

# A BAYESIAN NON-LINEAR MIXED EFFECTS REGRESSION MODEL FOR THE CHARACTERISATION OF EARLY BACTERICIDAL ACTIVITY OF TUBERCULOSIS DRUGS

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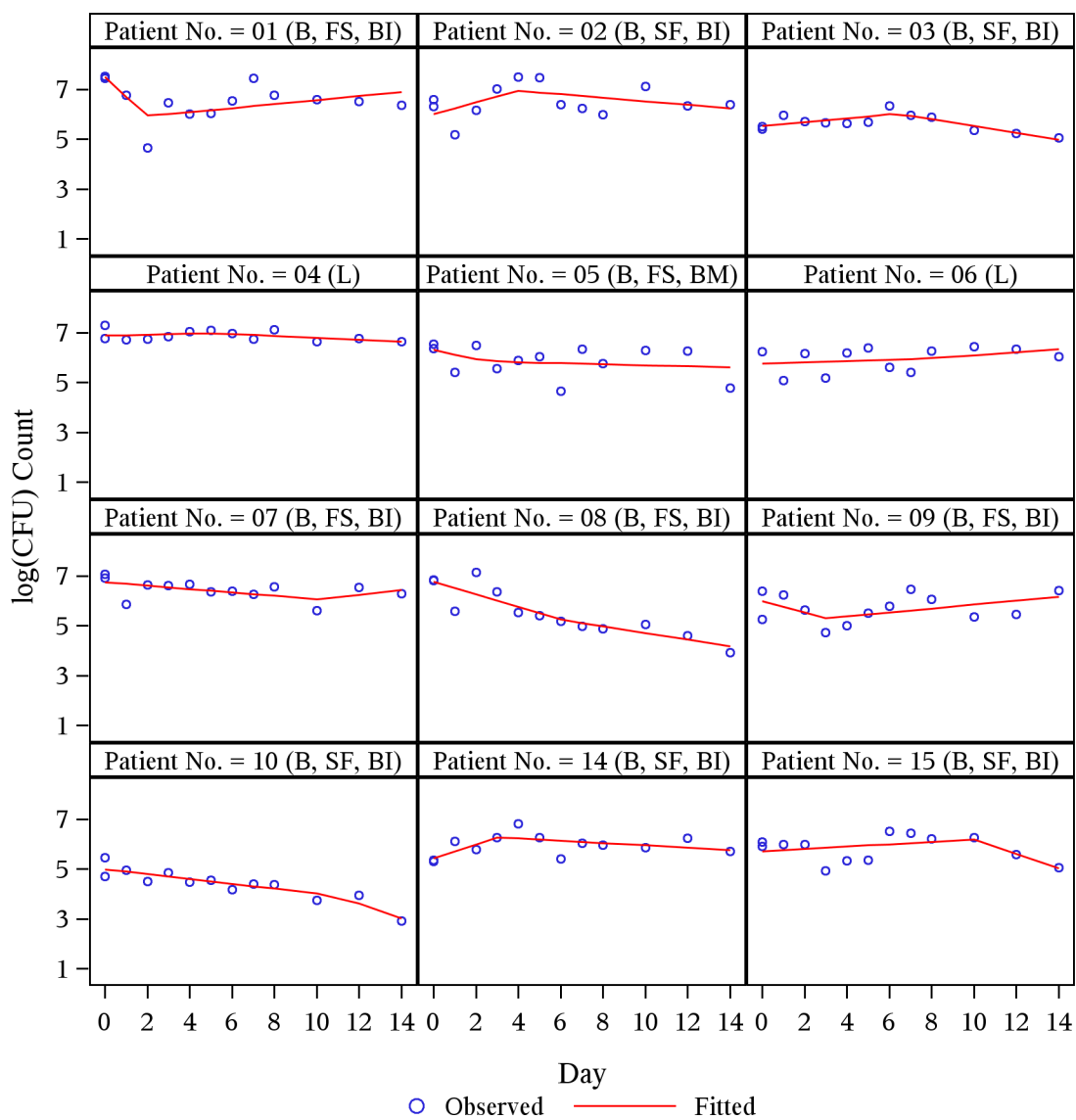
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SUPPLEMENTARY MATERIAL

## A EMPIRICAL STUDY

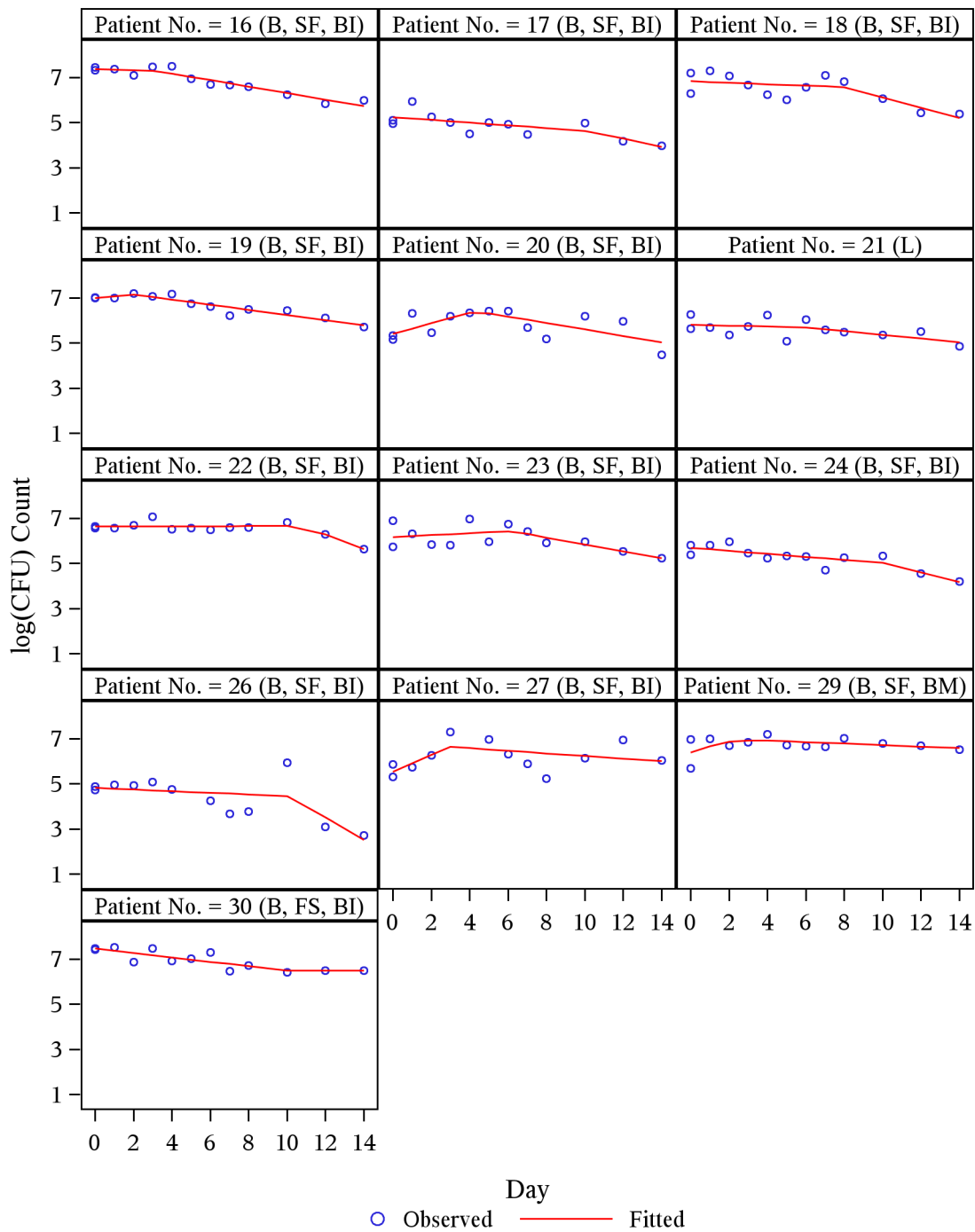
**Figure A.1:** Observed and Fitted log(CFU) Count

Trial **CL001**, Treatment **TMC207 100 mg**



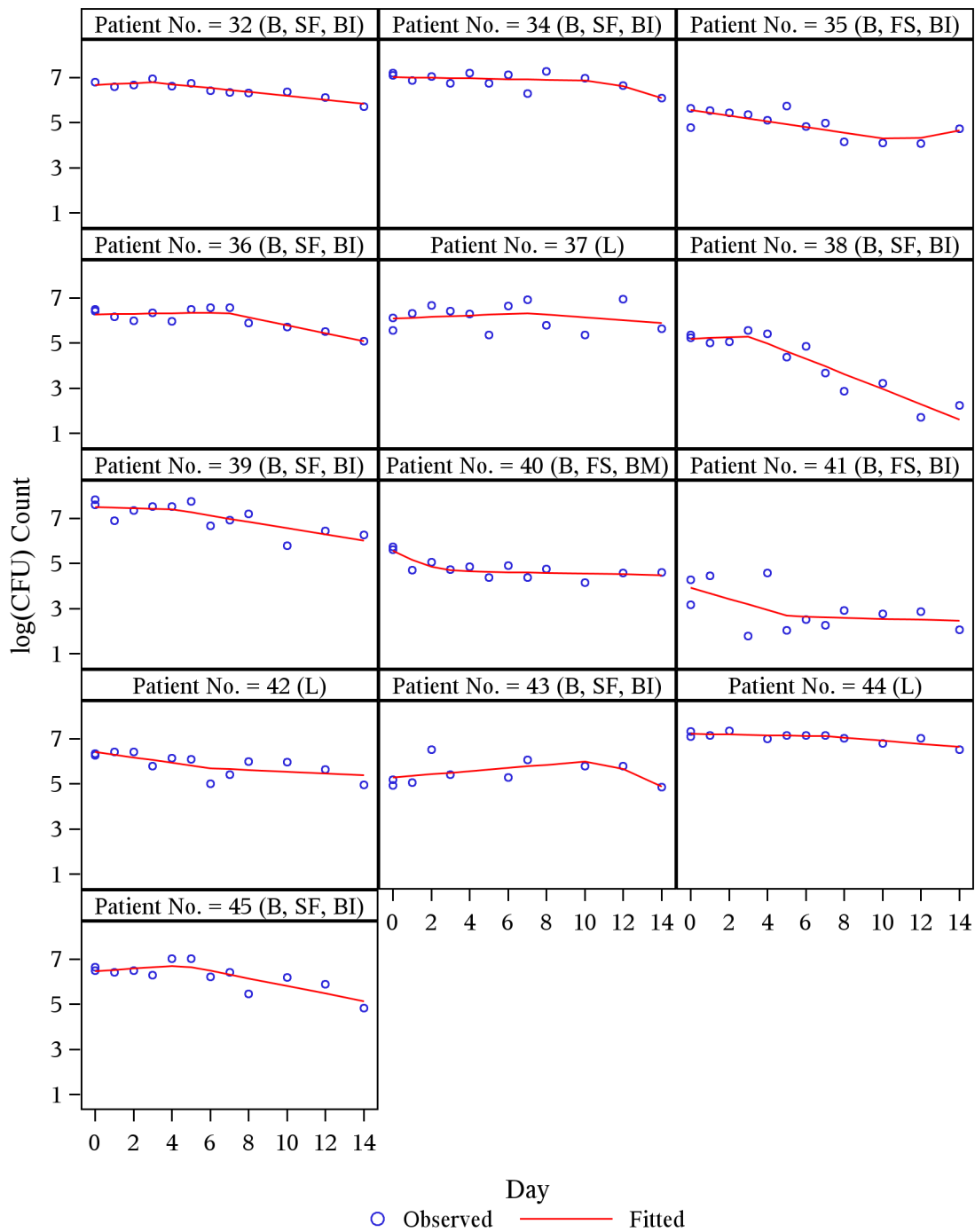
**Figure A.2:** Observed and Fitted log(CFU) Count

Trial **CL001**, Treatment **TMC207 200 mg**



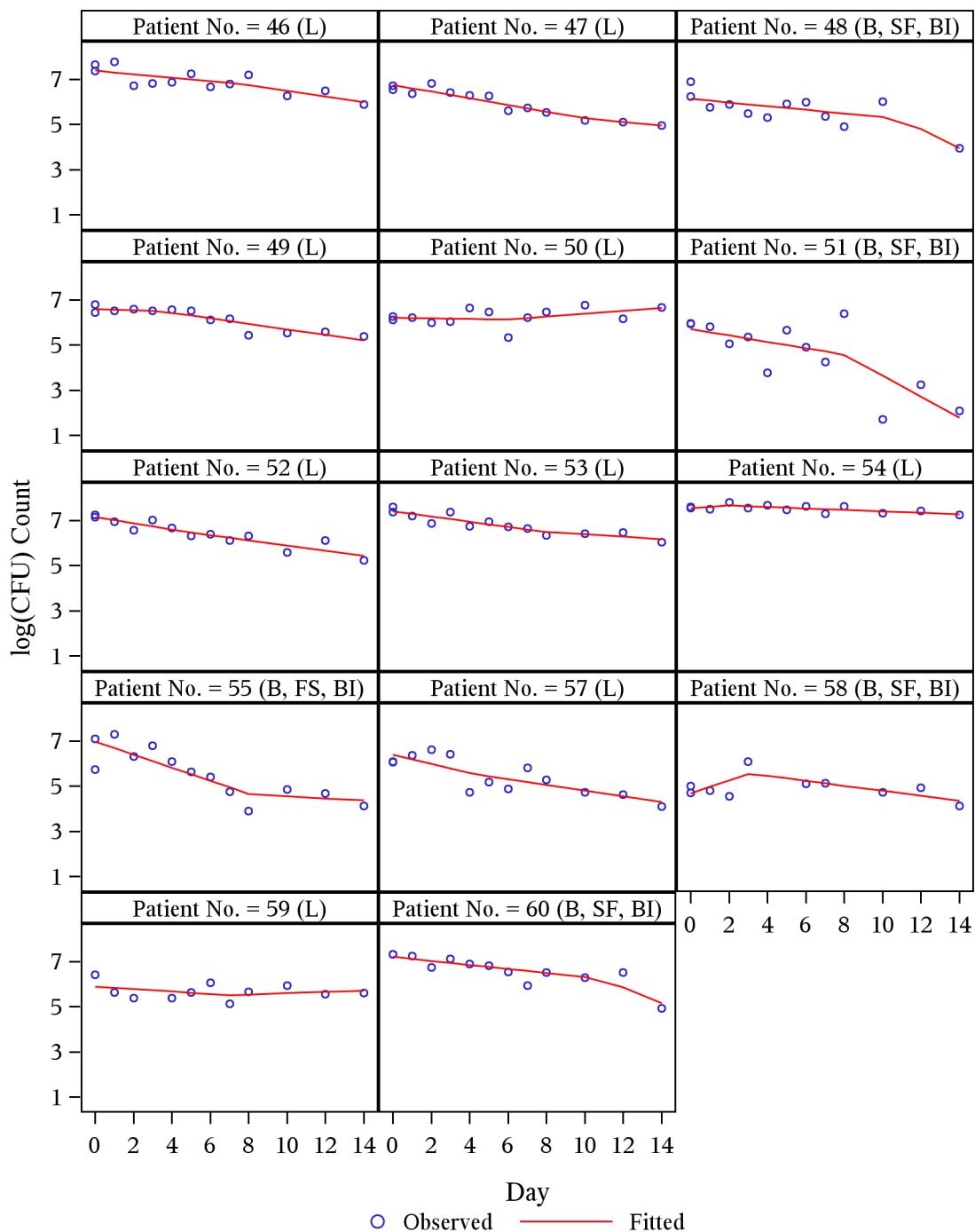
**Figure A.3:** Observed and Fitted log(CFU) Count

Trial **CL001**, Treatment **TMC207 300 mg**

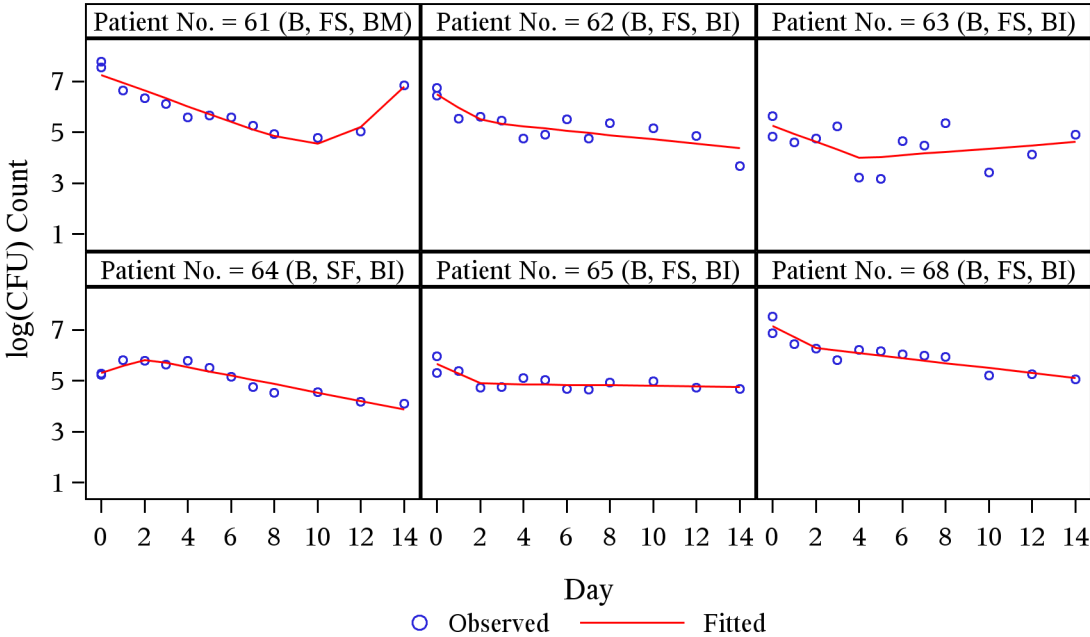


**Figure A.4:** Observed and Fitted log(CFU) Count

Trial **CL001**, Treatment **TMC207 400 mg**

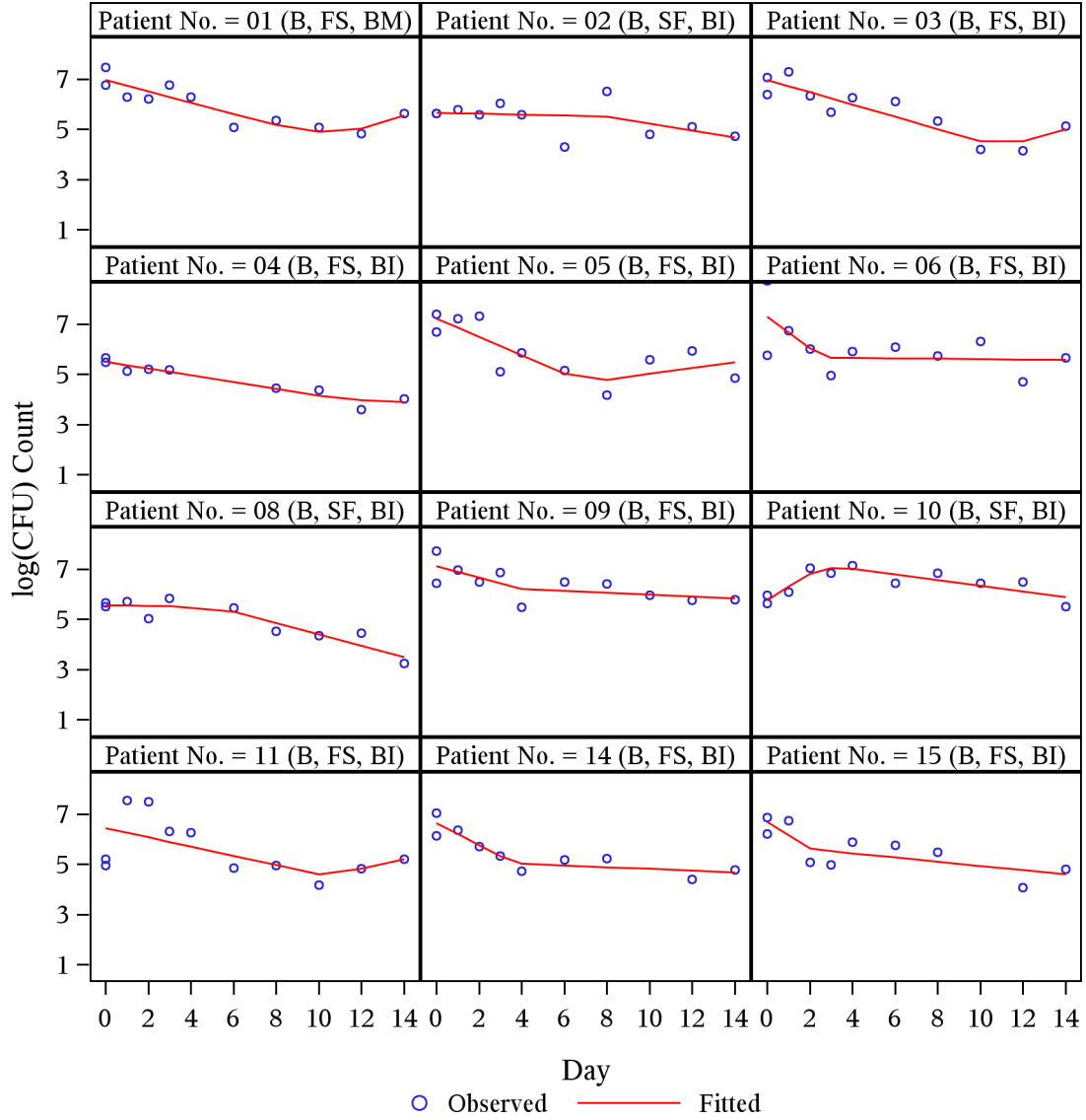


**Figure A.5:** Observed and Fitted  $\log(\text{CFU})$  Count  
 Trial **CL001**, Treatment **Rifafour**



**Figure A.6:** Observed and Fitted log(CFU) Count

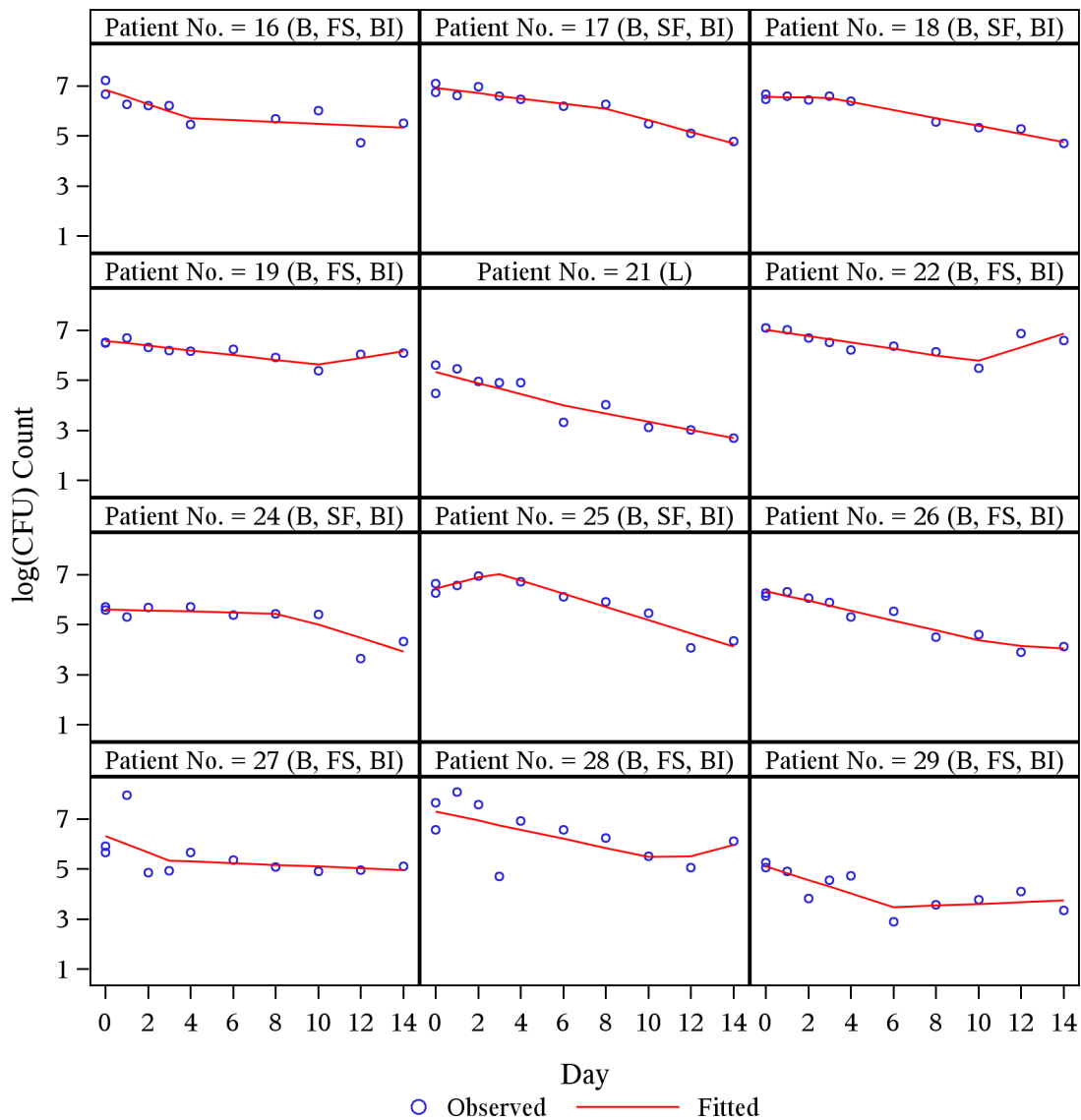
Trial **CL007**, Treatment **PA-824 200 mg**





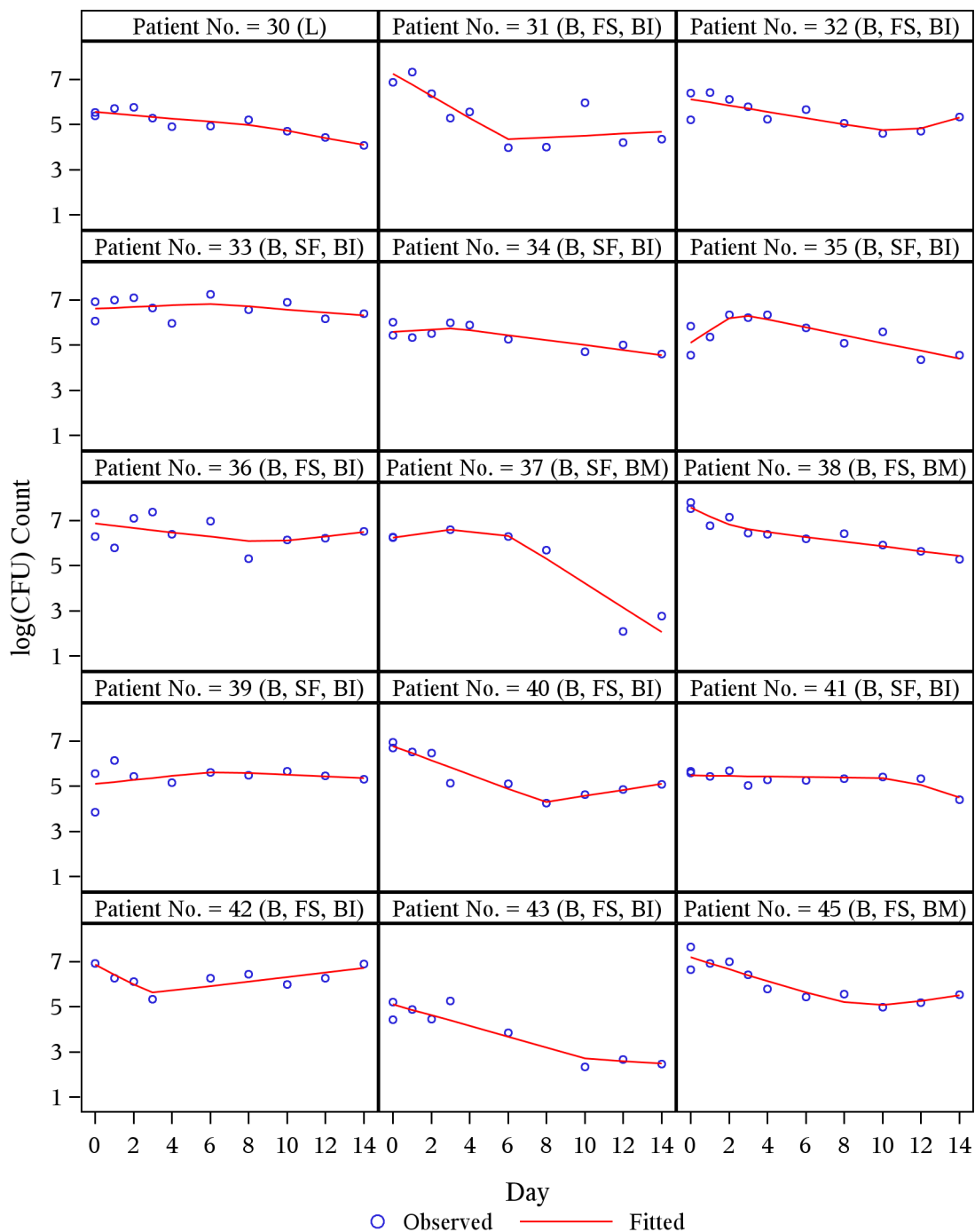
**Figure A.7:** Observed and Fitted log(CFU) Count

Trial **CL007**, Treatment **PA-824 600 mg**



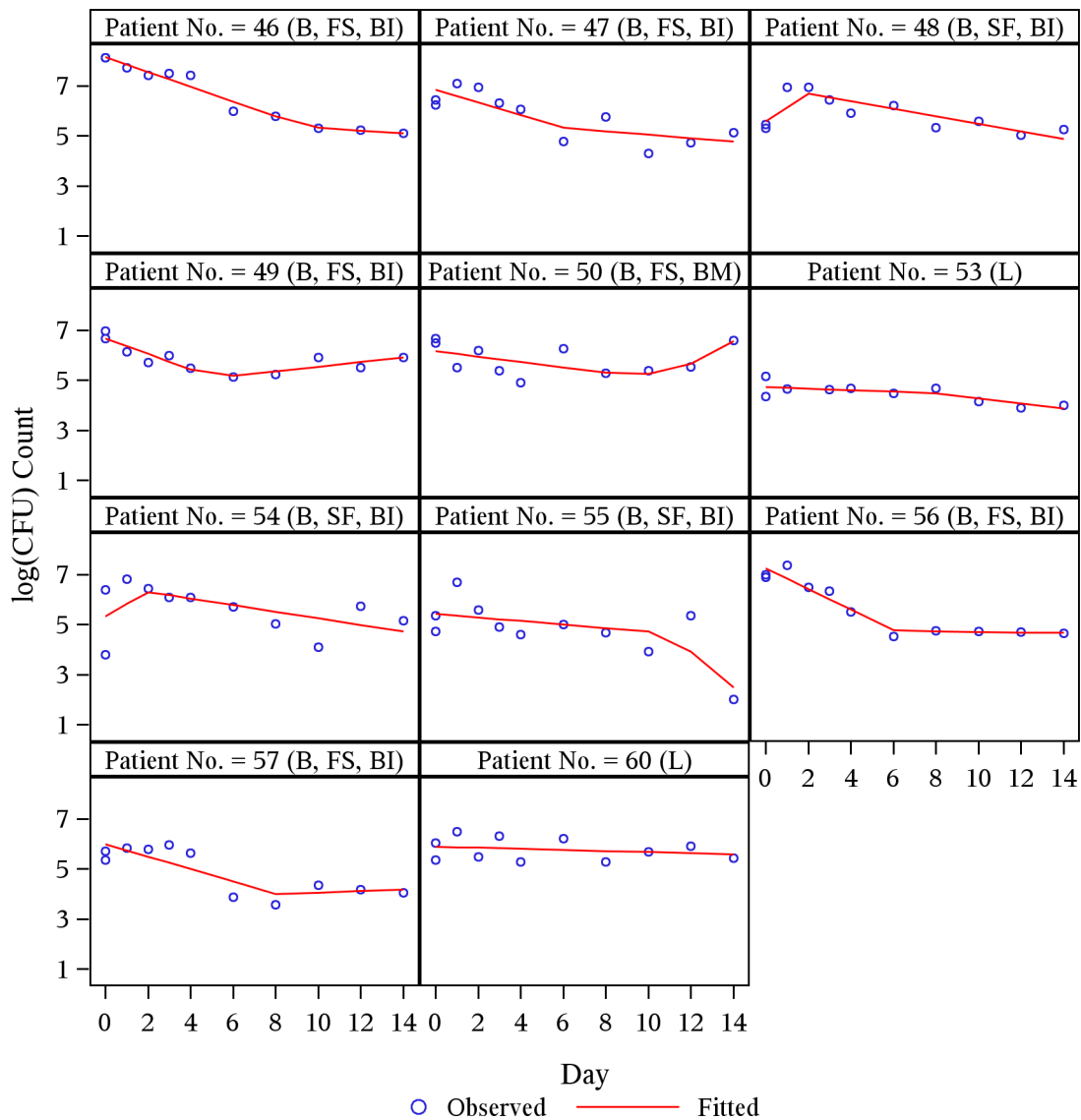
**Figure A.8:** Observed and Fitted log(CFU) Count

Trial **CL007**, Treatment **PA-824 1000 mg**



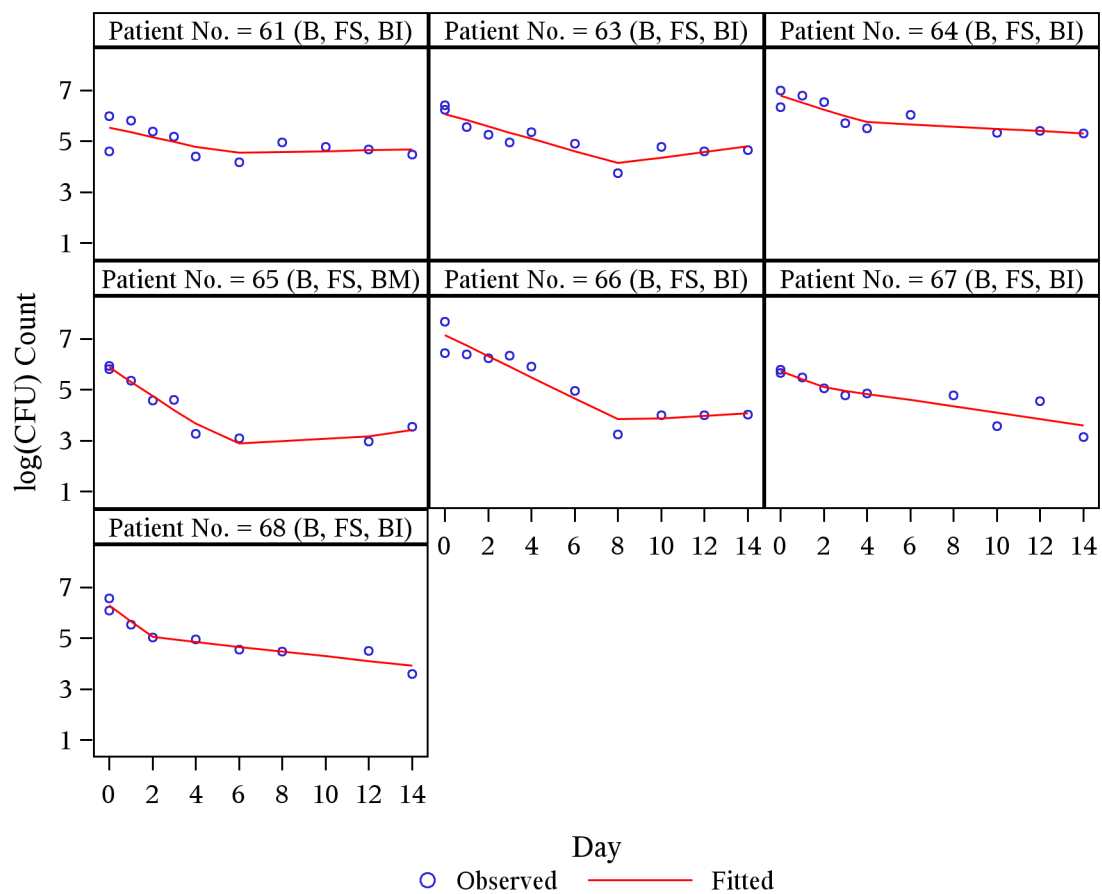
**Figure A.9:** Observed and Fitted log(CFU) Count

Trial **CL007**, Treatment **PA-824 1200 mg**



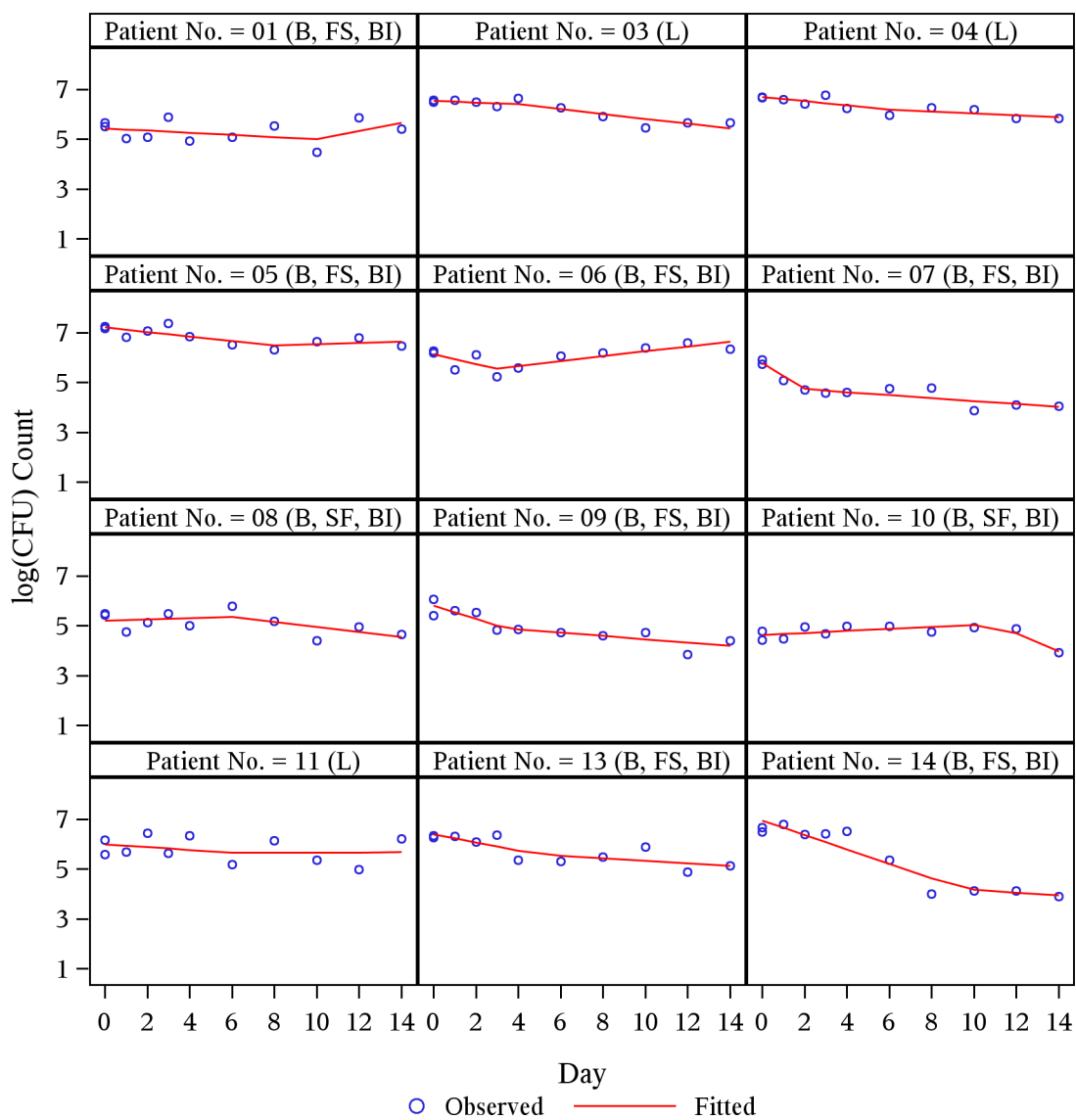
**Figure A.10:** Observed and Fitted  $\log(\text{CFU})$  Count

Trial **CL007**, Treatment **Rifafour**



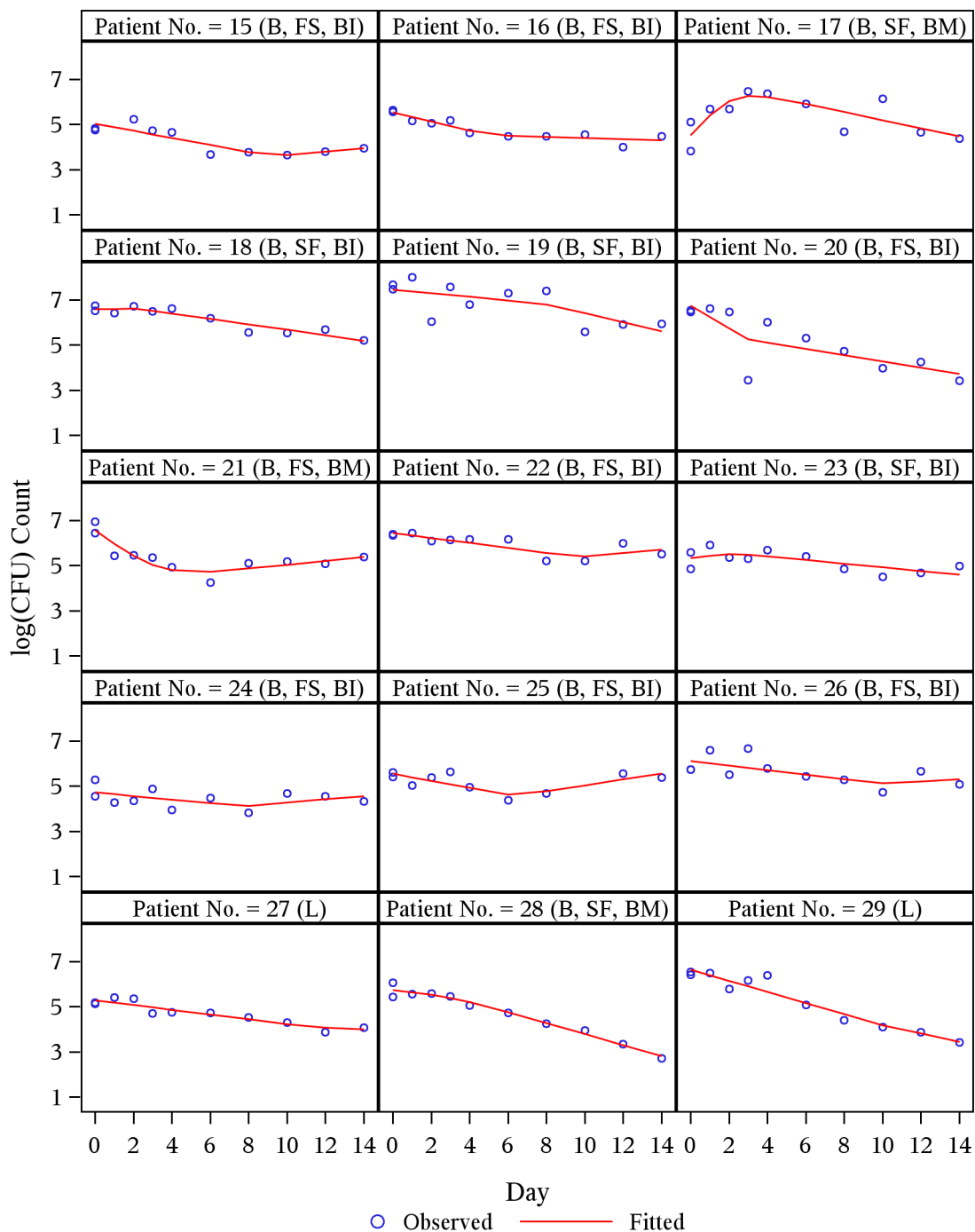
**Figure A.11:** Observed and Fitted log(CFU) Count

Trial **CL010**, Treatment **PA-824 50 mg**



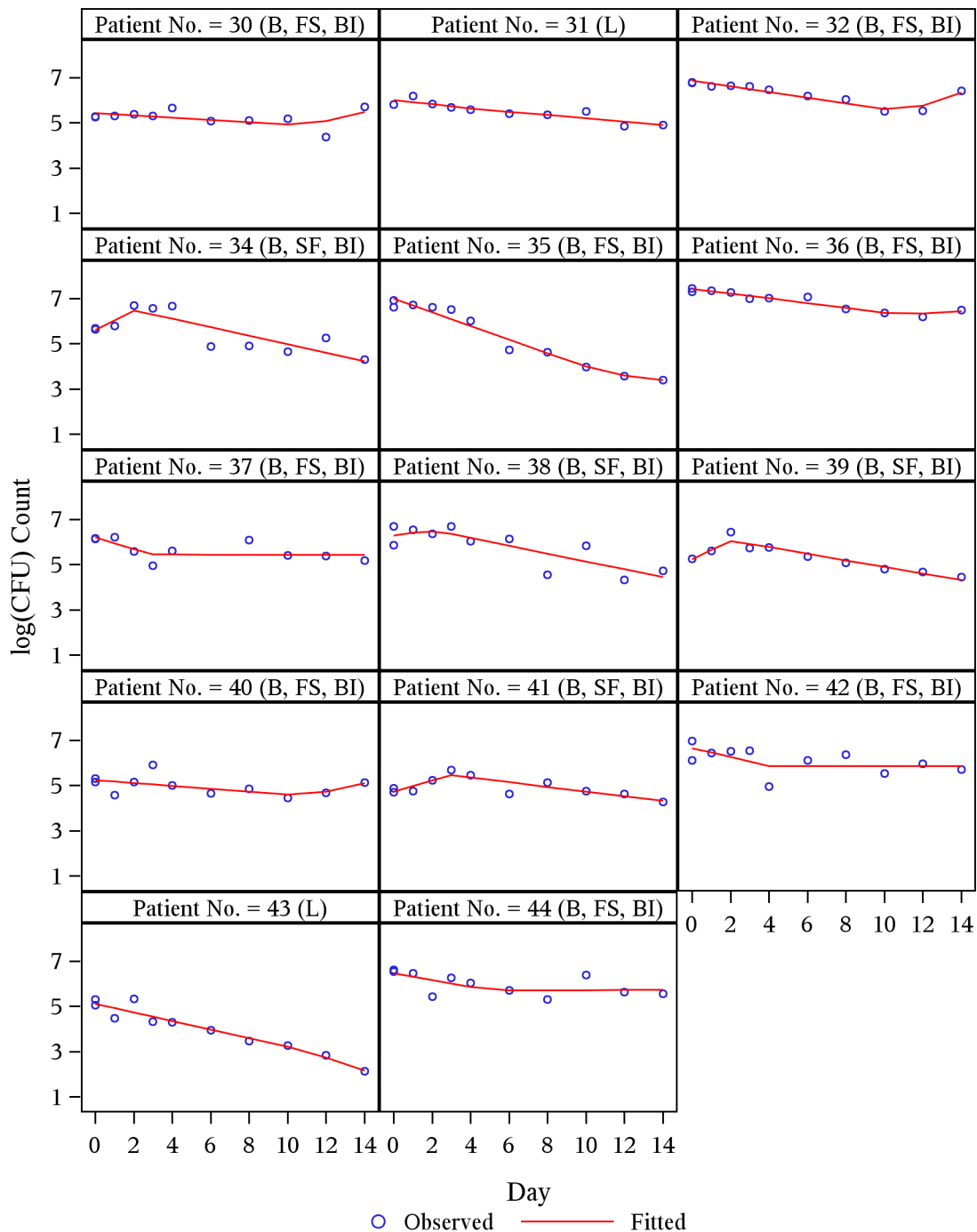
**Figure A.12:** Observed and Fitted log(CFU) Count

Trial CL010, Treatment PA-824 100 mg



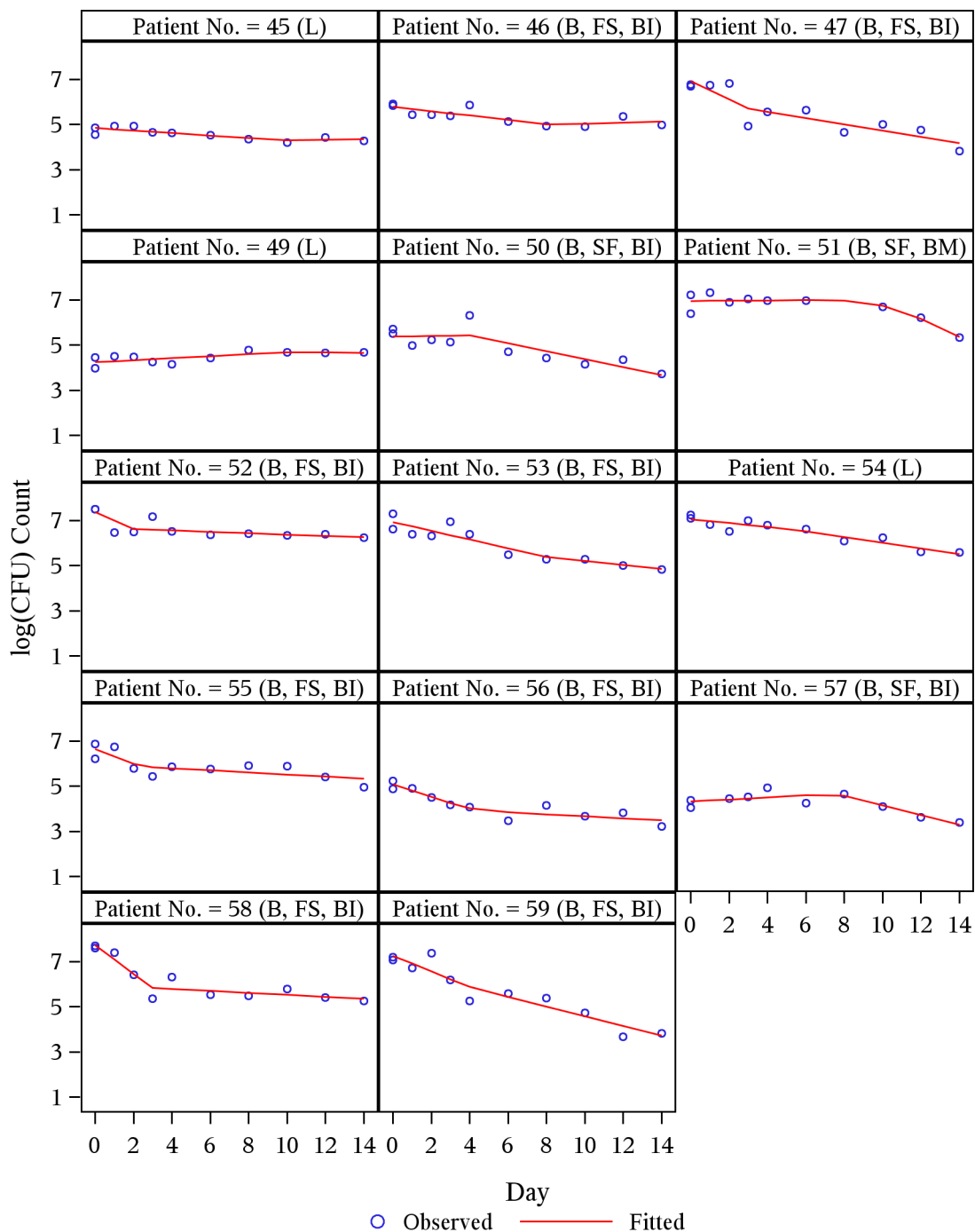
**Figure A.13:** Observed and Fitted log(CFU) Count

Trial CL010, Treatment PA-824 150 mg



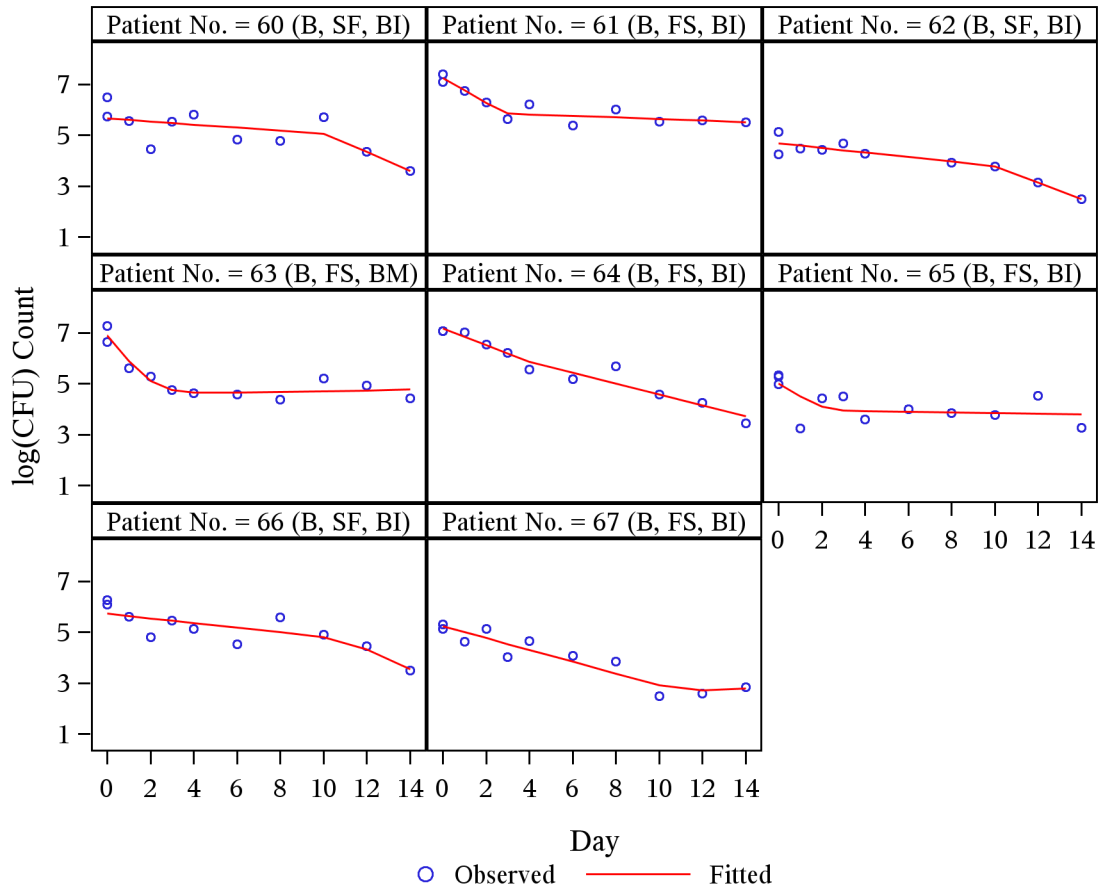
**Figure A.14:** Observed and Fitted log(CFU) Count

Trial CL010, Treatment PA-824 200 mg



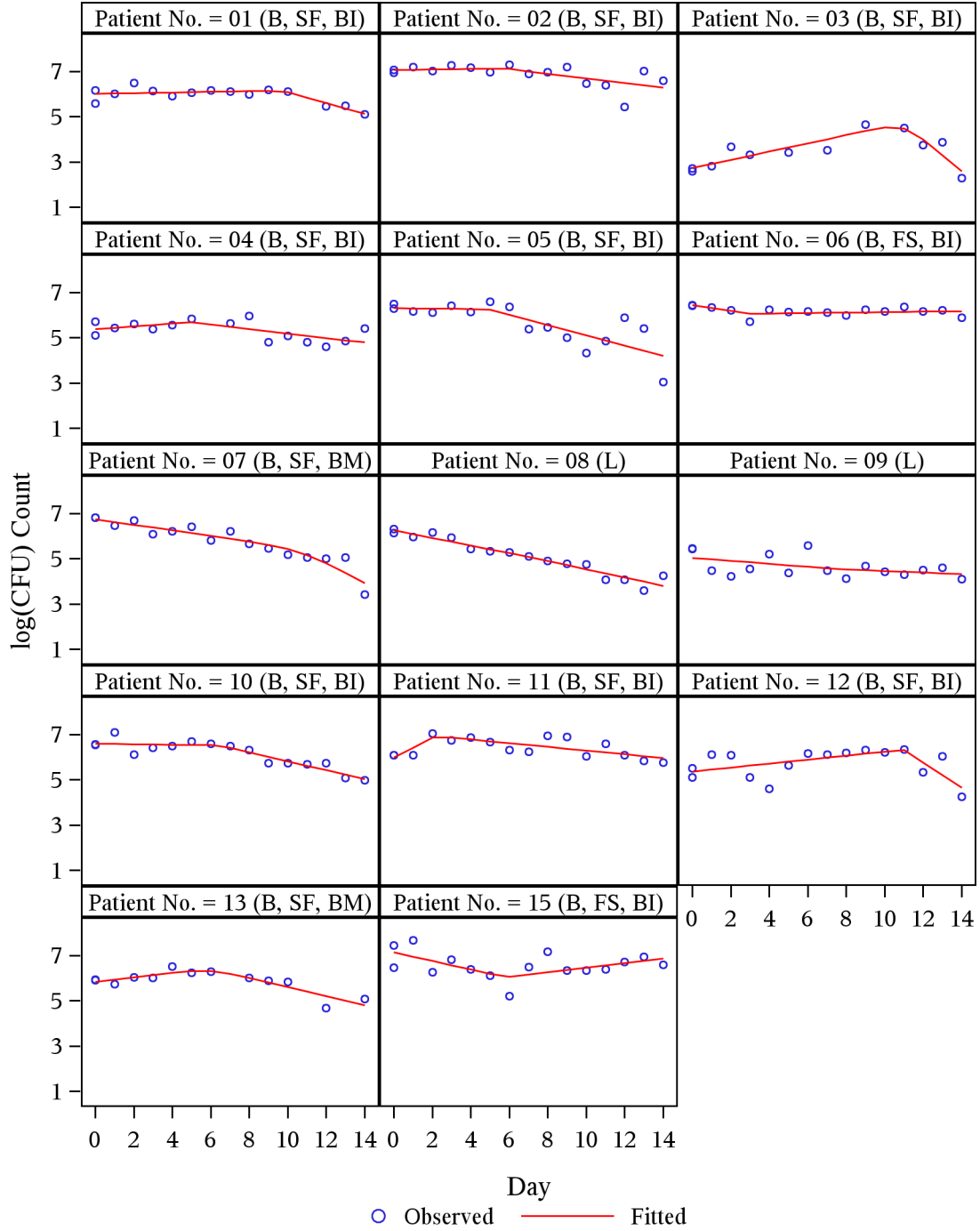


**Figure A.15:** Observed and Fitted  $\log(\text{CFU})$  Count  
 Trial **CL010**, Treatment **Rifafour**



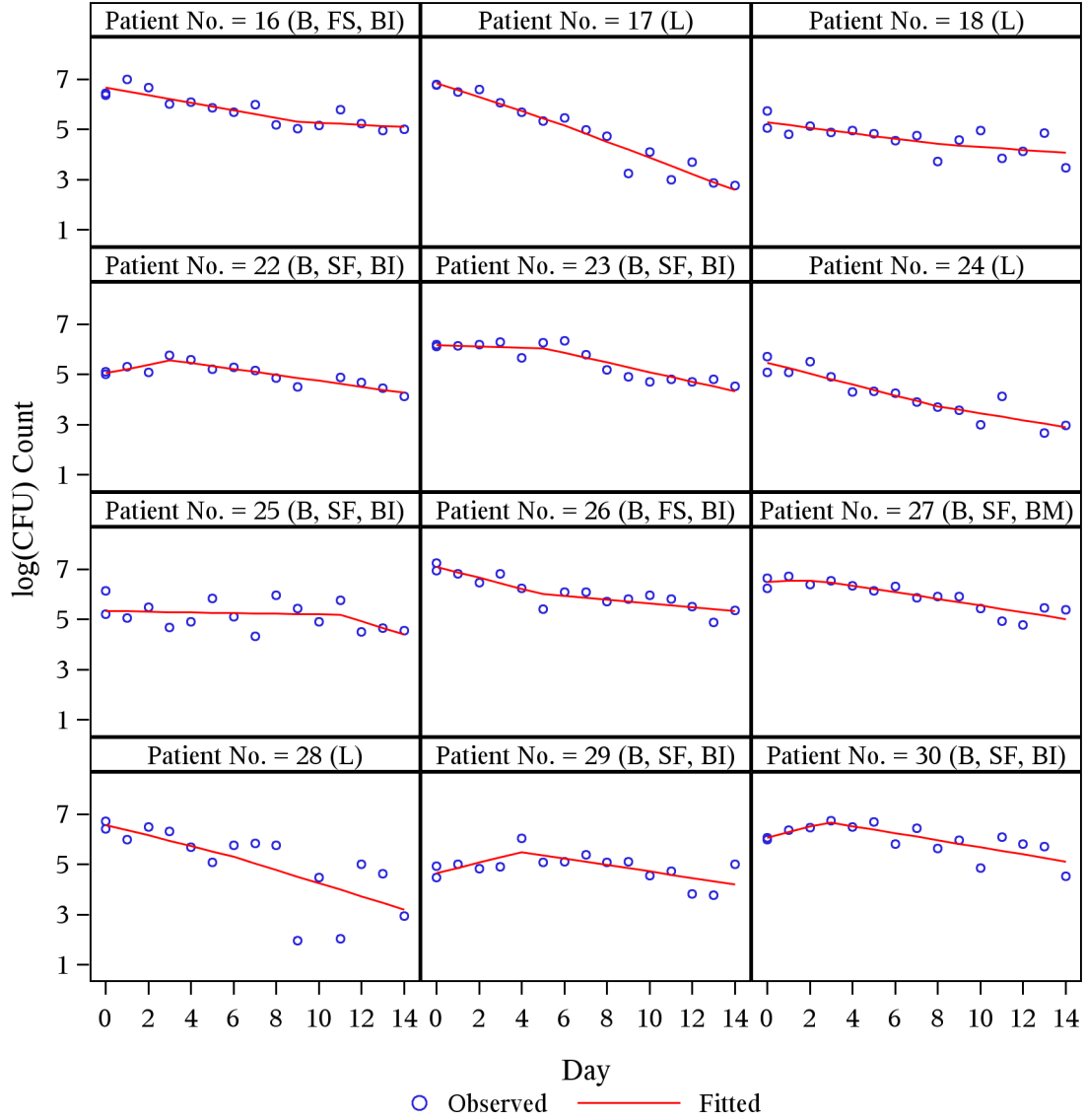
**Figure A.16:** Observed and Fitted log(CFU) Count

Trial NC001, Treatment J



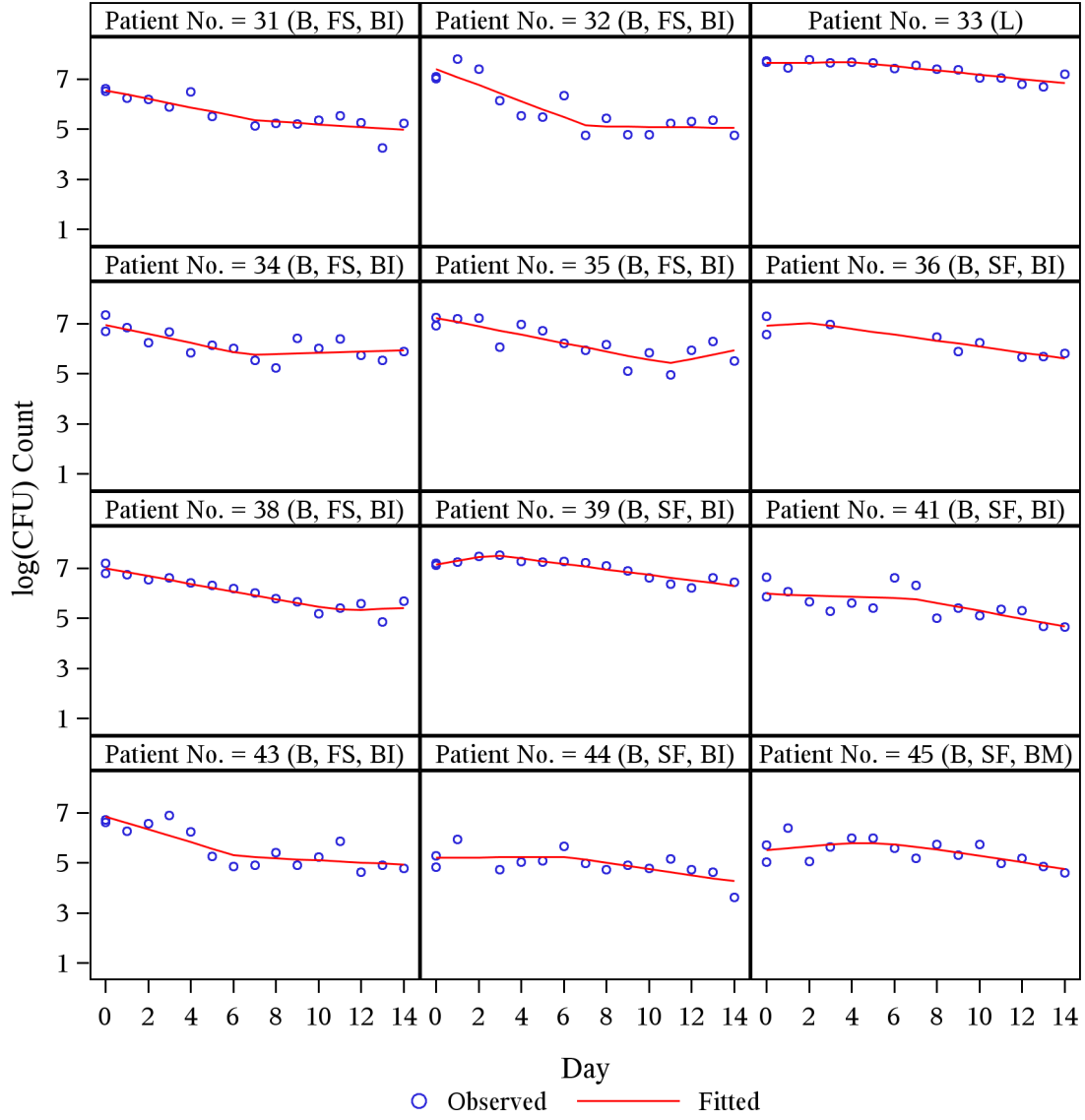
**Figure A.17:** Observed and Fitted  $\log(\text{CFU})$  Count

Trial NC001, Treatment J-Z



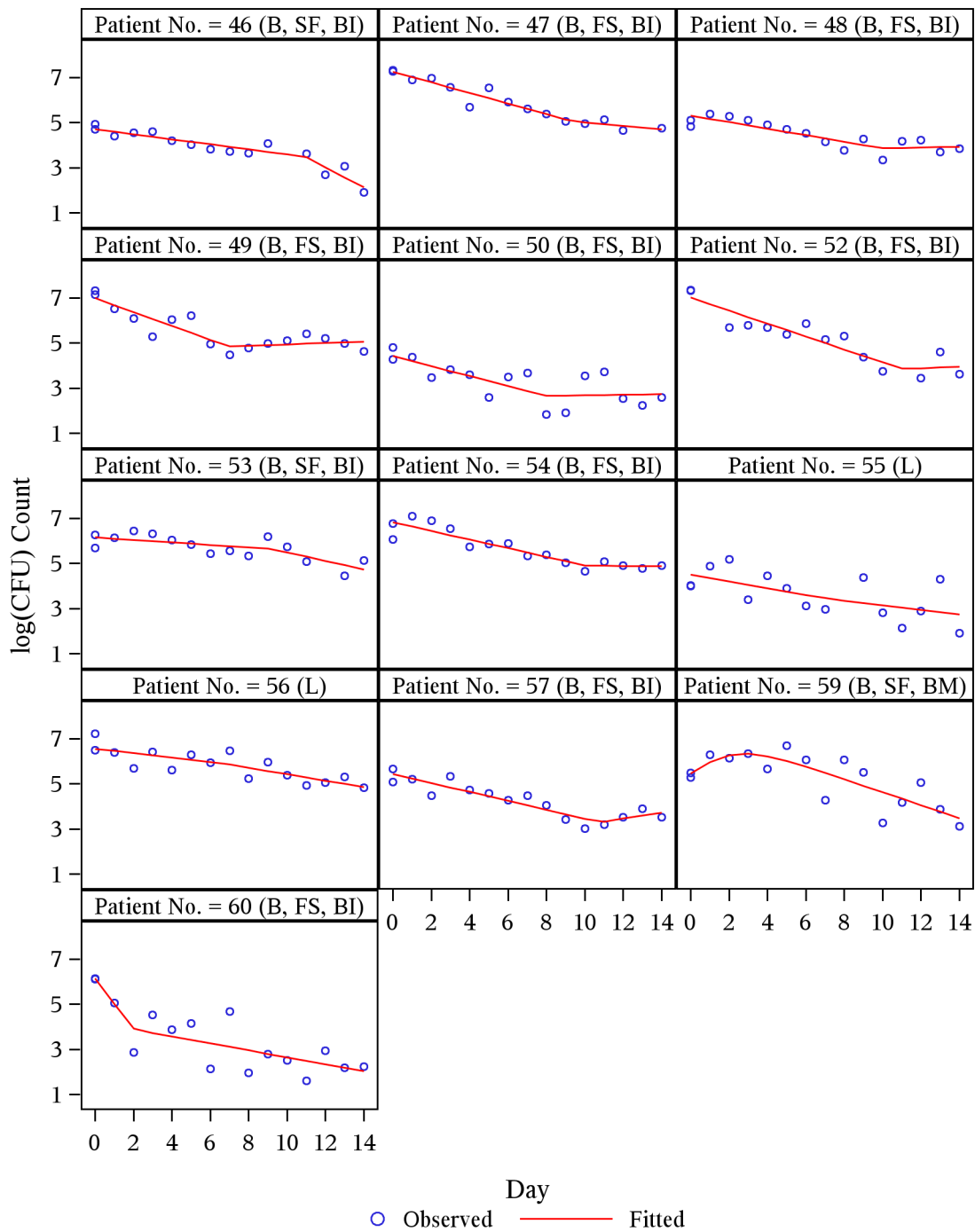
**Figure A.18:** Observed and Fitted log(CFU) Count

Trial NC001, Treatment J-Pa



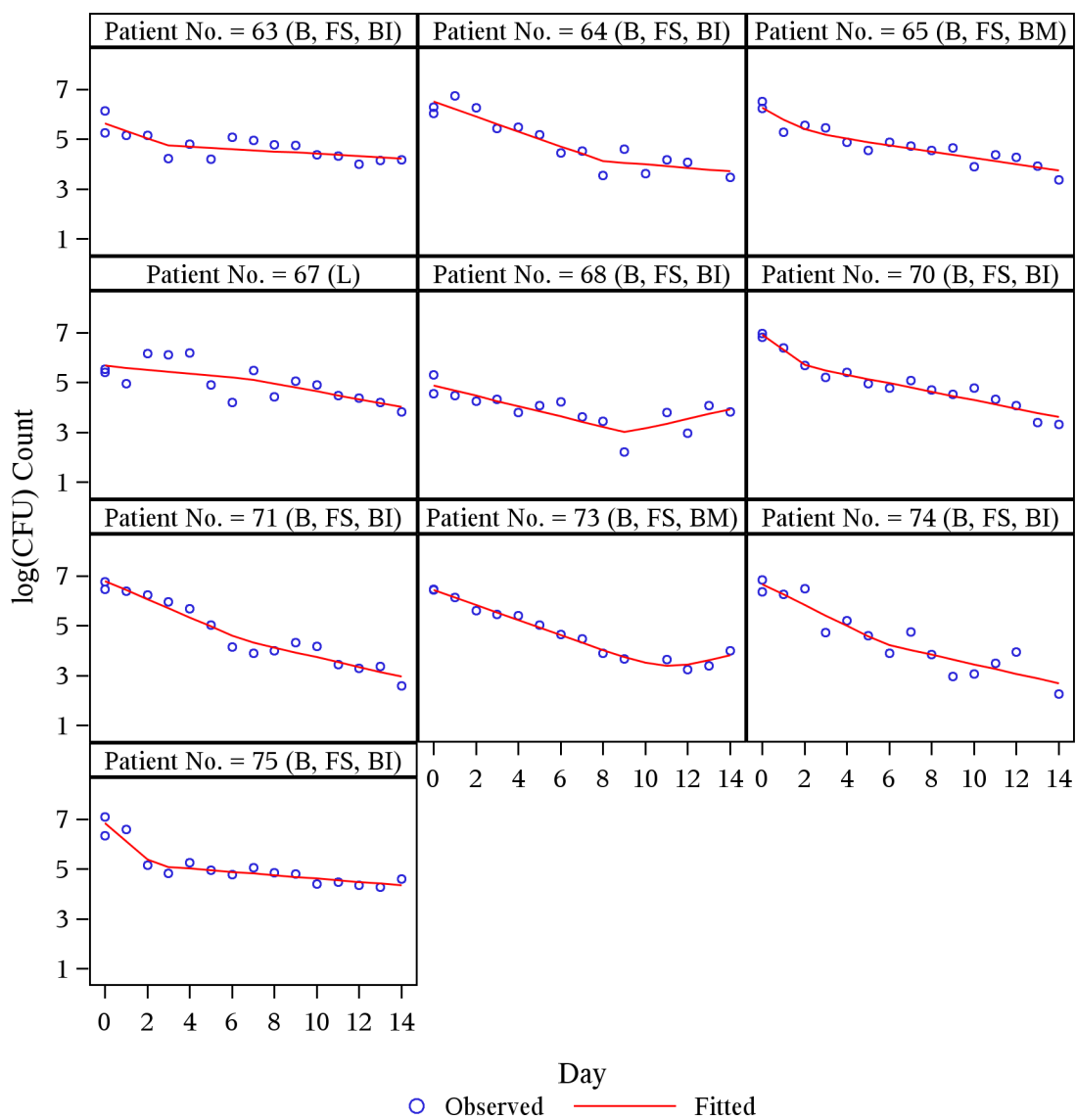
**Figure A.19:** Observed and Fitted log(CFU) Count

Trial NC001, Treatment **Pa-Z**



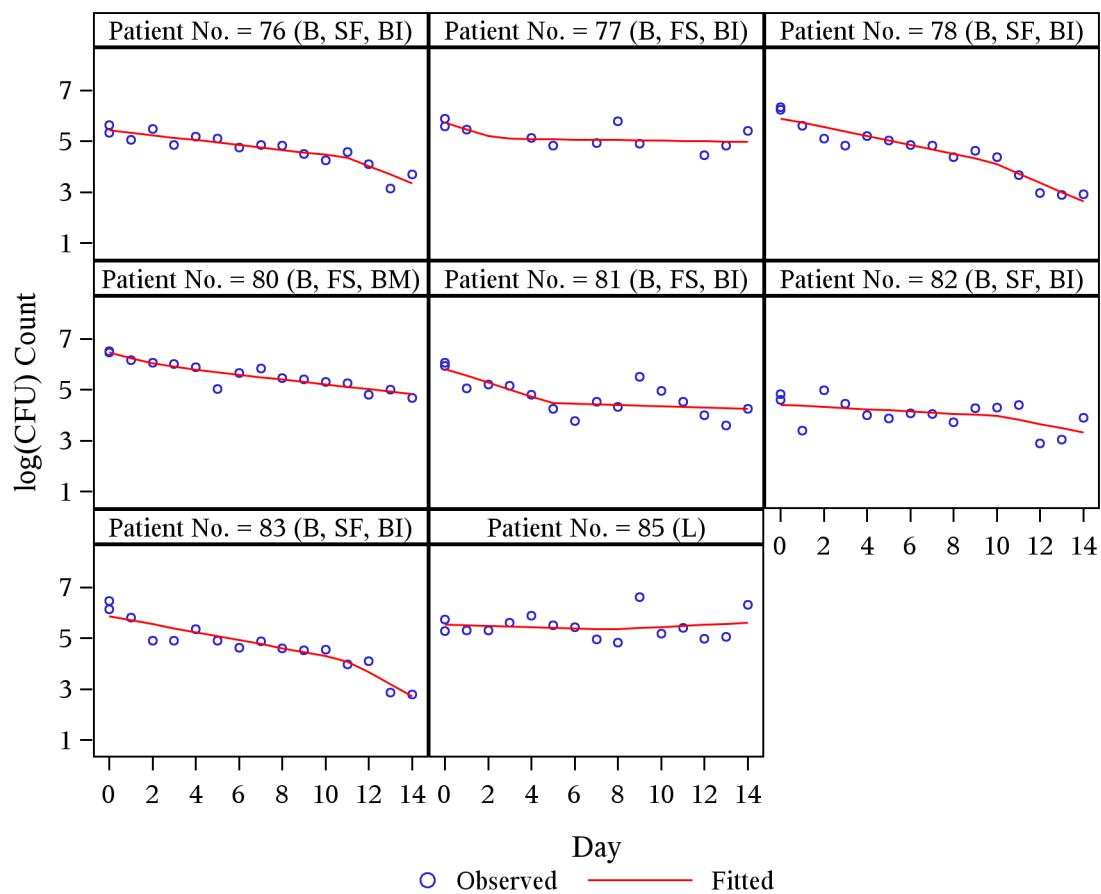
**Figure A.20:** Observed and Fitted log(CFU) Count

Trial NC001, Treatment Pa-Z-M



**Figure A.21:** Observed and Fitted  $\log(\text{CFU})$  Count

Trial **NC001**, Treatment **Rifafour**



## B EXAMPLE OF APPLICATION: ADDITIONAL RESULTS

**Table B.1:** Model 1 – Inferential Statistics for Regression Model Parameters

Parameter	Treatment	n	Mean	
			Estimate	95% BCI
$\alpha$	J (N=15)	15	5.965	[5.362; 6.578]
	J-Z (N=15)	15	5.912	[5.416; 6.392]
	J-Pa (N=15)	15	6.535	[5.909; 7.152]
	Pa-Z (N=15)	15	5.934	[5.380; 6.498]
	Pa-Z-M (N=15)	15	5.844	[5.131; 6.560]
	Rifafour (N=10)	10	5.507	[4.923; 6.094]
$\beta_1$	J (N=15)	15	0.081	[0.029; 0.132]
	J-Z (N=15)	15	0.116	[0.057; 0.174]
	J-Pa (N=15)	15	0.100	[0.059; 0.141]
	Pa-Z (N=15)	15	0.149	[0.101; 0.199]
	Pa-Z-M (N=15)	15	0.262	[0.136; 0.392]
	Rifafour (N=10)	10	0.150	[0.072; 0.230]
$\lambda_1$	J (N=15)	15	-0.002	[-0.088; 0.084]
	J-Z (N=15)	15	0.066	[-0.047; 0.172]
	J-Pa (N=15)	15	0.105	[0.018; 0.187]
	Pa-Z (N=15)	15	0.179	[0.079; 0.278]
	Pa-Z-M (N=15)	15	0.316	[0.159; 0.470]
	Rifafour (N=10)	10	0.155	[0.019; 0.299]

*Note:* Treatment Group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M = PA-824 + Pyrazinamide + Moxifloxacin, Rifafour = Rifafour e-275<sup>®</sup>. EBA( $t_1 - t_2$ ): Early bactericidal activity over Day  $t_1$  to Day  $t_2$ ; BCI: Bayesian credibility interval. n = Number of patients in each category.



**Table B.1:** Model 1 – Inferential Statistics for Regression Model Parameters

Parameter	Treatment	n	Mean	
			Estimate	95% BCI
$\beta_2$	J (N=15)	15	0.083	[0.002; 0.167]
	J-Z (N=15)	15	0.051	[-0.038; 0.140]
	J-Pa (N=15)	15	-0.005	[-0.080; 0.073]
	Pa-Z (N=15)	15	-0.030	[-0.118; 0.059]
	Pa-Z-M (N=15)	15	-0.053	[-0.223; 0.136]
	Rifafour (N=10)	10	-0.004	[-0.128; 0.118]
$\beta_{2f}$	J (N=15)	15	0.083	[-0.213; 0.384]
	J-Z (N=15)	15	0.050	[-0.290; 0.387]
	J-Pa (N=15)	15	-0.004	[-0.268; 0.267]
	Pa-Z (N=15)	15	-0.030	[-0.345; 0.285]
	Pa-Z-M (N=15)	15	-0.054	[-0.651; 0.563]
	Rifafour (N=10)	10	-0.003	[-0.381; 0.388]
$\lambda_2$	J (N=15)	15	0.164	[0.064; 0.275]
	J-Z (N=15)	15	0.167	[0.064; 0.271]
	J-Pa (N=15)	15	0.095	[0.008; 0.184]
	Pa-Z (N=15)	15	0.119	[0.014; 0.219]
	Pa-Z-M (N=15)	15	0.209	[-0.051; 0.492]
	Rifafour (N=10)	10	0.146	[-0.006; 0.299]

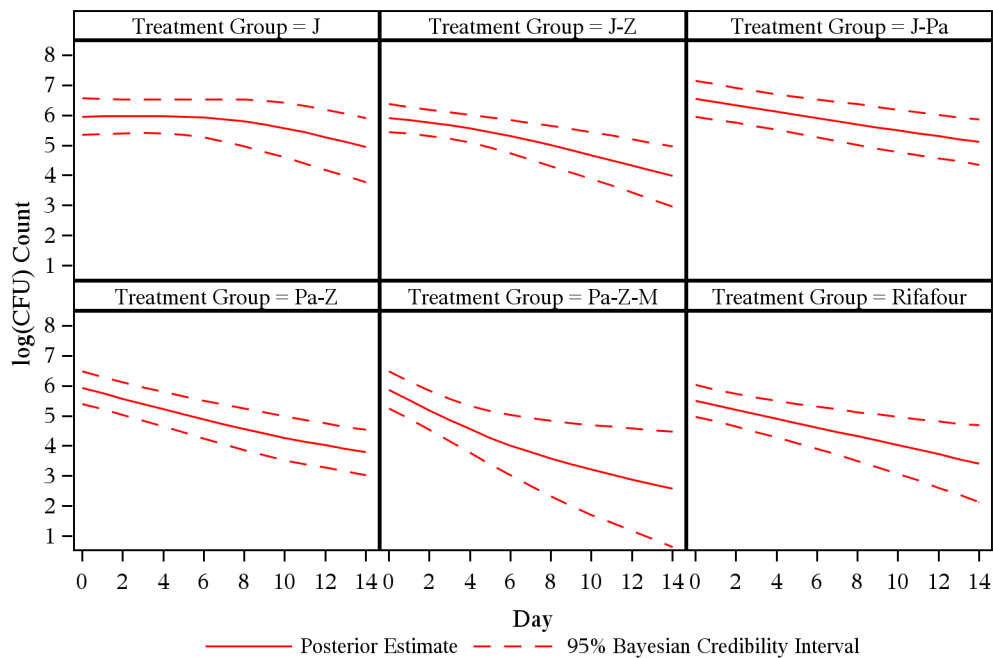
*Note:* Treatment Group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M = PA-824 + Pyrazinamide + Moxifloxacin, Rifafour = Rifafour e-275<sup>®</sup>. EBA( $t_1 - t_2$ ): Early bactericidal activity over Day  $t_1$  to Day  $t_2$ ; BCI: Bayesian credibility interval. n = Number of patients in each category.

**Table B.1:** Model 1 – Inferential Statistics for Regression Model Parameters

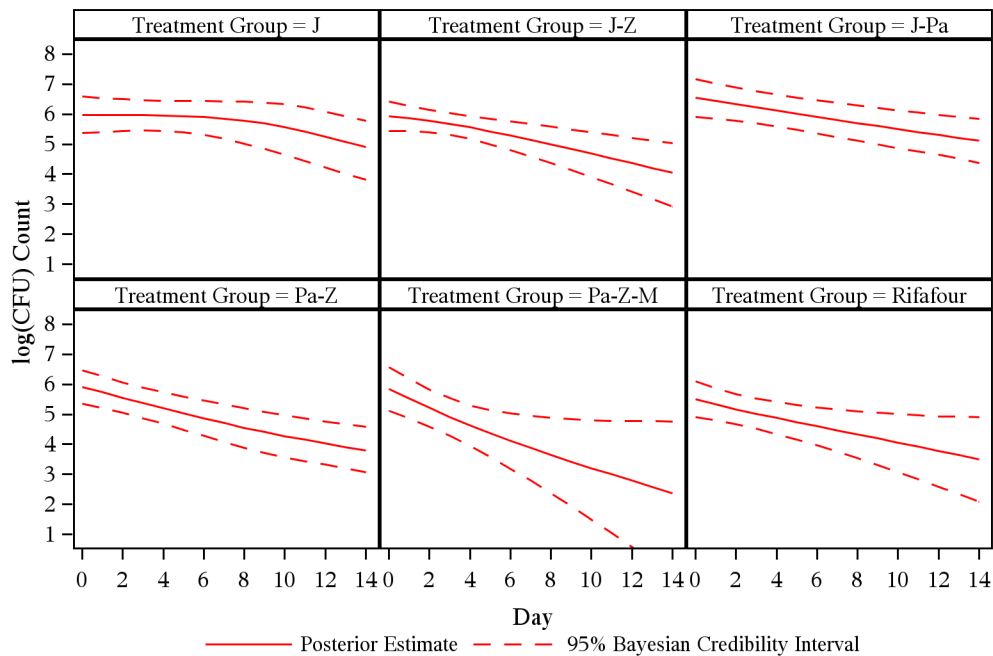
Parameter	Treatment	n	Mean	
			Estimate	95% BCI
$\kappa$	J (N=15)	15	7.568	[2.797; 10.810]
	J-Z (N=15)	15	4.718	[2.088; 10.030]
	J-Pa (N=15)	15	7.448	[2.642; 10.810]
	Pa-Z (N=15)	15	7.799	[2.614; 10.880]
	Pa-Z-M (N=15)	15	4.561	[2.083; 9.941]
	Rifafour (N=10)	10	5.446	[2.116; 10.570]
$\gamma$	J (N=15)	15	1.043	[0.147; 1.953]
	J-Z (N=15)	15	1.096	[0.154; 1.958]
	J-Pa (N=15)	15	1.069	[0.150; 1.955]
	Pa-Z (N=15)	15	1.067	[0.149; 1.954]
	Pa-Z-M (N=15)	15	1.029	[0.143; 1.950]
	Rifafour (N=10)	10	1.069	[0.151; 1.955]

*Note:* Treatment Group: J = TMC207, J-Z = TMC207 + Pyrazinamide, J-Pa = TMC207 + PA-824, Pa-Z = PA-824 + Pyrazinamide, Pa-Z-M = PA-824 + Pyrazinamide + Moxifloxacin, Rifafour = Rifafour e-275<sup>®</sup>. EBA( $t_1 - t_2$ ): Early bactericidal activity over Day  $t_1$  to Day  $t_2$ ; BCI: Bayesian credibility interval. n = Number of patients in each category.

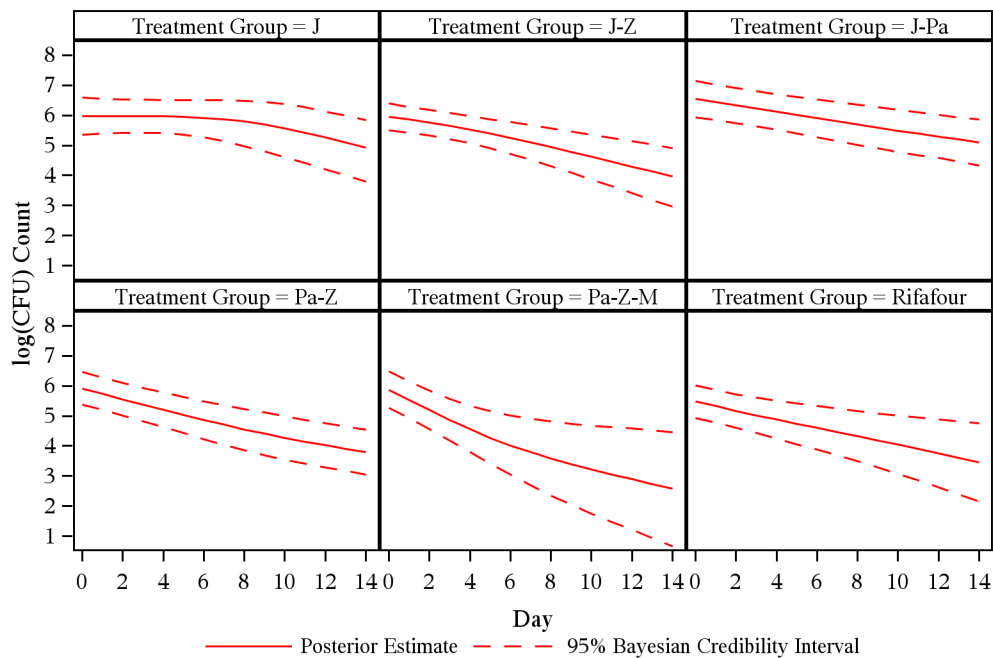
**Figure B.1:** Model 2 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



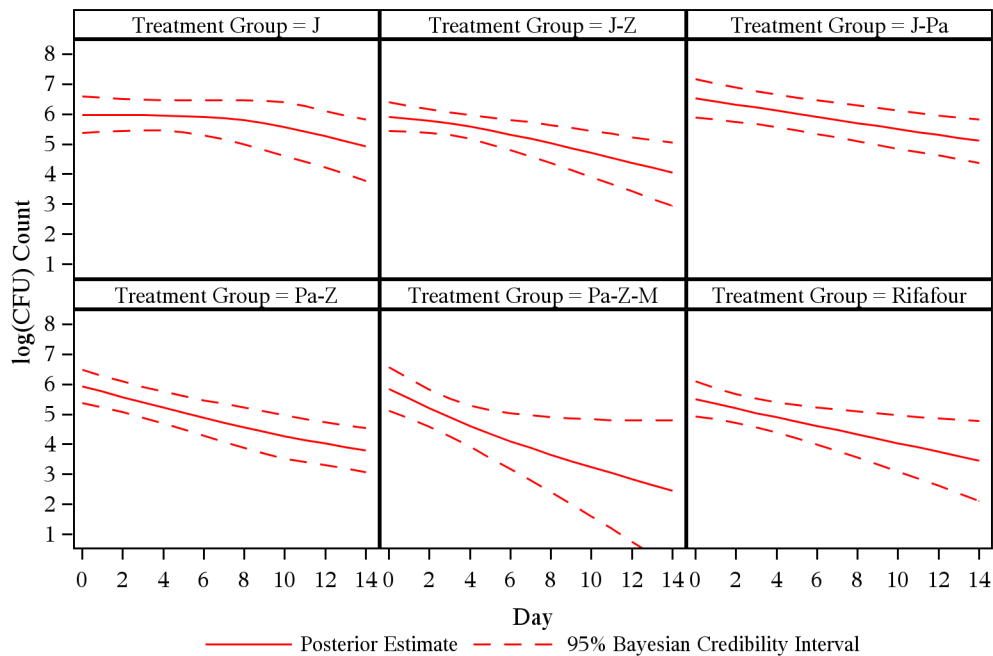
**Figure B.2:** Model 3 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



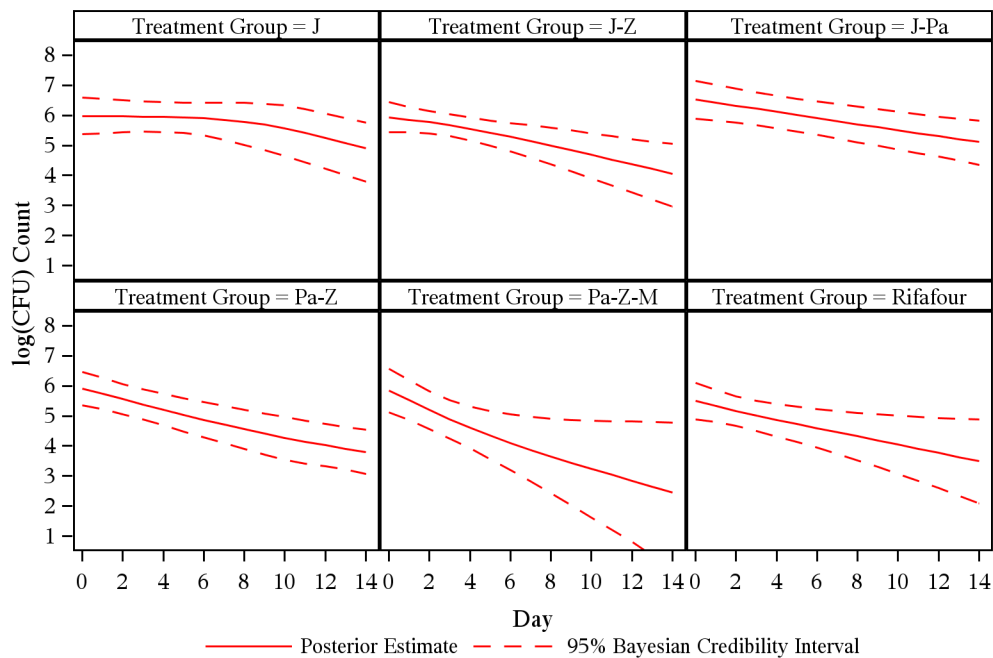
**Figure B.3:** Model 4 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



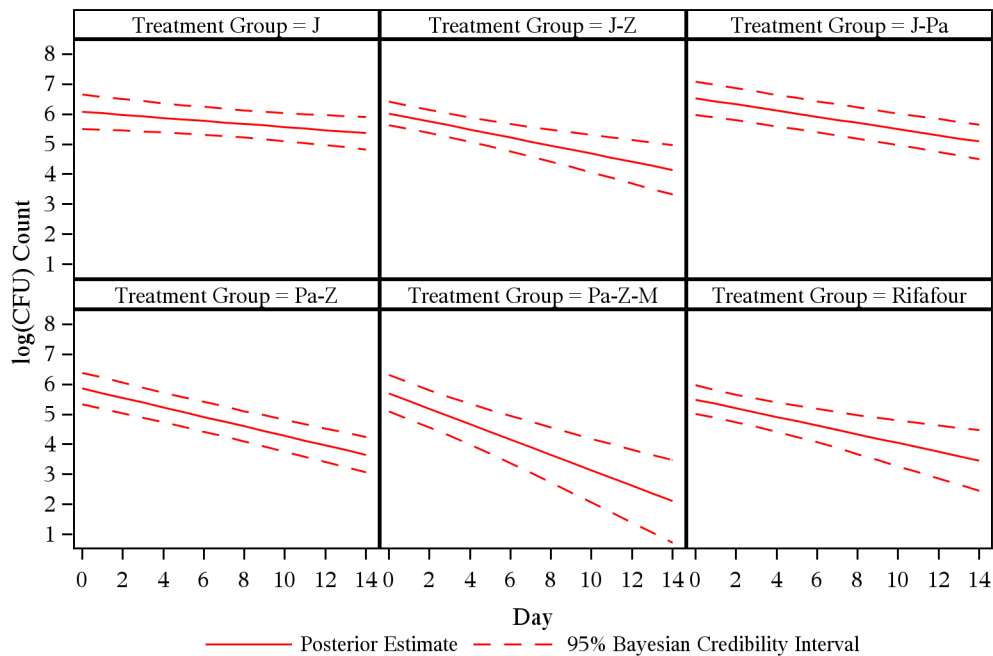
**Figure B.4:** Model 5 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



**Figure B.5:** Model 6 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



**Figure B.6:** Model 7 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time



**Figure B.7:** Model 8 – Posterior Estimates and Corresponding 95% BCIs for Mean  $\log(\text{CFU})$  Count Over Time

