

5 FIGURES AND TABLES

Figure 1. Steady state AUC of linezolid after oral dose administration to rats (top panel) and dogs (lower panel) in chronic toxicology studies. Data from 2-week dosing of linezolid in humans is included for comparison.

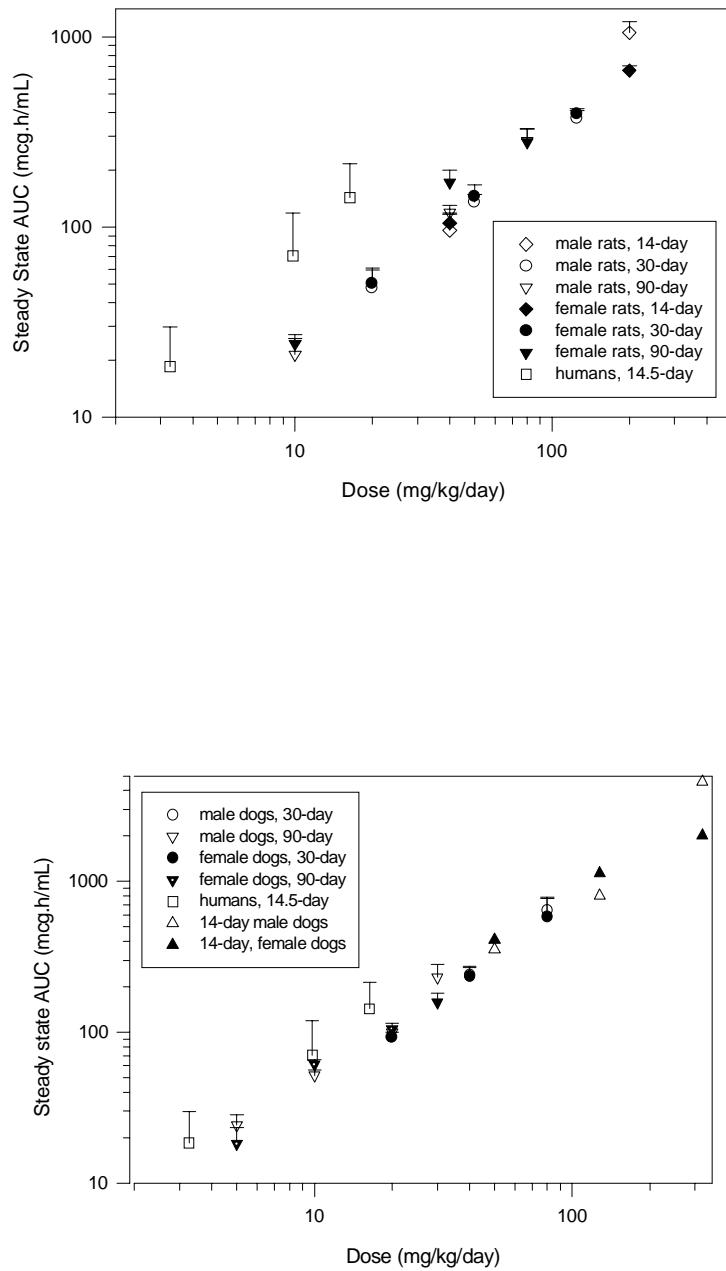


Figure 2. Steady state AUC of linezolid after intravenous dose administration to rats (top panel) and dogs (lower panel) in chronic toxicology studies. Data from 1-week dosing of linezolid in humans is included for comparison.

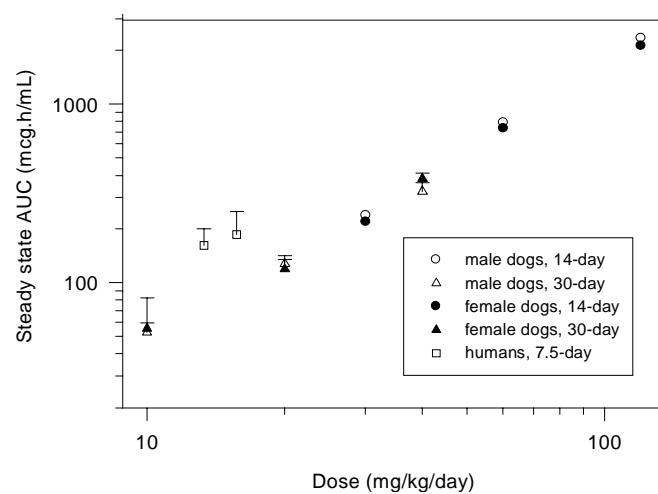
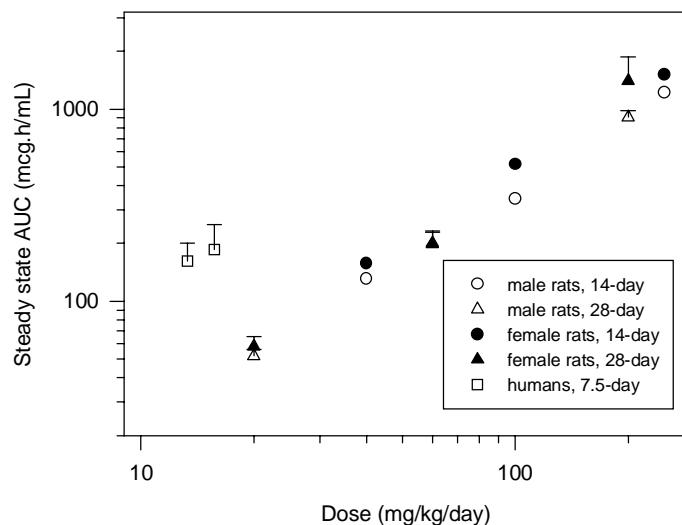


Figure 3. Images of representative autoradiograms from male Sprague-Dawley rats taken at 20 min and 24 h following single intravenous administration of [¹⁴C]linezolid at 10 mg/kg. Image darkness is proportional to radioactivity content. Excellent penetration of most soft tissues was observed for this antibiotic compound.

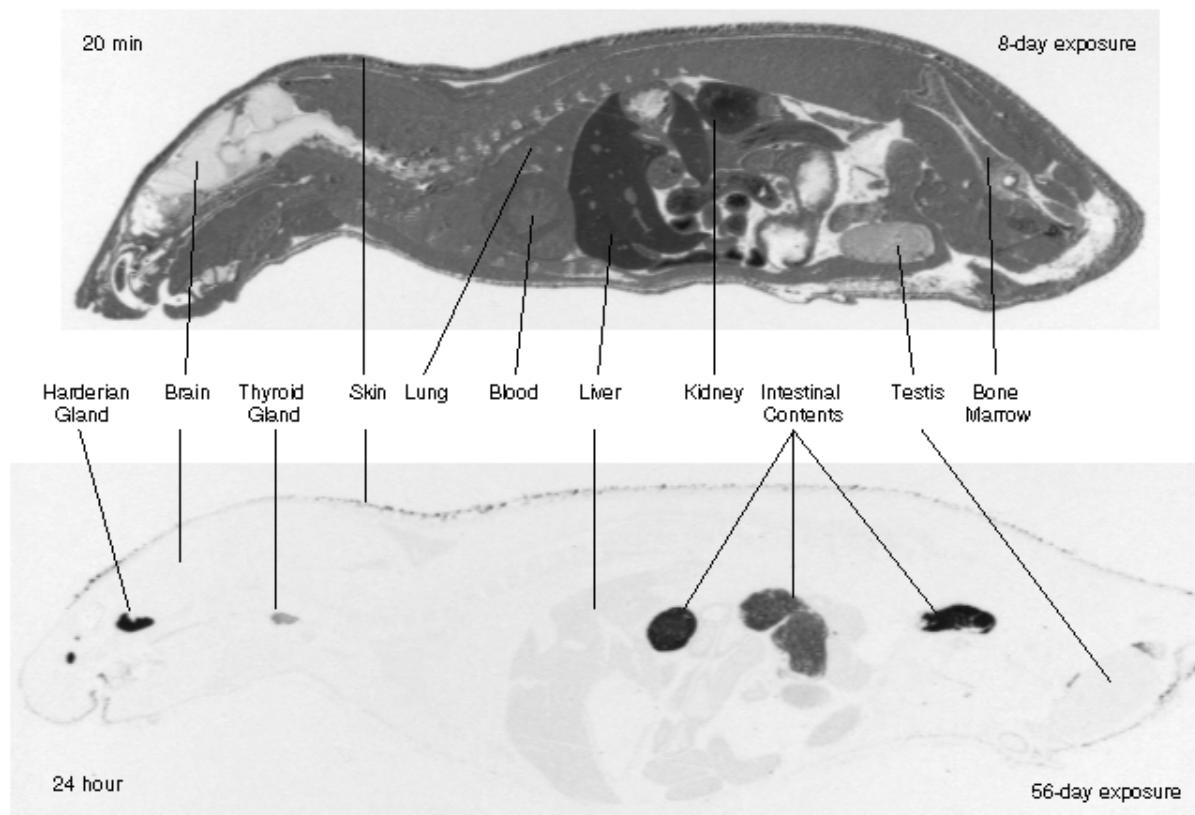


Figure 4. Metabolic Pathways for Linezolid in Mouse, Rat, Dog, and Human

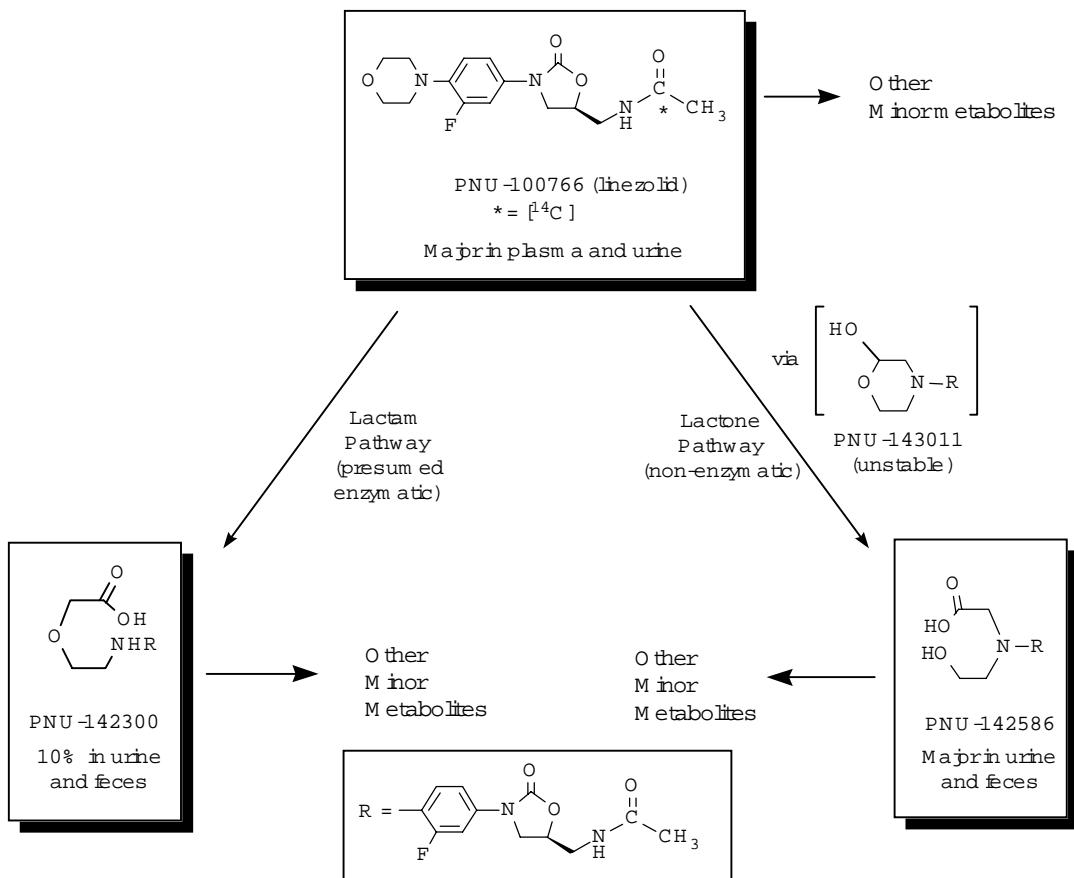


Table 1. Selected Pharmacokinetic Parameters of Linezolid in Mouse, Rat, and Dog

Species (Strain)	Route		Dose Level (mg/kg)	Mean Values of Parameters‡							Route of Elimination*
				tmax (h)	Cmax (μ g/mL) (μ g-eq/g)*	AUC (μ g·h/mL)	t1/2 (h)	Vss (L/kg)	CL (mL/min/kg)	F (%)	
Mouse (CH1-HSD)	IV††	3/time point female	4 mg/kg	-	10.5 ± 1.6†	2.2	0.3	0.45	30.2	100	-
			8 mg/kg	-	22.0 ± 4.5†	5.7	0.4	0.64	23.2	100	-
			12 mg/kg	-	41.9 ± 1.5†	14.2	0.5	0.49	14	100	-
	PO	3/time point female	4 mg/kg	0.2	1.7 ± 0.2	1.9	0.5	-	-	86	-
			8 mg/kg	0.2	6.0 ± 1.3	7.1	0.5	-	-	124	-
			12 mg/kg	0.3	11.4 ± 0.9	23.5	1.1	-	-	165	-
Mouse (CD-1)	PO	4 female	50 mg/kg	1	24.0 ± 2.3*	-	-	-	-	-	Urine, 53.1 ± 7.7%* Feces, 32.4 ± 5.0% Total, 92.5 ± 4.0% $^{14}\text{CO}_2$ 4.1% (N=2) (48 h)
Rat (Sprague-Dawley)	IV	3 male	10 mg/kg	-	15.0 ± 0.8†	15.5 ± 1.6	1.0 ± 0.1	0.72 ± 0.02	10.5 ± 1.1	100	-
	PO	3 male	25 mg/kg	0.3 ± 0.2	15.8 ± 3.3	42.6 ± 6.6	1.1 ± 0.3	-	-	109	-
Rat (Sprague-Dawley)	PO	4 male	25 mg/kg	-	-	-	-	-	-	-	Urine, 74.4 ± 2.0%* Feces, 23.6 ± 1.1%* Carcass, 0.6 ± 0.1%* $^{14}\text{CO}_2$, 2.7%* (n=2) (120 h)

- Not determined

* Radioactivity

† Concentration in first sample (2 min postdose)

†† β -Hydroxypropylcyclodextrin vehicle

‡ Some data rounded to facilitate comparison across studies

**Table 1. Selected Pharmacokinetic Parameters of Linezolid in Mouse, Rat, and Dog
(continued)**

Species (Strain)	Route	N Sex	Dose Level (mg/kg)	Mean Values of Parameters							Route of Elimination* Mean % of
				tmax (h)	Cmax (μ g/mL) (μ g·eq/g)*	AUC (μ g·h/mL)	t1/2 (h)	Vss (L/kg)	CL (mL/min/kg)	F (%)	
Dog (Beagle)	IV	3 male	25 mg/kg	-	29.6 ± 3.6†	214 ± 37	3.9 ± 0.4	0.63 ± 0.05	2.0 ± 0.3	100	-
		3 male	25 mg/kg capsule	1.0 ± 0.5	26.8 ± 1.5	206 ± 19	3.6 ± 0.1	-	-	96.6 ± 20.7	-
		3 male	25 mg/kg solution	0.8 ± 0.2	28.2 ± 4.1	206 ± 51	3.6 ± 0.4	-	-	97.3 ± 24.3	-
Dog (Beagle)	PO	3 male	25 mg/kg	=	=	=	=	-	-	-	Urine, 50.9 ± 4.9%* (0-168 h)
				=	=	=	=	-	-	-	Feces, 46.4 ± 4.8%* (0-168 h)

- Not determined.

= Not reported (data presented in Table 2)

* Radioactivity

† Concentration in first sample at 0.8 h postdose

Table 2. Exposure (AUC Values) at LOAEls and NOAEls in the Pivotal Animal Toxicology Studies Compared with Estimated Human Exposures

Study	NOAEL/LOAEL (mg/kg/day)	AUC (0-24 h) at NOAEL ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC (0-24 h) at LOAEL ($\mu\text{g}\cdot\text{h}/\text{mL}$)	Human AUC (0-24 h) ($\mu\text{g}\cdot\text{h}/\text{mL}$)*
1-Month Oral Rat	20: NOAEL 50: mild bone marrow effects	49	140	150/275†
1-Month Juvenile Rat	25: NOAEL 63: mild clinical chemistry changes, hair loss	144 (Day 1) 48 (Day 2)	460 (Day 1) 128 (Day 2)	150/275
1-Month Oral Dog	20: NOAEL 40: mild bone marrow hypocellularity	93	236	150/275
3-Month Rat	10: NOAEL 40: minimal reversible effects, including ↓ RBC (m); ↑ MCH (m); ↑ MCV (m); epididymal epithelial cell hypertrophy	23	195	150/275
3-Month Dog	20: NOAEL 30: inappetence/anorexia, ↓ RBC, HCT, HGB, RTC	102	195	150/275
Fertility-Adult Rat‡	15: NOAEL 50: decreased male fertility	67§	222§	150/275
Fertility-Juvenile rat	25/50: NOAEL 50/100: decreased male rat fertility (50 on days 1-36; 100 on days 37-55)	126 (Day 1) 52 (Day 36) 125 (Day 43)	324 (Day 1) 112 (Day 36) 296 (Day 43)	242§
Embryo-Fetal Development Mouse	150: NOAEL 450: maternal toxicity, effects on embryo and fetus	287	1150	150/275
Embryo-Fetal Development Rat	2.5: NOAEL 15: decreased fetal body weights and delayed skeletal ossification	3.3	38	242
Peri-Postnatal Development Rat	15: NOAEL 50: decreased postnatal pup survival and developmental delays	38	176	242

* Human exposure at 800 and 1200 mg/day for soft skin infections and other indications, respectively

† 150 and 275 are AUCs for adults given doses of 800 and 1200 mg/day, respectively

‡ AUC values were estimated from reference 24. Males given 100 mg/kg/day had mean AUC (0-24) = 444; assuming linear kinetics, AUC at 15 mg/kg/day ≈ 67 $\mu\text{g}\cdot\text{h}/\text{mL}$ and AUC at 50 mg/kg/day ≈ 222.

§ Data from pediatric study M/1260/0028. Mean AUC for 600 mg given IV twice daily was extrapolated from the mean AUC for a single 600 mg IV dose of 121 $\mu\text{g}\cdot\text{h}/\text{mL}$.

Abbreviations: AUC = area under the concentration-time curve; HCT = hematocrit; HGB = hemoglobin; LOAEL = lowest-observed-adverse-effect level; m = males; MCH = mean cell hemoglobin; MCV = mean cell volume; NOAEL = no-observed-adverse-effect level; RBC = red blood cell count; RTC = reticulocyte count;
 ↓ = decrease; ↑ = increase.

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
SAFETY PHARMACOLOGY STUDIES					
Cardio-Pulmonary Profile, Anesthetized Dog (Beagle)	IV	0 (vehicle), 3, 10, 30 mg/kg	Sequential, single dose	(A1)1510-5014-TJF-170A-J255	No
Anticonvulsant and Analgesic Activities and Effects on Thiopental-Induced Hypnosis, Rat (Crj:CD[SD])	Anti-convulsant Activity IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
	Analgesic Activity IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose		
	Thiopental-Induced Hypnosis IV	<u>Main Study:</u> 0 (vehicle), 6, 30, 125 mg/kg <u>Additional Study:</u> 0 (vehicle), 6, 15, 30 mg/kg	Single dose		
Gastrointestinal Profile, Guinea Pig (Hartley)	Isolated Guinea Pig Ileum Test In vitro	10^{-4} , 3×10^{-4} M	Single dose	(A1)1510-5014-TJF-170A-J255	No
Gastrointestinal Profile, Rat (Crj:CD[SD])	Gastric Secretion Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
	Gastric Emptying Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose		
	Intestinal Fluid Volume Test PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose		

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Gastrointestinal Profile, Rat (Crj:CD[SD])	Gastric Secretion Test IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
	Gastric Emptying Test IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose		
Gastrointestinal Propulsion, Rat (Crl:CD[SD]BR)	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
Renal Profile, Rat (Crj:CD[SD])	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	Yes
Functional Observational Battery, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 6.25, 62.5, 100 mg/kg	Single dose	(A1)1510-5014-TJF-170A	No
Functional Observational Battery, Rat (Crl:CD[SD]BR)	IV	0 (vehicle), 6, 30, 125 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
TOXICOLOGY STUDIES					
Single-Dose Toxicity Studies					
Acute Toxicity, Rat (Crj:CD[SD])	PO	0 (vehicle), 1000, 3000, 5000 mg/kg/day (0, 500, 1500, 2500 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Acute Comparative Toxicity, Rat (CD[SD]BR)	IV	0 (vehicle), 75 (THS), 75 (NH), 150 (THS), 150 (NH) mg/kg	Single dose	(C)5014-TJF-490A	No
Acute Toxicity, Rat (Crj:CD[SD])	IV	0 (vehicle), 100, 200, 400 mg/kg/day (0, 50, 100, 200 mg/kg/dose)	Divided dose (6 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Acute Toxicity, Dog (Beagle)	PO	500, 1000, 2000 mg/kg/day (250, 500, 1000 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	Yes
Repeated-Dose Toxicity Studies					
Comparative Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 200 mg/kg/day of either PNU-100766 or PNU-96403*	Twice daily; 7 days	(D2)1500-5148-JLH-48M	No
Range-Finding Toxicity, Rat (Crj:CD[SD])	PO	0 (vehicle), 40, 200, 1000 mg/kg/day (0, 20, 100, 500 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Range-Finding Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day (0, 50 mg/kg/dose)	Twice daily; 1 month	27080-DAV-101A	No
Toxicity with Recovery, Rat (Crj:CD[SD])	PO	0 (vehicle), 20, 50, 125 mg/kg/day (0, 10, 25, 62.5 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicity with Recovery, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months Recovery: 1 month	(D)5014-TJF-864	Yes
Range-Finding Toxicity, Male Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 12.5, 25, 50, 100 mg/kg/day	Daily; 4 weeks	(D)5014-TJF-904	No
Toxicity with Recovery, Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 10, 25, 63 mg/kg/day	Daily; 1 month Recovery: 6 weeks	(D)5014-TJF-864	Yes
Toxicity, Juvenile Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day	Daily; 53 days	(D)5014-TJF-864	No
Toxicity, Rat (Crj:CD[SD])	IV	0 (vehicle and environmental [saline] controls), 40, 100, 250 mg/kg/day (0, 0, 20, 50, 125 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Rat (Crj:CD[SD])	IV	0 (vehicle), 20, 60, 200 mg/kg/day (0, 10, 30, 100 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
Range-Finding Toxicity, Male Rabbit (NZW)	PO	0 (vehicle), 25, 50, 100 mg/kg/day (0, 12.5, 25, 50 mg/kg/dose)	Twice daily; 7 days	(D)5014-TJF-904	No
Range-Finding Toxicity, Dog (Beagle)	PO	0 (control), 50, 128, 320 mg/kg/day (0, 25, 64, 160 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Dog (Beagle)	PO	0 (control), 20, 40, 80 mg/kg/day (0, 10, 20, 40 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(A1)1510-5014-TJF-170A-J255	Yes
Toxicity with Recovery, Dog (Beagle)	PO	0 (vehicle), 5, 10, 20, 40/30 mg/kg/day (0, 2.5, 5, 10, 20/15 mg/kg/dose)	Twice daily; 3 months Recovery: 2 months	(D)5014-TJF-864	Yes
Toxicity, Dog (Beagle)†	IV	60, 150 mg/kg/day (30, 75 mg/kg/dose)	Twice daily; 5 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity, Dog (Beagle)	IV	0 (vehicle), 30, 60, 120 mg/kg/day (0, 15, 30, 60 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Toxicity with Recovery, Dog (Beagle)	IV	0 (vehicle), 10, 20, 40 mg/kg/day (0, 5, 10, 20 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(C)5014-TJF-490A	Yes
Reproductive Function Studies					
Fertility with Reversibility, Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 50, 100 mg/kg/day	Males: daily; 9 weeks Females: untreated Reversibility: up to 12 weeks	(D)5014-TJF-904	Yes
Toxicity and Fertility, Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 100 mg/kg/day	Males: daily; 10 weeks Females: untreated Reversibility: up to 14 weeks	(D)5014-TJF-864	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicity and Fertility with Testosterone Supplementation, Male Rat (Crl:CD[SD]BR)	PO	100 mg/kg/day with placebo or testosterone implant	Daily; 10 weeks	(D)5014-TJF-904	No
Toxicity and Fertility with Reversibility, Juvenile Male Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 12.5/25, 25/50, 50/100 mg/kg/day (0, 12.5, 25, 50 mg/kg/day on days 1-36 followed by a dose escalation to 0, 25, 50, 100 mg/kg/day, respectively, on days 37-49.	Daily; 7 weeks Reversibility: up to 19 weeks	(D)5014-TJF-864	Yes
Embryo-Fetal and Perinatal Toxicity Studies					
Preliminary Reproduction, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 5, 25, 75, 150 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
Supplementary Preliminary Reproduction, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 450, 1000 mg/kg/day	Daily; Gestation days 6-15	(A1)1510-5014-TJF-170A-J255	No
Developmental Toxicity, Mouse (Crl:CD-1 [ICR] BR)	PO	0 (vehicle), 50, 150, 450 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
Preliminary Reproduction, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 5, 25, 75, 125 mg/kg/day	Daily; Gestation days 6-21	(A1)1510-5014-TJF-170A-J255	No
Developmental Toxicity, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Daily; Gestation days 6-19	(C)5014-TJF-490A	Yes
Combined Segment I and III Fertility, General Reproductive Performance, and Postnatal Development, Rat (Crl:CD[SD]BR)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Males: Daily; 4 weeks prior to and throughout cohabitation until sacrifice F0 Females that Delivered: 2 weeks prior to cohabitation throughout cohabitation, gestation, and postpartum until sacrifice at weaning F0 Supplementary Phase Treated Females: 2 weeks prior to cohabitation until sacrifice on gestation day 13	(C)5014-TJF-490A	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Mutagenic Potential Studies					
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i>	In vitro	0 (DMSO), 6.8, 20, 61, 183, 550 µg/plate with and without metabolic activation	2-day incubation	(A1)1510-5014-TJF-170A	Yes
Unscheduled DNA Synthesis (UDS) Assay, Rat Primary Hepatocytes	In vitro	0, 3, 10, 30, 100, 300, 600, 1000, 2000 µg/mL	18-20 hour incubation	(A1)1510-5014-TJF-170A	Yes
AS52/XPRT Mammalian Cell Mutation Assay With and Without Metabolic Activation	In vitro	0 (DMSO), 125, 150, 450, 900, 1800, and 3600 µg/mL with metabolic activation, and 0 (solvent, DMSO), 112.5, 225, 450, 900, 1800, and 3600 µg/mL without metabolic activation	18-20 hour incubation	(A1)1510-5014-TJF-170A	Yes
Chromosome Aberration Assay, Human Peripheral Lymphocytes	In vitro	<u>Experiment a1:</u> 0 (McCoy's 5A medium), 500, 1000, 2000 µg/mL without metabolic activation <u>Experiment a2:</u> 0 (McCoy's 5A medium), 250, 500, 1000 µg/mL without metabolic activation <u>Experiment b:</u> 0 (McCoy's 5A medium), 500, 1000, 2000 µg/mL with and without metabolic activation	<u>Experiment a1:</u> 24-hour incubation <u>Experiment a2:</u> 48-hour incubation <u>Experiment b:</u> 3-hour incubation	(A1)1510-5014-TJF-170A	Yes
Micronucleus Test in Bone Marrow Cells, Mouse	PO	0 (vehicle), 1000, 2500, 5000 mg/kg	Single dose	(A1)1510-5014-TJF-170A	Yes
Other Studies					
Handler Safety Studies					
Ocular Irritation, Rabbit (NZW)	Topical	100 mg/eye 20 mg/eye/day	Single dose Daily; 5 days	(A1)1510-5014-TJF-170A	No
Dermal Irritation, Rabbit (NZW)	Topical (intact and abraded skin sites)	500 mg/site 100 mg/site/day	Single dose Daily; 5 days	(A1)1510-5014-TJF-170A	No
MAO Inhibition Studies					
NovaScreen Data	In vitro	10^{-8} , 10^{-6} , 10^{-1} M	60 minutes	NR	No
Monoamine Oxidase Inhibition	In vitro	2, 20, 200 µM	30 minutes	NR	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Development of Microtiter Plate-Based Assays for MAO-A and MAO-B	In vitro	NA	NA	NA	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	IV	0 (vehicle), 5, 15 mg/kg	Single dose	NR	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	PO	0 (vehicle), 30, 100 mg/kg/day (0, 15, 50 mg/kg/dose)	Divided dose administered twice daily for 3.5 days	(D)5014-TJF-864	No
Cardiovascular and Sympathomimetic Vasopressor Responses, CUP-Anesthetized Rat	PO	0 (vehicle), 30, 90 mg/kg/day (0, 10, 30 mg/kg/dose)	One-third dose administered three times daily for 14.3 days	(D)5014-TJF-904	No
Effects of MAOs, Isoniazid, and Oxazolidinone Antibiotics (PNU-100766, PNU-100592 and PNU-108812) on Vasopressor Response to Oral Tyramine, Conscious Rat (SD)	PO	0 (vehicle), 5, 15, 50 mg/kg/dose	Divided dose, twice daily for 2.5 days	(C)5014-TJF-490A	No
Further Evaluation of Selected MAOs, PNU-100766, and PNU-108812 for Oral Tyramine Potentiation, Male Rat (SD)	PO	<u>Study B:</u> 0 (vehicle), 50 mg/kg/dose <u>Study C:</u> 0 (vehicle), 15, 50, 100 mg/kg <u>Study D:</u> 0 (vehicle, 15, 50 mg/kg	<u>Study B:</u> Divided dose, twice daily for 0.5, 1.5, or 2.5 days (1, 3, or 5 doses) <u>Study C:</u> Single dose <u>Study D:</u> Single dose	(C)5014-TJF-490A	No
Tyramine Potentiation in Conscious Rats Treated with Oxazolidinone Antibiotics, Male Rat (HDS[SD])	PO or IV	50 mg/kg PO 10 mg/kg bolus + 12 mg/kg/hr IV	Single dose Single bolus injection + 2.75 hr infusion	NR	No
Oral Tyramine Potentiation in Conscious Rats Treated with Oxazolidinone Antibiotics, Male Rat (HDS[SD])	PO or IV	50 mg/kg PO 10 mg/kg bolus + 12 mg/kg/hr IV	Single dose Single bolus injection + 1.25 hr infusion	NR	No
Evaluation of Vasopressor Interactions Between PNU-100766 and Five Marketed Cold Remedies, Conscious Male Rat (SD)	PO	5, 15, 50 mg/kg/dose	Divided dose, twice daily for 2.5 days	(C)5014-TJF-490A	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Vasopressor Responses to Aqueous Formulations of Phenylpropanolamine, Pseudoephedrine, and Dextromethorphan in Rats Treated with MAOs and PNU-100766, Male Rat (SD)	PO	15, 50 mg/kg	Single dose	(C)5014-TJF-490A	No
Cardiovascular Responses to Tyramine and Decongestant Amines After Treatment with PNU-100766, Conscious Female Dog (Beagle)	PO	<u>Pilot Test:</u> 10 mg/kg (day 2) and 25 mg/kg (day 3) <u>Definitive Study:</u> 0 (control), 20 mg/kg/dose	<u>Pilot Test:</u> Single dose <u>Definitive Study:</u> Twice daily for 3.5 days than crossover 1 week later for 3.5 days	(C)5014-TJF-490A	No
Monoamine Oxidase Inhibition, Male Mouse (CF)	PO	0 (vehicle), 50 mg/kg	Single dose	NR	No
Effects on Rat Brain Monoamine Levels After Acute and Chronic Exposure, Male Rat (SD)	<u>Acute:</u> SC <u>Chronic:</u> PO	<u>Acute Study:</u> 30, 90 mg/kg <u>Chronic Study:</u> 10, 30 mg/kg/dose	<u>Acute Study:</u> 2 hours <u>Chronic Study:</u> TID for 14 days with 0, 2, 5, or 13 days recovery	NR	No
Effects in Rabbit Model of Hyperpyrexia, Rabbit	PO	50, 150 mg/kg/dose	2 doses	NR	No
Serotonin Syndrome, Rabbit (NZW)	PO	50 mg/kg/dose	1 dose 18 hours before surgery and 1 dose the morning of surgery	NR	No
Studies on Impurities and Degradation Products					
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> with PNU-105368†	In vitro	0 (DMSO), 313, 625, 1250, 2500, 5000 µg/plate with and without metabolic activation	2-day incubation	29419-DAU-107A	Yes
Ames Assay in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> with PNU-141535	In vitro	0 (sterile water), 7, 21, 62, 185, 555 µg/plate with metabolic activation 0 (sterile water), 62, 185, 556, 1667, 5000 µg/plate without metabolic activation	2-day incubation	(A)410-FCW-43	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 50, 100, 200, 300, 500, 750 µg/mL <u>Experiment 2:</u> 50, 100, 200, 300, 500, 750 µg/mL	18-20 hour incubation	29419-DAU-107A	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 3, 10, 30, 100, 300, 1000 µg/mL <u>Experiment 2:</u> 100, 200, 300, 500, 750, 1000 µg/mL	18-20 hour incubation	NR	No
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 30, 100, 300, 600, 1000, 3000 µg/mL <u>Experiment 2:</u> 30, 60, 200, 600, 2000, 3000 µg/mL	18-20 hour incubation	(A)410-FCW-43	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat Primary Hepatocytes	In vitro	<u>Experiment 1:</u> 10, 30, 100, 300, 1000, 3000 µg/mL <u>Experiment 2:</u> 100, 300, 600, 1000, 2000, 3000 µg/mL	18-20 hour incubation	NR	No
Unscheduled DNA Synthesis (UDS) Assay with PNU-105368‡, Rat (Fischer 344)	In vivo (IP) and in vitro	0 (DMSO), 100, 200, 400 mg/kg	Single dose 2 or 16 hours before sacrifice	29419-DAU-107A	Yes
Unscheduled DNA Synthesis (UDS) Assay with PNU-141535§, Rat (Fischer 344)	In vivo (IV) and in vitro	0 (saline), 500, 1000, 2000 mg/kg	Single dose 2 or 16 hours before sacrifice	(A)410-FCW-43	Yes
AS52/XPRT Mammalian Cell Mutation Assay with PNU-105368‡, AS52 Chinese Hamster Cells	In vitro	<u>Experiment 1:</u> 0 (DMSO), 10, 100, 1000, 2000, 4000 µg/mL without metabolic activation 0 (DMSO), 100, 500, 1000, 2500, 5000 µg/mL with metabolic activation <u>Experiment 2:</u> 0 (DMSO), 500, 1000, 2000, 3000, 4000 µg/mL without metabolic activation 0 (DMSO), 500, 1000, 2000, 3000, 4000, 5000 µg/mL with metabolic activation	5-hour incubation	29419-DAU-107A	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
AS52/XPRT Mammalian Cell Mutation Assay with PNU-141535§, AS52 Chinese Hamster Cells	In vitro	<u>Experiment 1:</u> 0 (sterile water), 100, 500, 1000, 2500, 5000 µg/mL with and without metabolic activation <u>Experiment 2:</u> 0 (sterile water), 250, 500, 1000, 2500, 5000 µg/mL with and without metabolic activation	5-hour incubation	(A)410-FCW-43	Yes
Chromosome Aberration Assay in Human Lymphocytes Peripheral with PNU-105368‡	In vitro	0 (solvent), 100, 200, 400 µg/mL without metabolic activation 0 (solvent), 750, 1500, 3000 µg/mL with metabolic activation	24- and 48-hour incubation 3-hour incubation	29419-DAU-107A	Yes
Chromosome Aberration Assay in Human Peripheral Lymphocytes with PNU-141535§	In vitro	0 (solvent), 156.3, 312.5, 625 Tg/mL without metabolic activation 0 (solvent), 1250, 2500, 5000 Tg/mL with metabolic activation	24- and 48-hour incubation 3-hour incubation	(A)410-FCW-43	Yes
Micronucleus Test in Bone Marrow Cells with PNU-105368‡, Mouse	PO	Males: 0 (vehicle), 150, 375, 750 mg/kg Females: 0 (vehicle), 200, 500, 1000 mg/kg	Single dose	29419-DAU-107A	Yes
Micronucleus Test in Bone Marrow Cells with PNU-141535§, Mouse	IV	0 (saline), 400, 1000, 2000 mg/kg	Single dose	(A)410-FCW-43	Yes

ADME STUDIES

Methodology					
HPLC Plasma Assay, Mouse	NA	LLOQ = 0.01 µg/mL	NA	Reference standard lot; (C)5014-TJF-490A-J363	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.05 µg/mL	NA	(A1)1510-5014-TJF-170A-J255	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.005µg/mL	NA	(C)5014-TJF-490A-J370	NA
HPLC Plasma Assay, Rat, Dog	NA	LLOQ = 0.01 µg/mL	NA	(A1)1510-5014-TJF-170A-J255	NA
HPLC Plasma Assay Validation Report, Rat	NA	LLOQ = 0.02 µg/mL	NA	(D2)1500-5148-JLH-48	NA
HPLC Plasma Assay, Rabbit	NA	LLOQ = 0.01 µg/mL	NA	(A1)1510-5014-TJF-170A	NA

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Metabolite Syntheses & Activity	NA	PNU-142300E, PNU-142586, PNU-142618, PNU-142620, PNU-143010, PNU-143011, PNU-143131, PNU-144089 [105] PNU-173558: [109] PNU-100440/PNU-105368: Linezolid synthetic intermediates [108] Metabolite antibacterial activity [147]	NA	Various	NA
¹⁴ C Radiolabel Synthesis 1	NA	NA	NA	27983-JPM-40B	NA
¹⁴ C Radiolabel Synthesis 2	NA	NA	NA	27792-EHC-76A¶	NA
Single-Dose Pharmacokinetics/Toxicokinetics					
Bioavailability, Mouse (CH1-HSD)	IV, PO	4, 8, 12 mg/kg	Single dose	(D)5014-TJF-967	No
¹⁴ C Pharmacokinetics-Label Stability-Distribution-Excretion, Female Mouse (CD-1)	PO	50 mg/kg	Single dose	30994-JAE-75A	No
¹⁴ C Pharmacokinetics-Excretion-Distribution, Female Mouse (CD-1)	PO	50, 450 mg/kg	Single dose	PNU-100766, GLP10361, GLP10360 [¹⁴ C]PNU-100766, 30994-JAE-75A, 74A	Yes
Bioavailability, Male Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	27774-DAU-71-A	No
Renal Pharmacokinetics, Male Rat (Sprague-Dawley)	IV	0.8 mg/mL loading dose, 0.3 mg/mL PNU-100766, infusion	Infusion	(A1)1510-5014-TJF-170-A	No
Renal Pharmacokinetics, Male Rat (Sprague-Dawley)	IV	2.5 mg	Single	(C) 5014-TJF-490A	No
¹⁴ C Pharmacokinetics, Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: A1(1510)-5014-TJF-170A-J255, [¹⁴ C]PNU-100766: 37792-EHC-7UA	No
¹⁴ C Excretion-Label Stability, Male Rat (Sprague-Dawley)	PO	25 mg/kg	Single dose	PNU-100766: 27774-DAU-71A, [¹⁴ C]PNU-100766: 27983-JPM-40B; RA 0231.	No
Pharmacokinetics/ Hydroxypropylcyclodextrin Vehicle Effect, Rat (Sprague-Dawley)	IV	5 mg/kg	Single dose	(C) 5014-TJF-490A	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 1000, 3000, 5000 mg/kg/day (0, 500, 1500, 2500 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle), 100, 200, 400 mg/kg/day (0, 50, 100, 200 mg/kg/dose)	Divided dose (6 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
Bioavailability, Male Dog (Beagle)	PO, IV	25 mg/kg	Single dose	(A1)1510-5014-TJF-170A-J255	No
Toxicokinetics, Male Dog (Beagle)	PO	500, 1000, 2000 mg/kg/day (250, 500, 1000 mg/kg/dose)	Divided dose (8 hours apart) for 1 day	(A1)1510-5014-TJF-170A-J255	No
¹⁴ C Pharmacokinetics-Excretion, Male Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	(A1)1510-5014-TJF-170A-J255, [¹⁴ C]PNU-100766: 37792-EHC-7UA	No
¹⁴ C Pharmacokinetics-Excretion, Female Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	[¹⁴ C] 30484-JAE-47A & 5014-TJF-864	Yes
Studies On Metabolite PNU-105368					
PNU-105368 Metabolite Toxicokinetics, Mouse (CD-1)	PO	50, 500, 2000 mg/kg (range finding) 150, 375, 750 mg/kg (definitive)	Single dose	29419-DAU-107A	No
PNU-105368 Metabolite Toxicokinetics, Rat (Fischer 344)	IP	100, 200, 400 mg/kg	Single dose	29419-DAU-107A	No
Studies On Process Impurity PNU-141535					
PNU-141535 Process Impurity Toxicokinetics, Mouse (CD-1)	PO IV IV	50, 500, 2000 mg/kg (range finding) 50, 500, 2000 mg/kg (range finding) 400, 1000, 2000 mg/kg (definitive)	Single dose	[A] 410-FCW-43	No
PNU-141535 Process Impurity Toxicokinetics, Rat (Fischer 344)	IV	500, 1000, 2000 mg/kg	Single dose	(A)410-FCW-43	No
Repeated-Dose Pharmacokinetics/Toxicokinetics					
Gestational Toxicokinetics, Female Mouse (CD-1)	PO	0 (vehicle), 50, 150, 450 mg/kg/day	Daily; Gestation days 6-16	(C)5014-TJF-490A	Yes
7-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	200 mg/kg/day	Twice daily; 7 days	PNU-100766, (D2)1500-5148-JLH-48M	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
14-Day Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle and environmental [saline] controls), 40, 100, 250 mg/kg/day (0, 0, 20, 50, 125 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
Range-Finding 14-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 40, 200, 1000 mg/kg/day (0, 20, 100, 500 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
28-Day Toxicokinetics, Rat (Sprague-Dawley)	IV	0 (vehicle), 20, 60, 200 mg/kg/day (0, 10, 30, 100 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
28-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 20, 50, 125 mg/kg/day (0, 10, 25, 62.5 mg/kg/dose)	Twice daily; 1 month Recovery: 1 month	(A1)1510-5014-TJF-170A-J255	Yes
28-Day Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 12.5, 25, 50 and 100 mg/kg	Once daily, 28 days	[A1]1510 5014-TJF-170A	No
53-Day Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Daily; 53 days	(D)5014-TJF-864	No
90-Day Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months Recovery: 1 month	(D)5014-TJF-864	Yes
Segment I and III Toxicokinetics, Rat (Sprague-Dawley)	PO	0 (vehicle), 2.5, 15, 50 mg/kg/day	Males: Daily; 4 weeks prior to and throughout cohabitation until sacrifice F0 Females that Delivered: 2 weeks prior to cohabitation throughout cohabitation, gestation, and postpartum until sacrifice at weaning F0 Supplementary Phase Treated Females: 2 weeks prior to cohabitation until sacrifice on gestation day 13	(C)5014-TJF-490A	Yes
9-Week Fertility Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 50, 100 mg/kg/day	Males: daily; 9 weeks Reversibility: up to 12 weeks	(D)5014-TJF-904	Yes
28-Day Toxicokinetics, Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 25, 63 mg/kg/day	Daily; 1 month Recovery: 6 weeks	(D)5014-TJF-864	Yes
7-Week Fertility Toxicokinetics, Male Juvenile Rat (Sprague-Dawley)	PO	0 (vehicle), 12.5/25, 25/50, 50/100 mg/kg/day (0, 12.5, 25, 50 mg/kg/day on days 1-36 followed by a dose escalation to 0, 25, 50, 100 mg/kg/day, respectively, on days 37-49.	Daily; 7 weeks Reversibility: up to 19 weeks	(D)5014-TJF-864	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
10-Week Fertility Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Once daily, 10 weeks Reversibility up to 14 weeks	D2-1500-5148-JLH-48	Yes
10-Week Toxicokinetics, Male Rat (Sprague-Dawley)	PO	0 (vehicle), 100 mg/kg/day	Once daily, 10 weeks Testosterone supplemented	D2-1500-5148-JLH-48	No
7-Day Toxicokinetics, Male Rabbit (NZW)	PO	0, 25, 50 and 100 mg/kg/day	Twice daily, 7 days	(A1)1510-5014-TJF-170A-	No
14-Day Toxicokinetics, Dog (Beagle)	IV	0 (vehicle), 30, 60, 120 mg/kg/day (0, 15, 30, 60 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
14-Day Toxicokinetics, Dog (Beagle)	PO	0 (control), 50, 128, 320 mg/kg/day (0, 25, 64, 160 mg/kg/dose)	Twice daily; 14 days	(A1)1510-5014-TJF-170A-J255	No
1-Month Toxicokinetics, Dog (Beagle)	PO	0 (control), 20, 40, 80 mg/kg/day (0, 10, 20, 40 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(A1)1510-5014-TJF-170A-J255	Yes
1-Month Toxicokinetics, Dog (Beagle)	IV	0 (vehicle), 10, 20, 40 mg/kg/day (0, 5, 10, 20 mg/kg/dose)	Twice daily; 1 month Recovery: 6 weeks	(C)5014-TJF-490A	Yes
90-Day Toxicokinetics, Dog (Beagle)	PO	0 (vehicle), 5, 10, 20, 40/30 mg/kg/day (0, 2.5, 5, 10, 20/15 mg/kg/dose)	Twice daily; 3 months Recovery: 2 months	(D)5014-TJF-864	Yes
Distribution					
Caco-2, In VitroTransport	In vitro	NA	NA	PNU-100766 (D)5014-DJH-274A	No
Caco-2/ MDCK, In Vitro Transport	In vitro	NA	NA	[¹⁴ C]PNU-100766, 30994-JAE-130A	No
Tissue Distribution-Excretion, Male Rat (Sprague-Dawley and Long Evans)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: (A1)1510-5014-TJF-170A-J255, [¹⁴ C]PNU-100766: 27983-JPM-40B	No
Tissue Distribution-Excretion, Female Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766: (A1)1510-5014-TJF-170A-J255, [¹⁴ C]PNU-100766: 37792-EHC-7UA	No
Preliminary Tissue Distribution (WBA), Male Rat (Sprague-Dawley)	PO	250 mg/kg	Single	NS	No
Tissue Distribution/Placental Transfer (WBA), Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV (male) 25 mg/kg PO (pregnant female at 14 day or 18 day gestation)	Single	PNU-100766, (d2)1500-5148-JLH-48M. [¹⁴ C]PNU-100766, 30994-JAE-130A	Yes

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
¹⁴ C Lacteal Secretion, Female Rat (Sprague-Dawley)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single dose	PNU-100766, (D2)1500-5148-JLH-48M [¹⁴ C]PNU-100766, 30994-JAE-130A	Yes
Plasma Protein Binding, Rat (Sprague-Dawley), Dog (Beagle), Human	In vitro	0.1-100 ug/mL	NA	PNU-100766: (A1)1510-5014-TJF-170A-J255, [¹⁴ C]PNU 100766: 37792-EHC-7UA	No
Biotransformation					
In Vivo Studies					
¹⁴ C Quantitative Metabolite Profile, Mouse (CD-1)	PO	50, 450 mg/kg	Single	[A1]1510 5014-TJF-170A	No
¹⁴ C Quantitative Metabolite Profile in plasma, Rat (Sprague-Dawley)	PO	25 mg/kg	Single	[A1]1510 5014-TJF-170A	No
¹⁴ C Quantitative Metabolite Profile Biliary Excretion, Rat (Sprague-Dawley)	PO, IV	25 mg/kg PO, 10 mg/kg IV (male and female) Biliary excretion 25 mg/kg PO (males only)	Single	[A1]1510 5014-TJF-170A	No
Preliminary Metabolite Identification, Rat (Sprague-Dawley)	PO	25 mg/kg	Single	PNU-100766: 27774-DAU-71A. [¹⁴ C]PNU-100766: 27983-JPM-40B; RA 0231.	No
Preliminary Metabolite Identification, Rat (Sprague-Dawley) and Dog (Beagle)	PO	25 mg/kg	Single	NS	No
Quantitative Metabolite Profile, Dog (Beagle)	PO, IV	10 mg/kg IV, 25 mg/kg PO	Single	[A1]1510 5014-TJF-170A	No
Preliminary ¹⁹ F NMR Excretion, Human	IV	750 mg	Single	see clinical protocol M-1260-0003	No
Preliminary Metabolite Identification, Human	PO, IV and in vitro	Various	Single and multiple	see clinical protocol M-1260-0001-4	No
¹⁴ C and ¹⁹ F Quantitative Metabolite Profile/Minor Metabolite Identification, Human	PO	500 mg	Single radiochemical dose given alone or as the morning dose on day 4 of a 10 day bid regimen of unlabelled PNU-100766	[A1]1510 5014-TJF-170A	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
In Vitro Studies					
90-Day Enzyme Induction, Rat (Sprague-Dawley)	PO	0 (vehicle), 10, 40, 125/80 mg/kg/day (0, 5, 62.5/40 mg/kg/dose)	Twice daily; 3 months	(D)5014-TJF-864	Yes
Cytochrome P450 Inhibition (Cloned Isoforms), Human	In vitro	10 and 100 uM	NA	NS	No
Preliminary Biotransformation, Rat (Sprague-Dawley)	In vitro	Hepatocyte suspension : 5,000,000 cells/mL, 40 µg/mL (118.6 µM)	1 and 3 hours at 37 °C	NS	No
Preliminary Biotransformation Mechanism-Microsomes-CYP 450 Cloned Isoforms-Liver Slices, Human	In vitro	Various	Various	NS	No
Definitive Biotransformation Mechanism-Chemical oxidation-microsomes-CYP 450 Cloned Isoforms, Human	In vitro	Various	Various	NS	No
Electrochemical Oxidation	NA	Electrochemical anodic oxidation potential of morpholine ring	NA	28596-DMJ-3	No
Preliminary Biotransformation Liver Slices (Rat, Dog, Monkey, Human) and Plasma (Human)	In vitro	Liver slices; 20 mg/mL U-100766; 37°C for 6 or 24 h. Human plasma, 100 ug/mL PNU-100766 37°C for 2 h.	NA	NS	No
Preliminary Monoamine Oxidase Inhibition-Liver S9, Human	In vitro	2, 20, 200 µM	30 minutes	NS	No
Definitive MAO-A Ki-Purified Placental MAO-A, Human	In vitro	0- 500 uM 7-8 Data points	NA	[E] 5014-TJF-967	No
Process Impurity-Stability In Vitro					
PNU-141535 Stability in UDS Incubation Media	In vitro	<u>Experiment 1:</u> 30, 100, 300, 600, 1000, 3000 µg/mL <u>Experiment 2:</u> 30, 60, 200, 600, 2000, 3000 µg/mL	18-20 hour incubation	(A)410-FCW-43	No

Table 3. Database Table for Nonclinical Safety Pharmacology, Toxicology and ADME Studies with Linezolid

Study/Species/Strain	Route	Dose Levels	Dosage Regimen	Bulk Drug Lot	GLP Yes/No
PNU-141535 Stability In Ames Assay Incubation Medium and Hepatic S9, Rat (Sprague-Dawley)	In vitro	0 (sterile water), 7, 21, 62, 185, 555 µg/plate with metabolic activation 0 (sterile water), 62, 185, 556, 1667, 5000 µg/plate without metabolic activation	2-day incubation	(A)410-FCW-43	No

* PNU-96403 is a 4-pyridil derivative of oxazolidinone

† 5-day toxicity study in the beagle dog (Study No. 95-903) was summarized in a memo (Kaneko Y. U-100766: 5-Day intravenous toxicity study in two male and two female beagle dogs. Upjohn memo to list, 30 June 1995) and appended to Upjohn Technical Report 1470-95-033.

‡ PNU-105368 is a minor metabolite of PNU-100766

§ PNU-141535 is an impurity of PNU-100766

¶ This radio synthesis was repeated, subsequent lots are denoted by notebook reference "JAE".

Abbreviations: CUP = α -chloralose, urethane, and sodium pentobarbital; DMSO = dimethylsulfoxide; GLP = Good Laboratory Practice; HPLC = high performance liquid chromatography; IP = intraperitoneal; IV = intravenous; LLOQ = lower limit of quantitation; MAO = monoamine oxidase; NA = not applicable; NH = non-heated; NMR = nuclear magnetic resonance spectroscopy; NR = not reported; NS = not specified; NZW = New Zealand White; PO = oral; SD = Sprague-Dawley; THS = terminally heat sterilized; UDS = unscheduled DNA synthesis; WBA = whole body autoradiography