at baseline			
Late-onset (≥5 days)	58/78 (74)	52/73 (71)	3.1
Early-onset (<5 days)	28/48 (58)	27/49 (55)	3.2
Baseline APACHE II			
≤15	40/59 (68)	42/61 (69)	-1.1
>15	46/67 (69)	37/61 (61)	8.0

DORI-10: All-Cause Mortality (Intent-to-Treat)

Study period	Doripenem (N=262)	Imipenem (N=263)	Difference (Dori-Imi) (95% CI)*	Rel. Risk (Dori/Imi) (95% CI)
During iv	13 (5.0)	14 (5.3)	-0.4 (-4.5, 3.8)	0.9 (0.4, 1.9)
Days 1-28	30 (11.5)	26 (9.9)	1.6 (-4.1, 7.2)	1.2 (0.7, 1.9)
During therapy + 30 days	34 (13.0)	32 (12.2)	0.8 (-5.2, 6.9)	1.1 (0.7, 1.7)

* Confidence interval using a continuity correction

Combined Studies: Conclusions

- Significant issues limit ability to conclude noninferiority of doripenem to comparators
 - Both studies
 - Lack of blinding
 - Lack of Gram stain data for assessment of adequacy of lower respiratory tract specimens
 - Use of low Clinical Pulmonary Infection Scores as inclusion criterion for ventilated patients
 - DORI-09
 - Excessive use of adjunctive therapies, especially aminoglycosides
 - DORI-10
 - Lack of independent confirmation by radiologists of investigators' interpretations of screening x-rays