

Pharmacokinetics, Metabolism and Excretion of the Anti-Diabetic Agent Ertugliflozin (PF-04971729) in Healthy Male Subjects

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**Drug Metabolism and Disposition**

**I. Rat Mass Balance Summary**

**Supplementary Table 1.** Summary of mean radioactivity recovered in male and female Sprague-Dawley rats after administration of a single 25 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729 (N = 3/sex)

<b>Excretion Route (males)</b>	<b>Urine</b>	<b>Feces</b>	<b>Total<sup>a</sup></b>
<b>Time (h)</b>	<b>% of dose</b>		
<b>0-24</b>	25.7	59.6	85.3
<b>24-48</b>	0.7	4.7	5.4
<b>48-72</b>	0.1	0.3	0.4
<b>72-168</b>	0.2	0.2	0.4
<b>Total</b>	26.6	64.8	92.4

<b>Excretion Route (females)</b>	<b>Urine</b>	<b>Feces</b>	<b>Total<sup>a</sup></b>
<b>Time (h)</b>	<b>% of dose</b>		
<b>0-24</b>	33.8	54.1	87.9
<b>24-48</b>	0.9	4.2	5.1
<b>48-72</b>	0.1	0.2	0.3
<b>72-168</b>	0.4	0.2	0.6
<b>Total</b>	35.2	58.7	95.3

<sup>a</sup>includes cage wash.

**Supplementary Table 2.** Percentages (Mean  $\pm$  S.D.) of **urinary** metabolites of PF-04971729 in male and female Sprague Dawley rats after administration of a single 25 mg/kg oral dose of [ $^{14}$ C]-PF-04971729 (N = 3/sex)

Metabolite	m/z	$t_R$ (min)	Male Rats	Female Rats
<b>PF-04971729</b>	454	37.3	5.0 $\pm$ 0.3	14.4 $\pm$ 3.8
<b>M1</b>	470	30.4	0.9 $\pm$ 0.2	0.3 $\pm$ 0.0
<b>M2</b>	426	28.3	12.5 $\pm$ 1.9	13.3 $\pm$ 4.2
<b>M5a</b>	602	21.8	0.6 $\pm$ 0.3	0.3 $\pm$ 0.2
<b>M6<sup>a</sup></b>	442	21.6	6.1 $\pm$ 1.0	0.6 $\pm$ 0.2
<b>M7<sup>a</sup></b>	452	38.5	0.2 $\pm$ 0.0	0.5 $\pm$ 0.0
<b>M8<sup>a</sup></b>	442	25.7	0.2 $\pm$ 0.1	0.1 $\pm$ 0.1
<b>Total</b>			25.5 $\pm$ 1.1	29.5 $\pm$ 1.1

<sup>a</sup>M6, M7 and M8 are rat-specific metabolites and derived from oxidation(s) on the ethoxybenzyl-chlorophenyl moiety in PF-04971729.

**Supplementary Table 3.** Percentages (Mean  $\pm$  S.D.) of **fecal** metabolites of PF-04971729 in male and female Sprague Dawley rats after administration of a single 25 mg/kg oral dose of [ $^{14}$ C]-PF-04971729 (N = 3/sex)

Metabolite	m/z	$t_R$ (min)	Male Rats	Female Rats
<b>PF-04971729</b>	454	37.3	22 $\pm$ 2.8	27 $\pm$ 6.7
<b>M1</b>	470	30.4	5.3 $\pm$ 1.1	1.6 $\pm$ 0.2
<b>M2</b>	426	28.1	27.9 $\pm$ 4.6	25.5 $\pm$ 2.4
<b>M3</b>	470	31.7	1.2 $\pm$ 1.1	0.1 $\pm$ 0.1
<b>M6<sup>a</sup></b>	442	21.3	3.0 $\pm$ 0.7	0.3 $\pm$ 0.2
<b>M7<sup>a</sup></b>	452	38.5	1.4 $\pm$ 0.3	1.5 $\pm$ 0.3
<b>M8<sup>a</sup></b>	442	25.3	3.2 $\pm$ 1.0	1.8 $\pm$ 0.1
<b>M9<sup>a</sup></b>	470	32.6	0.4 $\pm$ 0.2	0.4 $\pm$ 0.2
<b>Total</b>			65.1 $\pm$ 1.0	58.8 $\pm$ 5.1

<sup>a</sup>M6, M7, M8 and M9 are rat-specific metabolites and derived from the oxidative metabolism of the parent compound.

**Supplementary Table 4. Circulating** metabolites of PF-04971729 in male and female Sprague Dawley rats after administration of a single 25 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Metabolite	m/z	t <sub>R</sub> (min)	% of Radioactivity		Mean
			Male Rats	Female Rats	
<b>PF-04971729</b>	454	36.9	86.5	94.0	90.3
<b>M1</b>	470	30.3	2.8	0.6	1.7
<b>M2</b>	426	28.0	4.2	2.3	3.3
<b>M4a</b>	630	29.9	0.7	0.3	0.5
<b>M4c</b>	630	33.5	0.7	0.3	0.5
<b>M5a<sup>b</sup></b>	602	27.6	0.0	0.0	0.0
<b>M6<sup>a</sup></b>	442	21.3	2.3	0.3	1.3
<b>M7<sup>a</sup></b>	452	38.2	2.8	2.3	2.6

<sup>a</sup>M6 and M7 are rat-specific metabolites and derived from the oxidative metabolism of the parent compound. <sup>b</sup>detected by mass spectrometry.

## II. Dog Mass Balance Summary

**Supplementary Table 5.** Summary of mean radioactivity recovered in male and female Beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729 (N = 2/sex)

<b>Excretion Route (males)</b>	<b>Urine</b>	<b>Feces</b>	<b>Total<sup>a</sup></b>
<b>Time (h)</b>	<b>% of dose</b>		
<b>0-24</b>	5.0	52.0	57
<b>24-48</b>	1.2	24.8	26
<b>48-72</b>	0.3	5.30	5.6
<b>72-144</b>	0.2	1.40	1.6
<b>Total</b>	6.8	83.6	92.1

<b>Excretion Route (females)</b>	<b>Urine</b>	<b>Feces</b>	<b>Total<sup>a</sup></b>
<b>Time (h)</b>	<b>% of dose</b>		
<b>0-24</b>	7.0	54.4	61.4
<b>24-48</b>	1.5	25.4	26.9
<b>48-72</b>	0.4	5.3	5.7
<b>72-96</b>	0.3	2.2	2.5
<b>Total</b>	9.2	87.4	94.8

<sup>a</sup>includes cage wash.

**Supplementary Table 6.** Percentages of **Urinary** metabolites of PF-04971729 in male and female Beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729 (N = 2/sex)

Metabolite	m/z	t <sub>R</sub> (min)	% of Dose	
			Male <sup>a</sup>	Female <sup>a</sup>
<b>PF-04971729</b>	454	36.6	3.7	3.2
<b>M1</b>	470	30.0	0.7	1.3
<b>M2</b>	426	27.8	0.5	0.6
<b>M4c</b>	630	34.4	0.4	0.6
<b>M5a</b>	602	21.7	0.9	1.6
<b>M6<sup>b</sup></b>	442	21.3	0.1	0.7
<b>M8<sup>b</sup></b>	618	15.6	0.4	1.2
<b>Total</b>			6.8	9.2

<sup>a</sup>Mean data from two dogs. <sup>b</sup>M6 and M8 are not seen in humans.

**Supplementary Table 7.** Percentages of **fecal** metabolites of PF-04971729 in male and female Beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729 (N = 2/sex)

Metabolite	m/z	t <sub>R</sub> (min)	% of Dose	
			Male <sup>a</sup>	Female <sup>a</sup>
<b>PF-04971729</b>	454	36.4	68.9	61.3
<b>M1</b>	470	29.6	4.8	9.5
<b>M2</b>	426	27.3	7.7	9.8
<b>M4c</b>	630	36.0	1.5	1.2
<b>M5a</b>	602	20.7	0.7	3.2
<b>Total</b>			83.6	85.0

<sup>a</sup>mean data from two dogs.

**Supplementary Table 8. Circulating metabolites of PF-04971729 in beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729 (N=2/sex)**

			% of Radioactivity	
Metabolite	m/z	t <sub>R</sub> (min)	Male <sup>a</sup>	Female <sup>a</sup>
<b>PF-04971729</b>	454	21.6	93.5	94.9
<b>M1</b>	470	29.9	3.27	1.8
<b>M4c</b>	630	34.4	3.25	2.8
<b>M5a</b>	602	36.7	N.D.	0.5
<b>Total</b>			100	100

<sup>a</sup>mean data from two dogs.

### III. Mass Balance Studies in Bile-duct Cannulated Rats

**Supplementary Table 9.** Summary of mean radioactivity recovered in bile duct cannulated male and female rats (N=2/sex) after administration of a single 25 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Excretion Route (males)	Urine	Feces	Bile	Total <sup>a</sup>
Time (h)	% of dose			
<b>0-24</b>	33.5	9.7	45.9	89.1
<b>24-48</b>	1.1	2.0	0.9	4.0
<b>Total</b>	34.6	11.7	46.8	93.7

<sup>a</sup>includes cage wash, rinse and cage wipe. Data shown represents the mean from two males.

Excretion Route (females)	Urine	Feces	Bile	Total <sup>a</sup>
Time (h)	% of dose			
<b>0-24</b>	42.3	13.0	31.7	87.0
<b>24-48</b>	1.4	1.4	0.8	3.6
<b>Total</b>	43.8	14.4	32.5	92.3

<sup>a</sup>includes cage wash, rinse and cage wipe. Data shown represents the mean from two females.

**Supplementary Table 10.** Percentage of biliary metabolites of PF-04971729 in bile duct cannulated male and female Sprague Dawley rats after administration of a single 25 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Metabolite	m/z	t <sub>R</sub> (min)	Male Rats	Female Rats
PF-04971729	454	37.1	1.7	3.1
M1	470	30.6	1.5	0.4
M2	426	28.1	2.0	0.1
M4a	630	29.7	1.6	1.2
M4b	630	31.8	1.8	2.4
M4c	630	35.1	15.8	17.3
M5a	602	21.6	16.3	6.3
M5b	602	27.5	2.7	0.5
<b>Total</b>			46.4	32.4

**Supplementary Table 11.** Percentage of fecal metabolites of PF-04971729 in bile duct cannulated male and female Sprague Dawley rats after administration of a single 25 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Metabolite	m/z	t <sub>R</sub> (min)	Male Rats	Female Rats
PF-04971729	454	36.8	71.8	85.4
M1	470	30.2	10.4	4.0
M2	426	27.8	17.5	10.2
M7	452	39.1	0.5	0.5
<b>Total</b>			100	100

#### IV. Mass Balance Studies in Bile-duct Cannulated Dogs

**Supplementary Table 12.** Summary of mean radioactivity recovered in bile duct cannulated male dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Excretion route	Urine	Feces	Bile	Total <sup>a</sup>
<b>Time (h)</b>	<b>% of Dose</b>			
0-24	7.06	21.2	63.3	91.6
24-48	0.3	1.2	2.3	3.8
<b>Total</b>	7.4	22.4	65.6	96.1

<sup>a</sup>mean data from two dogs and includes cage wash, rinse and cage wipe.

**Supplementary Table 13.** Percentage of biliary metabolites PF-04971729 in bile-duct cannulated male beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Metabolite	m/z	t <sub>R</sub> (min)	Mean % of dose
<b>PF-04971729</b>	454	36.6	9.6
<b>M1</b>	470	30.1	3.7
<b>M2</b>	426	27.7	0.7
<b>M4b</b>	630	31.4	1.3
<b>M4c</b>	630	34.3	44.2
<b>M5a</b>	602	21.7	3.2
<b>Total</b>			63

**Supplementary Table 14.** Percentage of fecal metabolites PF-04971729 in bile-duct cannulated male beagle dogs after administration of a single 10 mg/kg oral dose of [<sup>14</sup>C]-PF-04971729

Metabolite	m/z	t <sub>R</sub> (min)	Mean % of dose
<b>PF-04971729</b>	454	36.4	21
<b>M1</b>	470	29.6	0.7
<b>M2</b>	426	27.3	0.4
<b>M4c</b>	630	36.0	0.2
<b>Total</b>			22.4