Table S1. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae,* including the outlier isolate, among simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	99.6	100	100	99.9
0.03	78.6 (11/14)	85.7 (12/14)	99.5	100	100	99.8	96.0	100	100	82.8
0.06	80.0 (8/10)	100 (10/10)	95.7	100	100	76.7	87.6	100	100	10.4
0.12	50.0 (1/2)	50 (1/2)	87.5	100	100	6.52	74.1	100	100	0.06
0.25	NA	NA	73.8	100	100	0	55.1	94.9	89.5	0
0.5	NA	NA	56.8	98.3	95.9	0	36.4	28.8	17.3	0
1	NA	NA	38.5	47.1	31.2	0	20.0	0.24	0.12	0
Overall[h]										
All	78.6 (22/28)	89.3 (25/28)	95.6	100	99.9	74.2	87.9	99.9	99.8	24.7
Pen-S			96.0	100	100	77.3	88.7	99.9	99.9	27.8
Pen-I			94.9	99.8	99.8	69.9	86.6	99.6	99.6	20.0
Pen-R			94.0	100	100	60.9	84.8	100	100	13.1

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2
d. Using data for all *S. pneumoniae* isolates studied, total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *S. pneumoniae* isolates studied, the median total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 13.3 and 15.2, respectively (2).
f. Based on data for all *S. pneumoniae* isolates studied, the second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. Based on data for all *S. pneumoniae* isolates studied, the highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 200.6 and 180.0, respectively (2).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S2. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, excluding the outlier, among simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on days 1 and 2 among simulated patients[b,c]					
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets			Assessment of free-drug plasma exposures and AUC/MIC ratio targets		
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	100	100
0.03	78.6 (11/14)	85.7 (12/14)	100	100	100	100	100	100
0.06	80.0 (8/10)	100 (10/10)	100	100	100	100	100	100
0.12	50.0 (1/2)	50 (1/2)	100	100	100	100	100	100
0.25	NA	NA	100	100	100	97.5	100	99.9
0.5	NA	NA	99.3	100	100	75.4	85.2	42.2
1	NA	NA	82.9	96.3	67.0	34.3	0.96	0.02
Overall[g]								
All	78.6 (22/28)	89.3 (25/28)	100	100	100	99.9	99.9	99.9
Pen-S			100	100	100	100	100	99.9
Pen-I			99.9	100	99.9	99.8	99.7	99.7
Pen-R			100	100	100	100	100	100

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model, excluding the outlier (*S. pneumoniae* 1293) (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. The total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. The median/second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 13.3 and 15.2, respectively (2).
f. The highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S3. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, excluding the outlier, among simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]					
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets			Assessment of free-drug plasma exposures and AUC/MIC ratio targets		
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]	Randomly assigned based on PK-PD targets[d]	Median/second highest PK-PD targets[e]	Highest PK-PD target[f]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	100	100
0.03	78.6 (11/14)	85.7 (12/14)	100	100	100	100	100	100
0.06	80.0 (8/10)	100 (10/10)	100	100	100	100	100	100
0.12	50.0 (1/2)	50 (1/2)	100	100	100	99.7	100	100
0.25	NA	NA	99.9	100	100	91.0	97.9	89.5
0.5	NA	NA	95.5	99.6	95.9	59.9	44.9	17.3
1	NA	NA	67.9	66.0	31.2	22.5	1.04	0.12
Overall[g]								
All	78.6 (22/28)	89.3 (25/28)	100	100	99.9	99.9	99.9	99.8
Pen-S			100	100	100	99.9	99.9	99.9
Pen-I			99.9	99.9	99.8	99.6	99.7	99.6
Pen-R			100	100	100	99.9	100	100

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model, excluding the outlier isolate (*S. pneumoniae* 1293) (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. The total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. The median/second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 13.3 and 15.2, respectively (2).
f. The highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S4. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, including the outlier isolate, among simulated patients after the administration of omadacycline 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on days 1 to 2 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	100	100	100	100
0.03	78.6 (11/14)	85.7 (12/14)	100	100	100	100	98.5	100	100	99.7
0.06	80.0 (8/10)	100 (10/10)	98.1	100	100	99.2	92.0	100	100	31.5
0.12	50.0 (1/2)	50 (1/2)	91.4	100	100	18.7	80.6	100	100	0
0.25	NA	NA	79.8	100	100	0	63.6	100	99.9	0
0.5	NA	NA	64.4	100	100	0	44.2	71.0	48.8	0
1	NA	NA	45.8	89.2	72.8	0	26.0	0.26	0.04	0
Overall[h]										
All	78.6 (22/28)	89.3 (25/28)	97.7	100	100	90.9	92.1	99.9	99.9	42.5
Pen-S			98.0	100	100	93.5	92.8	100	99.9	46.0
Pen-I			97.2	100	99.9	87.4	91.1	99.7	99.7	37.3
Pen-R			96.6	100	100	79.3	89.7	100	100	28.5

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. Using data for all *S. pneumoniae* isolates studied, total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *S. pneumoniae* isolates studied, the median total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 15.5 and 17.4, respectively (2).
f. Based on data for all *S. pneumoniae* isolates studied, the second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. Based on data for all *S. pneumoniae* isolates studied, the highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 200.6 and 180.0, respectively (2).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S5. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, including the outlier isolate, among simulated patients after the administration of omadacycline 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.015	100 (2/2)	100 (2/2)	99.9	100	100	100	99.5	100	100	99.7
0.03	78.6 (11/14)	85.7 (12/14)	99.4	100	100	99.7	95.6	100	100	77.8
0.06	80.0 (8/10)	100 (10/10)	95.3	100	100	70.4	86.7	100	100	7.98
0.12	50.0 (1/2)	50 (1/2)	86.7	100	100	4.72	73.0	100	100	0.04
0.25	NA	NA	72.8	100	100	0	53.6	92.5	85.7	0
0.5	NA	NA	55.2	97.4	93.7	0	34.9	23.6	13.7	0
1	NA	NA	37.3	40.4	25.9	0	19.1	0.22	0.10	0
Overall[h]										
All	78.6 (22/28)	89.3 (25/28)	95.2	100	99.9	69.7	87.1	99.9	99.8	22.1
Pen-S			95.6	100	100	72.9	88.0	99.9	99.9	25.0
Pen-I			94.4	99.8	99.8	65.3	85.8	99.6	99.6	17.5
Pen-R			93.4	100	100	56.2	84.0	100	100	11.1

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model (2).
c. Based on the assessment of average 24-h total-drug ELF or free-drug plasma AUC values on days 1 and 2.
d. Using data for all *S. pneumoniae* isolates studied, total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *S. pneumoniae* isolates studied, the median total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 13.3 and 15.2, respectively (2).
f. Based on data for all *S. pneumoniae* isolates studied, the second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. Based on data for all *S. pneumoniae* isolates studied, the highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 200.6 and 180.0, respectively (2).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S6. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, excluding the outlier isolate, among simulated patients after the administration of omadacycline 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on days 1 to 2 among simulated patients[b,c]					
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets			Assessment of free-drug plasma exposures and AUC/MIC ratio targets		
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	100	100
0.03	78.6 (11/14)	85.7 (12/14)	100	100	100	100	100	100
0.06	80.0 (8/10)	100 (10/10)	100	100	100	100	100	100
0.12	50.0 (1/2)	50 (1/2)	100	100	100	100	100	100
0.25	NA	NA	100	100	100	98.0	100	99.9
0.5	NA	NA	99.5	100	100	77.2	89.0	48.8
1	NA	NA	84.5	97.5	72.8	36.4	1.56	0.04
Overall[g]								
All	78.6 (22/28)	89.3 (25/28)	100	100	100	99.9	99.9	99.9
Pen-S			100	100	100	100	100	99.9
Pen-I			99.9	100	99.9	99.8	99.7	99.7
Pen-R			100	100	100	100	100	100

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model, excluding the outlier isolate (*S. pneumoniae* 1293) (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. The total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. The median/second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 15.5 and 17.4, respectively (2).
f. The highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S7. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *S. pneumoniae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, excluding the outlier isolate, among simulated patients after the administration of omadacycline 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]					
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets			Assessment of free-drug plasma exposures and AUC/MIC ratio targets		
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]	Randomly assigned based on PK-PD targets[d]	Median/second highest of PK-PD targets[e]	Highest PK-PD target[f]
0.015	100 (2/2)	100 (2/2)	100	100	100	100	100	100
0.03	78.6 (11/14)	85.7 (12/14)	100	100	100	100	100	100
0.06	80.0 (8/10)	100 (10/10)	100	100	100	100	100	100
0.12	50.0 (1/2)	50 (1/2)	100	100	100	99.6	100	100
0.25	NA	NA	99.9	100	100	89.0	96.8	85.7
0.5	NA	NA	94.6	99.1	93.7	56.6	38.5	13.7
1	NA	NA	64.8	59.6	25.9	20.1	0.54	0.10
Overall[g]								
All	78.6 (22/28)	89.3 (25/28)	100	100	99.9	99.9	99.9	99.8
Pen-S			100	100	100	99.9	99.9	99.9
Pen-I			99.9	99.9	99.8	99.6	99.6	99.6
Pen-R			100	100	100	99.9	100	100

a. Based on data from patients with CABP and *S. pneumoniae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model, excluding the outlier isolate (*S. pneumoniae* 1293) (2).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. The total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. The median/second highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 13.3 and 15.2, respectively (2).
f. The highest total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were 17.6 and 19.7, respectively (2).
g. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S8. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *H. influenzae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* among simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 28 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.12	NA	NA	100	100	100	100	100	100	100	100
0.25	NA	NA	100	100	100	100	99.9	100	100	99.7
0.5	100 (1/1)	100 (1/1)	99.9	100	100	99.9	91.6	94.1	90.2	76.4
1	77.8 (14/18)	88.9 (16/18)	93.0	95.6	92.3	80.3	42.0	26.4	18.3	6.76
2	50.0 (6/12)	66.7 (8/12)	45.3	29.9	21.4	8.16	3.52	0.24	0.14	0
4	100 (1/1)	100 (1/1)	4.30	0.26	0.20	0.04	0.04	0	0	0
Overall[h]										
All	68.8 (22/32)	81.3 (26/32)	91.3	91.2	89.0	82.4	61.1	54.9	49.5	38.4
BL-Neg			91.3	91.1	88.8	82.3	61.4	55.4	50.2	39.0
BL-Pos			91.5	91.6	89.4	82.5	60.1	53.3	47.7	36.5

a. Based on data from patients with CABP and *H. influenzae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* based on data from one-compartment *in vitro* infection model (4).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. Using data for all *H. influenzae* isolates studied, total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *H. influenzae* isolates studied, the median total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 8.91 (4).
f. Based on data for all *H. influenzae* isolates studied, the second highest total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 9.73 (4).
g. Based on data for all *H. influenzae* isolates studied, the highest total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 11.6 (4).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S9. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *H. influenzae* at baseline and percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* among simulated patients after the administration of omadacycline 200 mg i.v. q24h on Day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 32 patients[a]		Percent probability of PK-PD target attainment by MIC on days 1 to 2 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.12	NA	NA	100	100	100	100	100	100	100	100
0.25	NA	NA	100	100	100	100	100	100	100	100
0.5	100 (1/1)	100 (1/1)	100	100	100	100	99.6	100	99.9	99.3
1	77.8 (14/18)	88.9 (16/18)	99.6	100	99.9	99.4	69.9	66.9	50.9	20.2
2	50.0 (6/12)	66.7 (8/12)	71.9	70.8	55.3	23.8	8.90	0.22	0.04	0
4	100 (1/1)	100 (1/1)	10.2	0.26	0.08	0	0	0	0	0
Overall[h]										
All	68.8 (22/32)	81.3 (26/32)	96.8	96.8	95.4	92.4	77.6	75.7	68.4	54.4
BL-Neg			96.8	96.8	95.3	92.2	77.7	75.8	68.7	55.0
BL-Pos			96.8	96.8	95.6	93.0	77.4	75.4	67.6	52.4

a. Based on data from patients with CABP and *H. influenzae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* based on data from a one-compartment *in vitro* infection model (4]).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC on days 1 and 2.
d. Using data for all *H. influenzae* isolates, total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *H. influenzae* isolates, the median total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 8.91 (4).
f. Based on data for all *H. influenzae* isolates studied, the second highest total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 9.73 (4).
g. Based on data for all *H. influenzae* isolates studied, the highest total-drug ELF/free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 11.6 (4).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution (3) for simulated patients.

Table S10. Comparison of observed percentages of successful clinical response by MIC among patients with CABP and *H. influenzae* at baseline and percent probabilities of PK-PD target attainment by MIC on day 3 based on total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* among simulated patients after the administration of omadacycline 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5

MIC (µg/mL)	% of successful clinical response by MIC (no./total) for 32 patients[a]		Percent probability of PK-PD target attainment by MIC on day 3 among simulated patients[b,c]							
			Assessment of total-drug ELF exposures and AUC/MIC ratio targets				Assessment of free-drug plasma exposures and AUC/MIC ratio targets			
	ECR at 72 to 120 hours	Clinical success at PTE	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]	Randomly assigned based on PK-PD targets[d]	Median of PK-PD targets[e]	Second highest PK-PD target[f]	Highest PK-PD target[g]
0.12	NA	NA	100	100	100	100	100	100	100	100
0.25	NA	NA	100	100	100	100	99.8	100	100	99.6
0.5	100 (1/1)	100 (1/1)	99.9	100	100	99.7	89.4	91.7	86.4	70.4
1	77.8 (14/18)	88.9 (16/18)	90.9	93.3	88.9	74.7	38.0	21.8	14.3	5.00
2	50.0 (6/12)	66.7 (8/12)	40.4	24.8	16.7	6.18	2.80	0.22	0.12	0
4	100 (1/1)	100 (1/1)	3.40	0.22	0.12	0.02	0	0	0	0
Overall[h]										
All	68.8 (22/32)	81.3 (26/32)	90.0	89.7	87.0	79.6	58.3	51.8	46.1	35.0
BL-Neg			90.0	89.6	86.9	79.6	58.7	52.4	46.7	35.6
BL-Pos			90.1	90.1	87.4	79.5	57.2	50.0	44.2	33.1

a. Based on data from patients with CABP and *H. influenzae* at baseline in the microITT population of the phase 3 OPTIC study (1). NA indicates the absence of data at a given MIC value.
b. Assessed using total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* based on data from a one-compartment *in vitro* infection model (4).
c. Based on the assessment of average 24-h total-drug ELF and free-drug plasma AUC values on days 1 and 2.
d. Using data for all *H. influenzae* isolates studied, total-drug ELF/free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC/MIC ratio targets associated with the same endpoint.
e. Based on data for all *H. influenzae* isolates studied, the median total-drug ELF and free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 8.91 (4).
f. Based on data for all *H. influenzae* isolates studied, the second highest total-drug ELF and free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 9.73 (4).
g. Based on data for all *H. influenzae* isolates studied, the highest total-drug ELF and free-drug plasma AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline was 11.6 (4).
h. "Overall" represents the percentage of successful clinical response among all observed patients or the percent probability of PK-PD target attainment weighted over the given MIC distribution ([3) for simulated patients.

Table S11. Omadacycline total-drug ELF and free-drug plasma AUC/MIC ratio targets for *S. pneumoniae* efficacy based on data from a neutropenic murine-lung infection model (2)

Matrix	*S. pneumoniae* isolate	MIC value (µg/mL)	AUC/MIC ratio targets by efficacy endpoint		
			Net bacterial stasis	1-log_{10} CFU reduction from baseline	2-log_{10} CFU reduction from baseline
Total-drug ELF	1293	0.06	17.8	200.6	-
	10813	0.06	14.2	17.6	23.2
	140	0.125	-	6.00	17.3
	49619	0.03	-	13.3	47.3
	Mean (SD)	-	16.0 (2.56)	59.4 (94.3)	-
	Mean without 1293 (SD)	-	-	12.3 (5.86)	29.3 (15.9)
	Median	-	-	15.5	-
	Median without 1293	-	-	13.3	23.2
Free-drug plasma	1293	0.06	19.8	180.0	-
	10813	0.06	15.8	19.7	25.1
	140	0.125	-	6.06	18.6
	49619	0.03	-	15.2	56.2
	Mean (SD)	-	17.8 (2.86)	55.2 (83.4)	-
	Mean without 1293 (SD)	-	-	13.6 (6.93)	33.3 (20.1)
	Median	-	-	17.4	-
	Median without 1293	-	-	15.2	25.1

Table S12. Omadacycline total-drug ELF/free-drug plasma[a] AUC/MIC ratio targets for *H. influenzae* efficacy based on data from a one-compartment *in vitro* infection model (4)

H. influenzae **isolate**	**MIC (µg/mL)**	**Total-drug ELF/free-drug plasma[a] AUC/MIC ratio targets by efficacy endpoint**		
		Net bacterial stasis	**1-$\log_{10}$ CFU reduction from baseline**	**2-$\log_{10}$ CFU reduction from baseline**
437	1	6.91	8.91	11.1
10929	1	7.09	9.73	12.9
2696	2	4.38	5.44	6.72
49247	2	8.76	11.6	15.5
543	2	4.45	5.78	7.45
Mean (SD)	–	6.32 (1.88)	8.30 (2.64)	10.7 (3.69)
Median	–	6.91	8.91	11.1

a. Total-drug ELF and free-drug plasma AUC/MIC ratio targets for *H. influenzae* were considered to be equivalent based on the assumption that any differences in the time-course of the plasma and ELF omadacycline exposures did not impact the magnitude of the AUC/MIC ratio necessary for efficacy.

Figure S1. Percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on the evaluation of the total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, including and excluding the outlier, among simulated patients after the administration of omadacycline 100 mg i.v.q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (A and B, respectively), and 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (C and D, respectively), overlaid on the MIC distribution for *S. pneumoniae*.

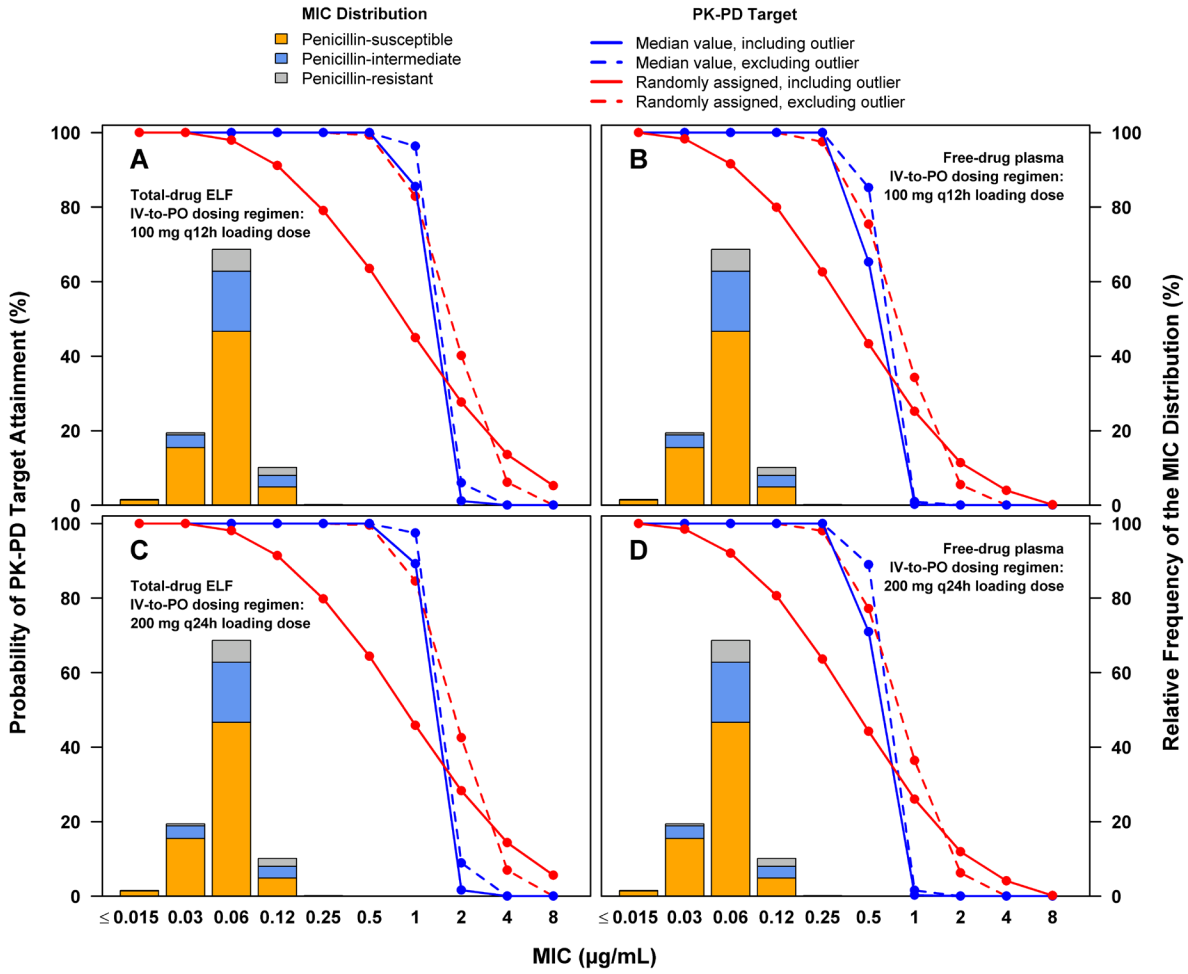
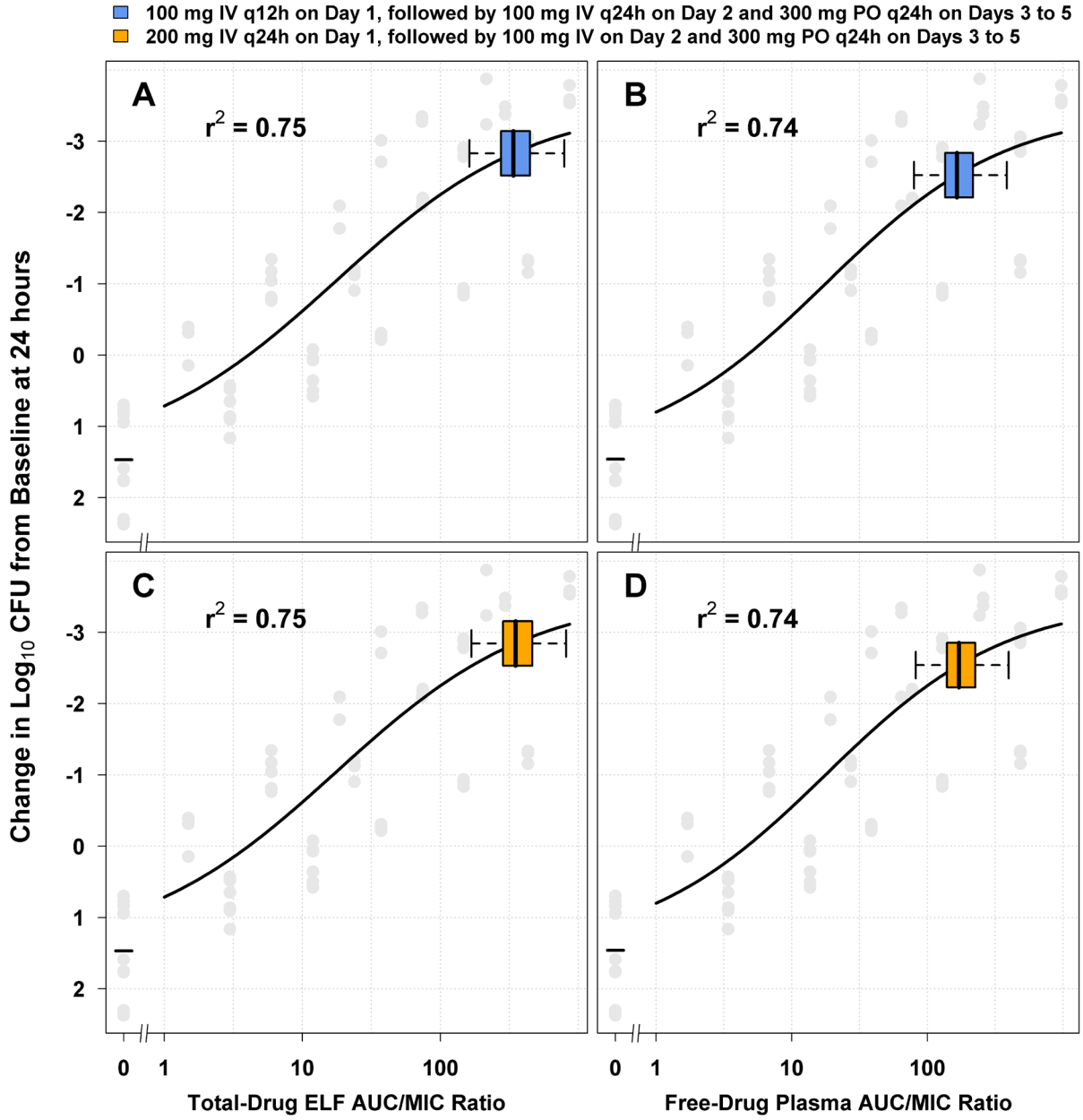


Figure S2. Non-clinical PK-PD relationship for efficacy for *S. pneumoniae*, overlaid with box-and-whisker plots of total-drug ELF and free-drug plasma AUC/MIC ratios on days 1 to 2 for simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (A and B, respectively), and 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (C and D, respectively). Horizontal box-and-whisker plots of total-drug ELF and free-drug plasma AUC/MIC ratios on days 1 and 2 for simulated patients after administration of omadacycline IV-to-PO dosing regimens are shown overlaid on the PK-PD relationship based on data from a neutropenic murine-lung infection model for *S. pneumoniae*.



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For each boxplot, the edge of the box represents the 25th to the 75th percentiles of the distribution for total-drug ELF or free-drug plasma AUC/MIC ratio. The line within the box represents with median total-drug ELF or free-drug plasma AUC/MIC ratio. The whiskers extend to the nearest value among those represented by 1.5 × IQR of the box edges, where IQR is interquartile range as defined by the distribution of total-drug ELF or free-drug plasma AUC/MIC ratio from the 25th to the 75th percentiles.

Figure S3. Percent probabilities of PK-PD target attainment by MIC on days 1 to 2 based on the evaluation of the total-drug ELF and free-drug plasma AUC/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *H. influenzae* among simulated patients after the administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (A and B, respectively), and 200 mg i.v. q24h on day 1, followed by 100 mg i.v. q24h on Day 2 and 300 mg p.o. q24h on days 3 to 5 (C and D, respectively), overlaid on the MIC distribution for *H. influenzae*.

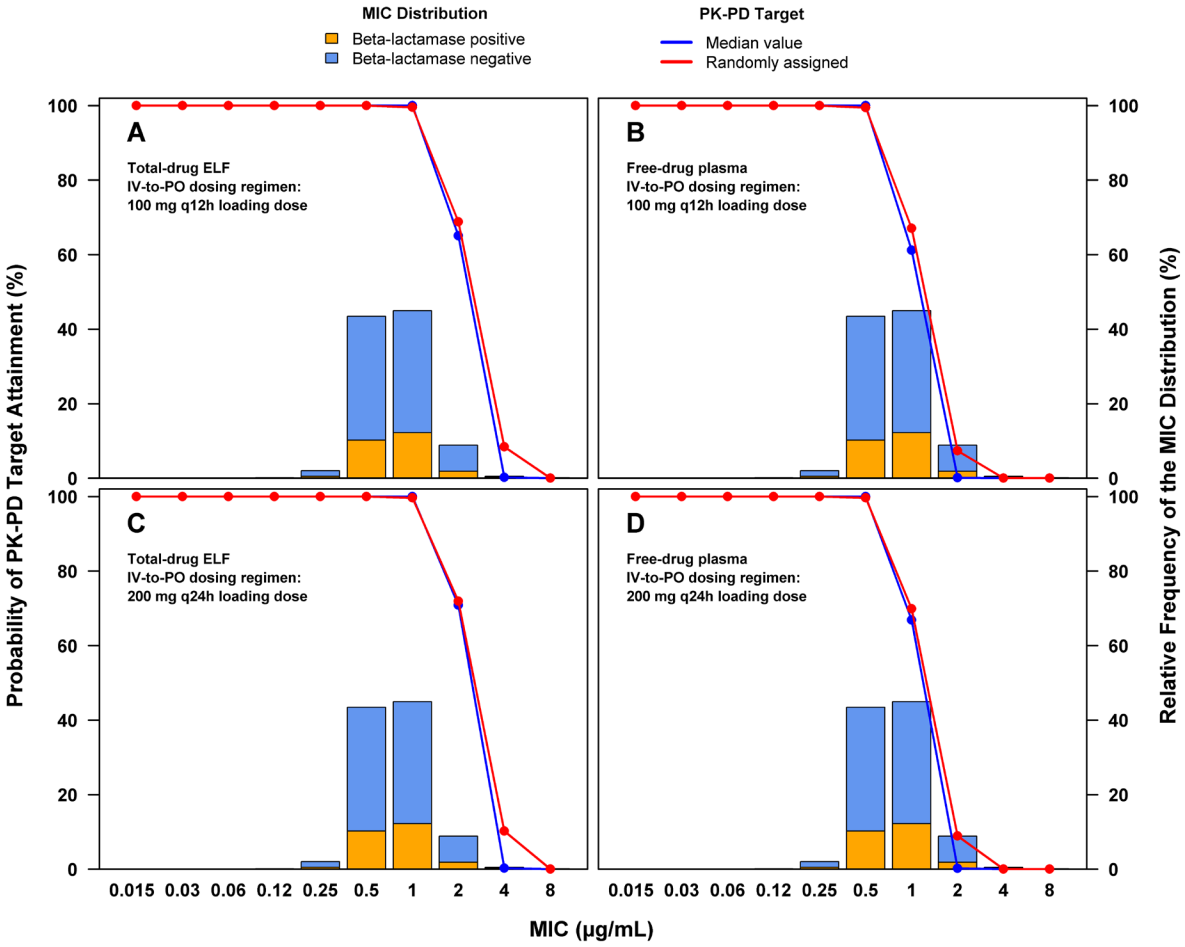
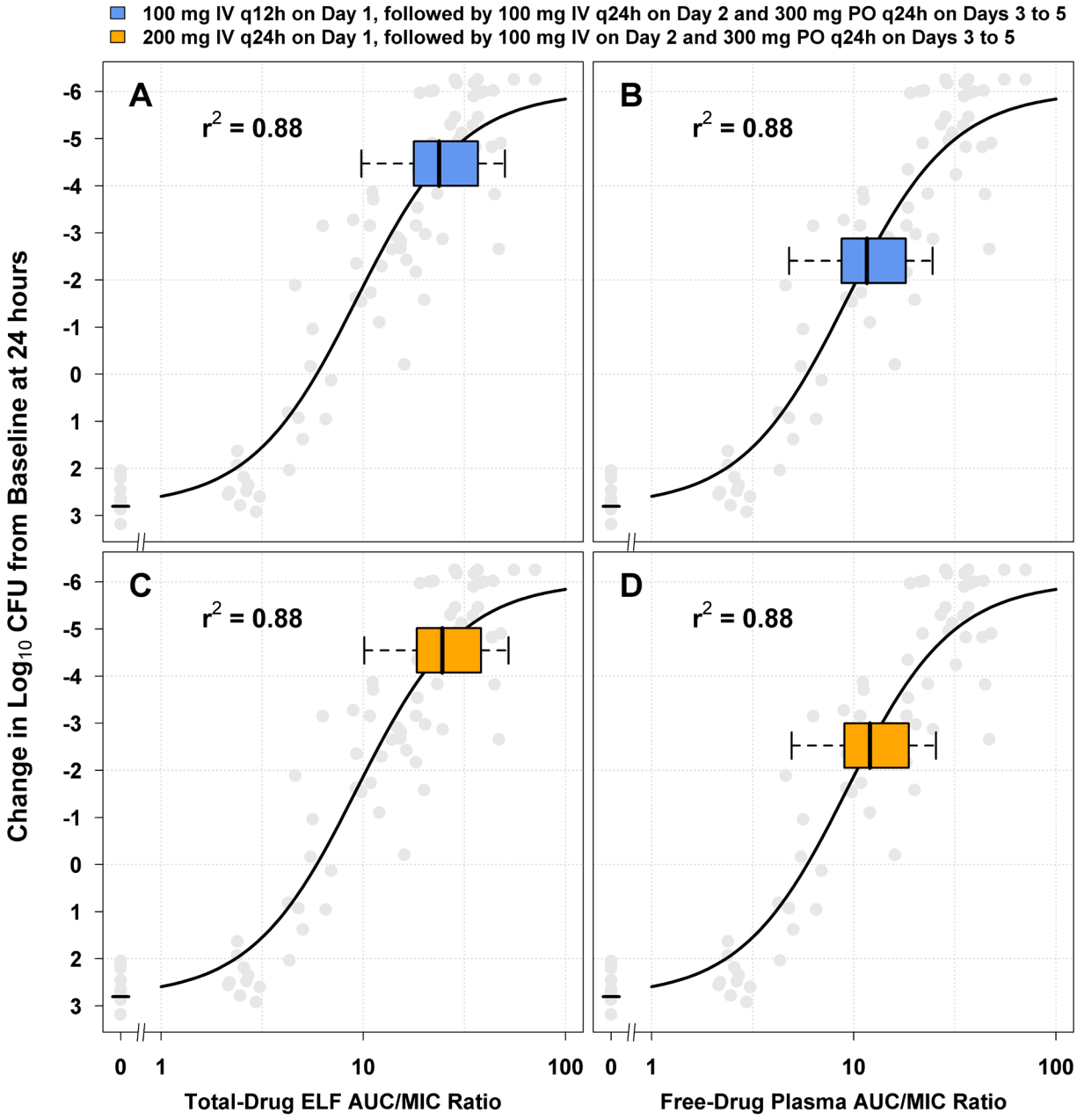
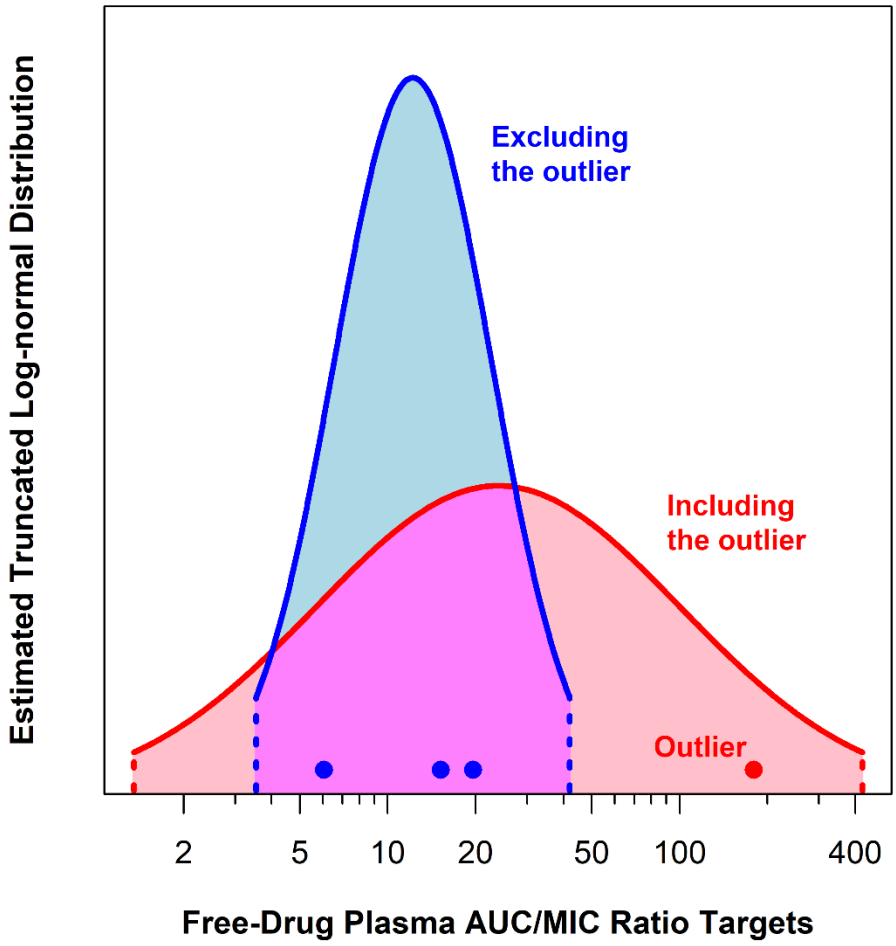


Figure S4. Non-clinical PK-PD relationship for efficacy for *H. influenzae*, overlaid with box-and-whisker plots of total-drug ELF and free-drug plasma AUC/MIC ratios on days 1 to 2 for simulated patients after administration of omadacycline 100 mg i.v. q12h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (A and B, respectively) and 200 mg i.v. q24h on day 1 followed by 100 mg i.v. q24h on day 2 and 300 mg p.o. q24h on days 3 to 5 (C and D, respectively). Horizontal box-and-whisker plots of total-drug ELF and free-drug plasma AUC/MIC ratios on days 1 and 2 for simulated patients after administration of omadacycline IV-to-PO dosing regimens are shown overlaid on the PK-PD relationship based on data from a one-compartment *in vitro* infection model for *H. influenzae*.



For each boxplot, the edge of the box represents the 25th to the 75th percentiles of the distribution for total-drug ELF or free-drug plasma AUC/MIC ratio. The line within the box represents with median total-drug ELF or free-drug plasma AUC/MIC ratio. The whiskers extend to the nearest value among those represented by 1.5 × IQR of the box edges.

Figure S5. Truncated log-normal distributions estimated using individual free-drug plasma AUC/MIC ratio targets for *S. pneumoniae* obtained from the neutropenic murine lung infection model associated with a 1-$\log_{10}$ CFU reduction from baseline, including and excluding the outlying highest individual plasma AUC/MIC ratio target



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