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SCY-078, a Novel Fungicidal Agent, Demonstrates Distribution to Tissues Associated with Fungal Infections during Mass Balance Studies with Intravenous and Oral [^{14}C]SCY-078 in Albino and Pigmented Rats

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ABSTRACT SCY-078, a fungicidal β-1,3-glucan synthesis inhibitor administered as intravenous or oral [^{14}C]SCY-078 to rats, was distributed primarily into tissues associated with invasive fungal disease (kidney, lung, liver, spleen, bone marrow, muscle, vaginal tissue, and skin) to levels exceeding those in plasma. Oral fraction absorbed was ~40%. Elimination was primarily via bile and feces (~90%) and urine (~1.5%). Mean half-time was ~8 h. Quantitative whole-body autoradiography showed a rapid distribution at 8 h and elimination by 168 h postdose.

KEYWORDS antifungal agents, mass balance

SCY-078 has broad and potent *in vitro* activity against *Candida* spp. and *Aspergillus* spp., including azole-resistant and most echinocandin-resistant strains of *Candida* spp. (1–4). *In vitro* SCY-078 is fungicidal against *Candida* spp. (5) and met efficacy endpoints preclinically in murine animal models of invasive candidiasis (6, 7) and aspergillosis (8). In phase 2 clinical studies, SCY-078 demonstrated efficacy for invasive candidiasis and moderate to severe vulvovaginal candidiasis (9–11). This study characterizes the tissue distribution by quantitative whole-body autoradiography (QWBA), mass balance, and elimination after single intravenous (i.v.) and oral doses of SCY-078 in albino and pigmented rats.

Male albino Wistar Han (WH; Charles River, Raleigh, NC) ($n = 38$) or male ($n = 18$) and female ($n = 3$) pigmented Long-Evans (LE; Hilltop Lab Animals, Inc., Scottdale, PA) rats received [^{14}C]SCY-078 by oral administration (15 mg/kg, ~150 μCi/kg, in aqueous 0.5% methylcellulose) or i.v. administration (5 mg/kg, ~108 μCi/kg, 7.5:1 molar ratio of Captisol:SCY-078 in saline) as a 1-h infusion (10 ml/kg/h). WH rats were used for mass balance and pharmacokinetic (PK) determinations after i.v. and oral doses, and both WH and LE rats were used for QWBA determinations. Dose levels were selected to reflect the clinically relevant 11.2-μg·h/ml target exposure for *Candida* spp. infections (6, 7). The concentration, homogeneity, radio purity, and stability of dosing formulations were confirmed to be acceptable before dosing.

The study was performed in accordance with the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the U.S. Office of Laboratory Animal Welfare. The study was not intended to be in accordance with Good Laboratory Practices as defined in 21 CFR part 58; nonetheless, it was performed in accordance with the study protocol and QPS standard operating procedures. There were no protocol deviations that adversely affected the study.

For elimination studies, urine samples were collected predose (overnight) and at 0 to 8 h, 8 to 24 h, and every subsequent 24-h interval until 168 h postdose. Feces samples were collected 0 to 24 h and at 24-h intervals until 168 h postdose. Bile

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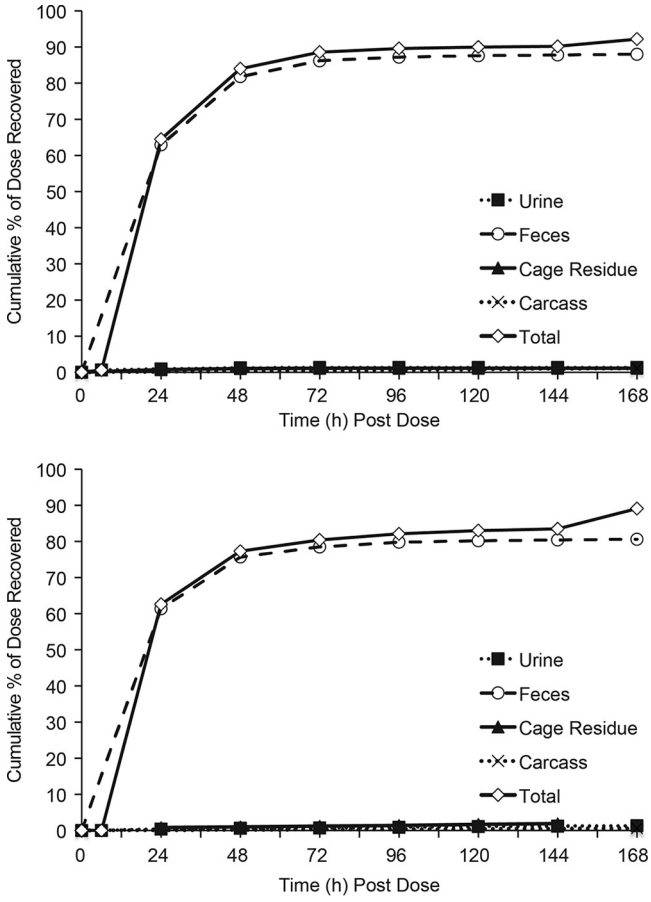

FIG 1 Time course of excretion of radioactivity for group 1 male rats after single a 5-mg/kg 1-h i.v. infusion or 15-mg/kg oral dose of [^{14}C]SCY-078.

samples were collected from bile duct-cannulated (BDC) animals predose and at 0 to 4 h, 4 to 8 h, 8 to 24 h, and every subsequent 24-h interval until 72 h postdose. Cage washes were collected daily. Blood samples were collected at frequent intervals from time 0 to 168 h postdose for determination of plasma PK. Samples were typically collected from 3 animals per group per time point.

For QWBA whole-body sections (~40 μm thick via Leica CM3600 cryomicrotome; Nussloch, Germany), where all major tissues, organs, and biological fluids were represented, sections were exposed for phosphor imaging (Fuji Biomedical, Stamford, CT) together with calibration standards. Animals were deeply anesthetized with isoflurane anesthesia and, after blood samples were obtained, were euthanized by freezing in a hexane/solid carbon dioxide bath for at least 15 min. The imaging plate was scanned with the GE Healthcare Typhoon FLA 9500 image acquisition system (GE/Molecular Dynamics, Sunnyvale, CA). Quantification was performed by image densitometry with MCID image analysis software (v. 7.0; Interfocus Imaging Ltd., Linton, Cambridge, UK), and a standard curve was constructed from the integrated response (molecular dynamics counts [MDC]/mm^2) and the nominal concentrations of the ^{14}C-calibration standards. The concentrations of radioactivity were expressed as [^{14}C]SCY-078 μg equiv/g tissue. The lower limit of quantitation was 0.024 and 0.049 μg equiv/g of tissue for i.v. and oral doses of SCY-078, respectively.

Excretion of radioactivity. The primary elimination route for radioactivity following i.v. administration of SCY-078 was via the feces (87.9% dose, >60% during 0 to 24 h) (Fig. 1) with little elimination in urine (1.4% dose). For BDC animals, the primary elimination route was in bile (49.9% dose, >45% by 48 h). An average of 0.6% and 32.3% of the administered dose was recovered in the urine and feces, respectively. The

TABLE 1 Mean PK parameters after single i.v. or oral doses of [^{14}C]SCY-078 in rats

Parameter	[^{14}C]SCY-078 dose	
	5 mg/kg i.v. (n = 3)	15 mg/kg PO (n = 3)
$t_{1/2}$ (h)	7.5	9.8
T_{max} (h)	1.0	4.0
C_{max} (μg equiv/ml)	1.80	0.72
AUC_{last} (μg equiv · h/ml)	11.69	14.42
AUC_{inf} (μg equiv · h/ml)	11.81	15.00

presence of radioactivity in feces in the BDC rats after i.v. administration indicates potential for intestinal secretion as a route of elimination.

After oral administration, elimination was primarily in feces (80.5% dose, >60% during 0 to 24 h) with little elimination in urine (1.3% dose). For BDC animals, the primary elimination route was in feces (68.2% dose, >50% by 24 h). An average of 0.1% and 20.3% of the administered dose was recovered in the urine and bile, respectively. Of the administered dose (i.v. and oral groups), recovery in the cage rinse, cage wash, cage wipe, and carcass generally averaged ~1% or less, with up to 10% for carcass in i.v.-dosed BDC rats. Total recovery of radioactivity (mass balance) was 92.2% and 91.8% of the administered i.v. and oral doses, respectively.

Plasma pharmacokinetics. After i.v. dosing, mean plasma concentrations were quantifiable through 48 h postdose, at which time the concentration was 0.011 μg equiv/ml. Mean maximum concentration of drug in serum (C_{max}) was 1.8 μg equiv/ml, mean plasma area under the curve from time 0 to the last quantifiable concentration (AUC_{last}) was 11.69 μg equiv·h/ml, mean plasma half-life ($t_{1/2}$) of total radioactivity was 7.6 h, and mean time to maximum concentration of drug in serum (T_{max}) was at the end of infusion (Table 1, Fig. 2). After oral dosing, mean plasma concentrations were quantifiable through 48 h postdose, at which time the concentration was 0.041 μg equiv/ml. Mean C_{max} was 0.716 μg equiv/ml, mean plasma AUC_{last} was 14.42 μg equiv·h/ml, mean plasma $t_{1/2}$ of total radioactivity was 9.8 h, and mean T_{max} was 4 h (Table 1, Fig. 2).

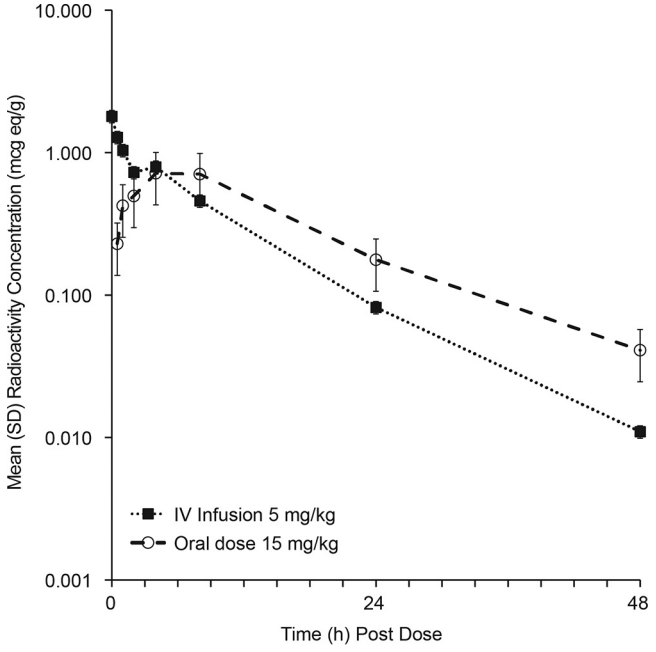

FIG 2 Time course of mean combined-sex plasma radioactivity concentrations after a 5-mg/kg 1-h i.v. infusion or 15-mg/kg oral dose of [^{14}C]SCY-078 in WH rats.

TABLE 2 Tissue-to-blood AUC ratios of total radioactivity after administration of [^{14}C]SCY-078 to male pigmented LE rats

Sample, by dosing method	C_{max} (μg equiv/g)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{all} (μg equiv · h/g)	Tissue:blood AUC
i.v., 5 mg/kg 1 h infusion					
Adipose (brown)	11.79	0.083	138.0	113.702	17.148
Adipose (white)	3.145	0.083	32.8	32.928	4.966
Adrenal gland	25.345	0.083	155.2	321.126	48.431
Blood (cardiac)	0.83	0.083	7.1	6.631	1.000
Bone	0.486	0.083	44.9	9.022	1.361
Bone marrow (femur)	12.033	8.0	13.7	238.388	35.953
Brain (cerebellum)	0.043	4.0	ND[a]	0.219	0.033
Brain (cerebrum)	0.059	8.0	ND	0.727	0.110
Brain (medulla)	0.028	2.0	38.1	0.136	0.020
Cecum	7.653	4.0	17.9	83.542	12.600
Epididymis	0.711	8.0	81.4	75.355	11.365
Esophagus	3.699	0.83	5.8	41.430	6.248
Exorbital gland	8.561	2.0	75.1	523.676	78.980
Eye (lens)	0.028	4.0	ND	0.084	0.013
Eye (uvea)	4.522	8.0	286.1	777.035	117.191
Harderian gland	7.483	8.0	60.3	927.358	139.862
Heart (myocardium)	9.523	0.083	6.4	66.558	10.038
Kidney (cortex)	18.949	0.083	14.8	165.880	25.018
Kidney (medulla)	16.288	0.083	16.9	136.610	20.603
Large intestine	5.519	0.083	5.3	57.682	8.727
Liver	38.837	0.083	57.1	374.517	56.484
Lung	11.439	0.083	14.0	175.593	26.483
Lymph node	8.581	0.083	51.0	251.036	37.861
Mammary gland region	2.492	2.0	24.4	32.117	4.844
Oral mucosa	1.464	2.0	22.8	36.782	5.547
Pancreas	10.471	0.083	9.4	110.455	16.659
Pituitary	19.684	8.0	22.7	640-809	96.645
Preputial gland	7.574	2.0	136.9	962.901	145.222
Prostate gland	2.533	2.0	11.3	61.301	9.245
Salivary gland	11.867	0.083	8.5	149.193	22.501
Seminal vesicle	1.047	8.0	12.4	26.827	4.046
Skeletal muscle	2.265	2.0	5.2	28.304	4.269
Skin (nonpigmented)	3.656	8.0	47.1	74.884	11.294
Skin (pigmented)	2.358	8.0	50.1	110.249	16.627
Small intestine	15.463	0.083	5.0	141.607	21.357
Spinal cord	0.053	0.083	ND	0.759	0.115
Spleen	32.78	0.083	237.5	507.638	75.561
Spleen (red pulp)	38.408	0.083	131.2	431.011	65.004
Spleen (white pulp)	31.424	8.0	80.7	1381.359	208.333
Stomach (gastric mucosa)	22.381	0.083	16.5	181.074	27.309
Testis	0.361	8.0	100.8	64.972	9.799
Thymus	5.394	8.0	30.4	195.608	29.501
Thyroid	37.287	0.083	27.5	291.187	43.916
Urinary bladder	6.391	0.083	30.3	45.955	6.931
Oral, 15 mg/kg					
Adipose (brown)	6.139	4.0	6.6	85.515	11.070
Adipose (white)	1.472	4.0	22.5	29.845	3.864
Adrenal gland	19.499	4.0	8.8	380.527	49.261
Blood (cardiac)	0.466	4.0	6.5	7.725	1.000
Bone	0.507	8.0	17.9	11.399	1.476
Bone marrow (femur)	8.779	8.0	10.2	191.142	24.744
Brain (cerebellum)	0.000	ND	ND	0.000	0.000
Brain (cerebrum)	0.000	ND	ND	0.000	0.000
Brain (medulla)	0.056	8.0	ND	0,560	0.072
Cecum	9.002	8.0	19.6	165.065	21.368
Epididymis	0.704	24.0	112.3	132.872	17.201
Esophagus	3.608	8.0	4.3	54.758	7.089
Exorbital gland	7.996	8.0	37.4	455.299	58.940
Eye (lens)	0.06	8.0	ND	0.600	0.078
Eye (uvea)	3.646	24.0	430.2	681.587	88.234
Harderian gland	10.257	24.0	57.9	1415.862	183.289
Heart (myocardium)	4.693	4.0	17.9	67.335	8.717
Kidney (cortex)	10.092	4.0	13.0	162.648	21.055
Kidney (medulla)	10.458	4.0	6.1	148.741	19.255

(Continued on next page)

TABLE 2 (Continued)

Sample, by dosing method	C_{max} (μg equiv/g)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{all} (μg equiv · h/g)	Tissue:blood AUC
Large intestine	2.822	8.0	12.1	47.846	6.194
Liver	22.076	4.0	67.6	387.337	50.142
Lung	12.462	8.0	8.7	241.411	31.252
Lymph node	6.176	8.0	9.9	181.554	23.503
Mammary gland region	1.95	4.0	19.3	40.604	5.256
Oral mucosa	1.021	8.0	23.5	30.481	3.946
Pancreas	6.60	4.0	6.2	102.103	13.218
Pituitary	12.532	8.0	23.1	357.973	46.341
Preputial gland	6.006	8.0	39.2	409.267	52.981
Prostate gland	1.0761	4.0	23.2	34.033	4.406
Salivary gland	8.409	8.0	6.3	143.875	18.625
Seminal vesicle	0.368	4.0	9.8	5.858	0.758
Skeletal muscle	2.12	4.0	5.3	29.752	3.852
Skin (nonpigmented)	1.765	4.0	20.0	93.490	12.103
Skin (pigmented)	1.502	4.0	ND	141.195	18.278
Small intestine	243.592	4.0	10.0	827.220	107.087
Spinal cord	0.065	8.0	ND	0.650	0.084
Spleen	16.663	4.0	99.8	418.910	54.230
Spleen (red pulp)	18.061	4.0	33.5	400.602	51.860
Spleen (white pulp)	9.445	4.0	91.8	825.024	106.803
Stomach (gastric mucosa)	13.046	4.0	5.3	168.163	21.769
Testis	0.442	24.0	146.8	104.051	13.470
Thymus	3.09	8.0	16.3	136.948	17.728
Thyroid	18.223	4.0	29.9	354.136	45.844
Urinary bladder	2.493	0.5	8.6	36.336	4.704

[a]ND, not determined.

Tissue distribution. Intravenous [^{14}C]SCY-078 in male LE rats was rapidly and widely distributed over 8 h to key tissues associated with fungal infections achieving total exposures exceeding that of blood (Table 2, Fig. 3). QWBA images showed distribution of radioactivity 5 min after completion of the i.v. infusion (T_{max}), when metabolism was minimal and thereby demonstrated distribution of primarily parent [^{14}C]SCY-078, and 4-h after oral dosing, which corresponded most closely to the plasma T_{max} for oral SCY-078 in rat (Fig. 3). Radioactivity was mostly eliminated (42 of 44 tissues) by 936 h. Exceptions were seen in spleen and pigmented uvea of the eye, which had concentrations of 0.024 and 0.141 μg equiv/g, respectively. Intravenous C_{max} in tissues (22 of 44) was at 5 min postdose (T_{max}). In general, i.v. distribution in albino WH rats was similar.

Oral [^{14}C]SCY-078 administration in male LE rats achieved maximal radioactivity in most tissues (21 of 44) at 4 h postdose. The highest concentration in plasma was 0.621 μg equiv/g at 4 h postdose. Tissue concentration versus time profiles showed that most tissues had a rapid distribution phase over the first 8 h, followed by a 24- to 168-h elimination phase. Tissue concentrations decreased steadily, and elimination was observed in all tissues at 912 h postdose, except in the pigmented skin and uvea of the eye, which had concentrations of 0.126 and 0.288 μg equiv/g, respectively. In general, levels of radioactivity in female LE rats after a single oral dose of [^{14}C]SCY-078 were similar to or higher than those observed in male LE rats. The highest concentration in plasma of female LE rats was 0.589 μg equiv/g at 4 h postdose, and key tissues had concentrations that were higher than that in blood at most time points. In female LE rats, the highest tissue concentrations were observed at 4 h postdose (T_{max}) for 22 of 43 tissues. Concentrations in most tissues were still detectable at 24 h (39 of 43 tissues), whereas only brain and spinal cord concentrations were below the quantifiable limit at 24 h. In general, tissue distribution in albino male WH rats after a single oral dose of [^{14}C]SCY-078 was lower at 2 h than that in pigmented male LE rats; however, it became comparable by 24 h (next sampling time for WH rats). The highest concentration in plasma of albino rats was 0.716 μg equiv/g at 4 h postdose, and key tissues had concentrations that were higher than that in blood at most time points. The highest

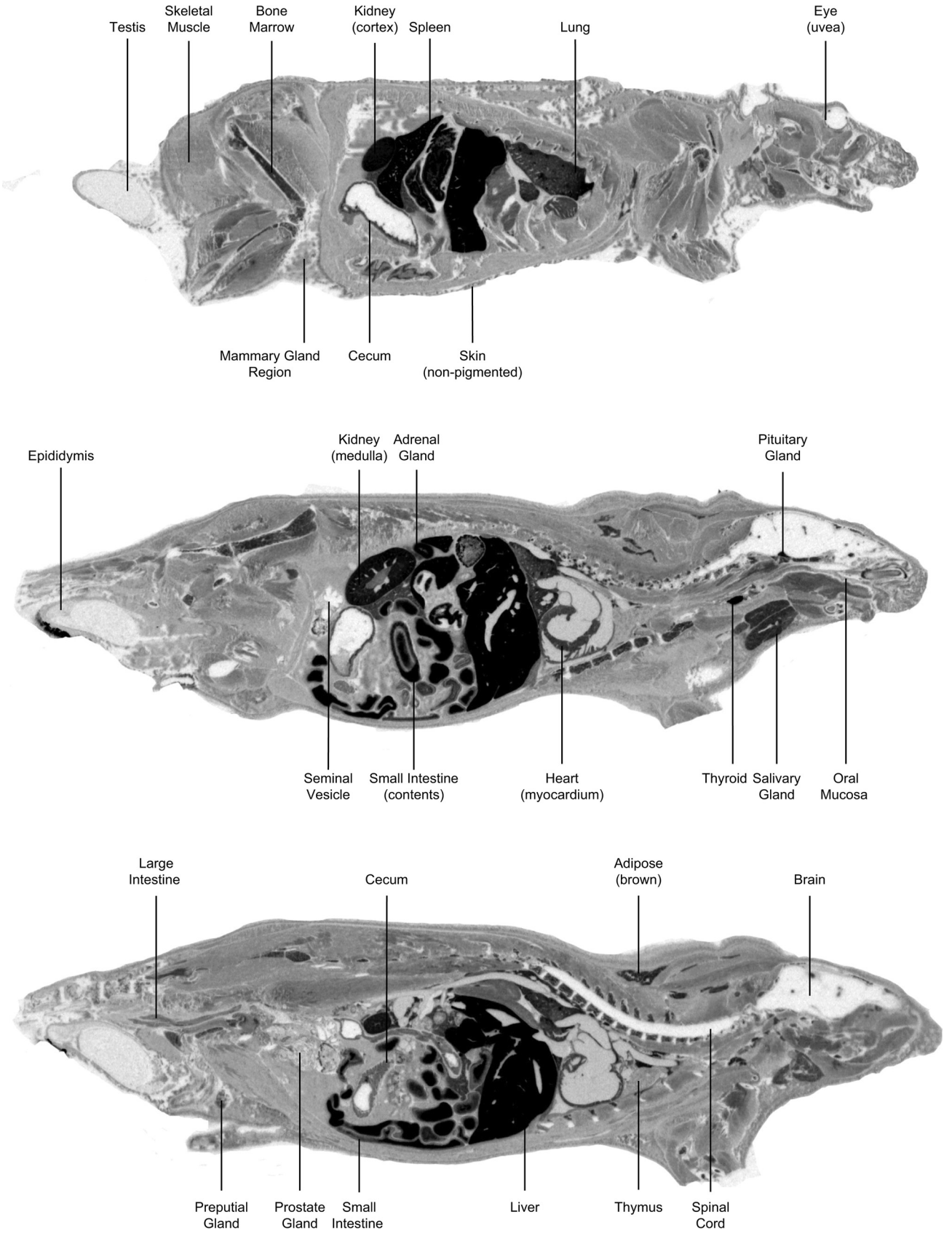

FIG 3 Whole-body autoradiograms in LE rats after 5 mg/kg i.v. administration 5 min postdose (top three images) or 15-mg/kg oral administration 4 h postdose (bottom three images) of [^{14}C]SCY-078.

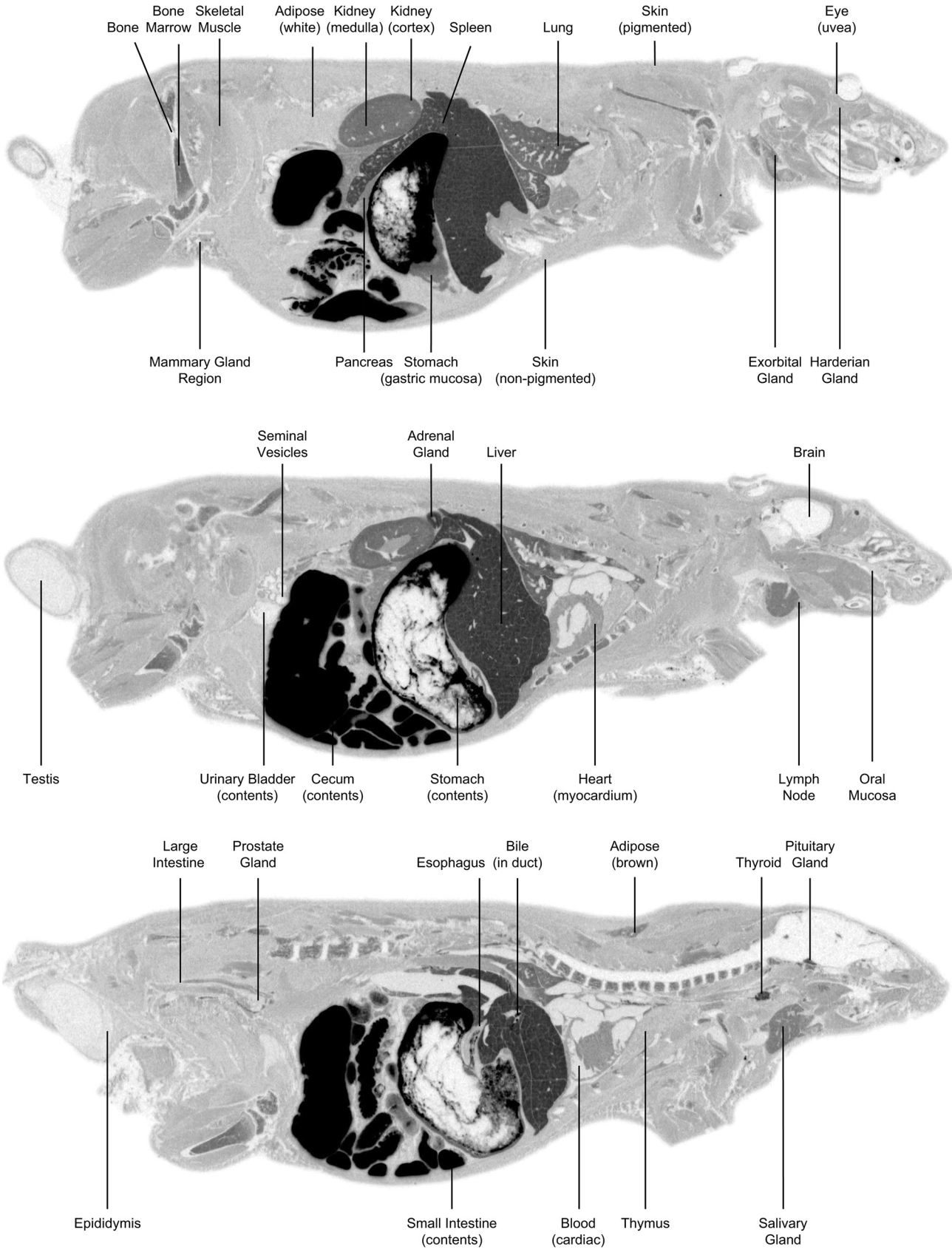

FIG 3 (Continued)

tissue concentrations in albino rats were observed at 24 h postdose (T_{max}) for 33 of 43 tissues.

Plasma concentrations were measurable at 48 h after both i.v. and oral doses of SCY-078. The elimination $t_{1/2}$ for SCY-078 in this study of rats was ~7 to 9 h, which was consistent with the previously reported $t_{1/2}$ of ~6 to 9 h in rats and ~9 h in dogs (7). A previous study in healthy subjects reported a $t_{1/2}$ of ~20 h (12); results from both animal and human studies support once-daily dosing of SCY-078. Values for AUC_{last} and AUC to infinity (AUC_{inf}) were higher with oral than with i.v. administration, reflecting the higher dose. The amount of oral fraction absorbed based on total radioactivity (AUC) in plasma was 42.3%.

SCY-078 was widely distributed in tissues throughout the body after i.v. and oral administration. After oral delivery, the tissue-to-blood AUC ratios in the organs typically associated with fungal disease were as follows: spleen, 54×; liver, 50×; lung, 31×; bone marrow, 25×; kidney, 20×; skin, 12× nonpigmented and 18× pigmented; vaginal tissue, 9×; and skeletal muscle, 4×. Distribution to central nervous system tissues was low, with little or no radioactivity detected in brain and spinal cord. Distribution to adipose tissue was low, supporting the high volume of distribution reported in previous studies (7) and reflected distribution to tissues other than fat. Except for in skin, the distribution profile was similar between pigmented and nonpigmented animals.

An earlier study with SCY-078 in mice reported that tissue concentrations in the kidney exceeded plasma concentrations by 20- to 25-fold (7), which is comparable to the kidney levels of radioactivity with both i.v. and oral dosing in the current study. Most of the [^{14}C]SCY-078 radioactivity was recovered over 48 h after a dose, and at least 80% of the administered dose was excreted in feces after i.v. and oral dosing. Based on these results, SCY-078 should be suitable by both oral and i.v. administration in patients with invasive infections that require prolonged courses of therapy or by the oral route for those with recurrent vulvovaginal infections.

Penetration of antifungal drugs into target tissues at an adequate fungicidal concentration is essential for treating serious fungal infections (13). The echinocandins anidulafungin, caspofungin, and micafungin, the only approved glucan synthesis inhibitors, distribute into most tissues (14, 15) and, similar to SCY-078, distribute into kidney, liver, lung, and spleen (16–18). However, echinocandins as a class exhibit poor oral bioavailability and consequently are approved for i.v. infusion only, thereby limiting these agents to parenteral administration.

Based on current data, SCY-078 represents a potential advance over existing antifungal agents, with its potency against wild-type and antifungal drug-resistant organisms, excellent distribution in tissues associated with fungal infections, and PK profile consistent with once-daily oral and i.v. administration. These attributes may be especially beneficial to patients requiring oral therapy for recurrent infections or prolonged courses of treatment.

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