Supplemental Tables and Figures

Bioavailability, Biotransformation, and Excretion of the Covalent BTK Inhibitor Acalabrutinib in Rats, Dogs, and Humans

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Table S1

Pharmacokinetic parameters for [^{14}C]acalabrutinib and metabolites in pooled plasma samples after a single oral dose of [^{14}C]acalabrutinib to rats (100 mg/kg)

Sex	Metabolite	C_{max} (ng eq/g)	T_{max} (h)	AUC_{0-t} (ng eq•h/g)	$AUC_{0-\infty}$ (ng eq•h/g)	$t_{1/2}$ (h)	% of Profile [a]	% of Parent [b]
Male *n* = 3	M1 (ACP-5197)	1330	1	1740	NC2	NC2	4.3	38.1
	M5 (ACP-5530)	1230	1	3430	4920	2.13 [c]	8.5	75.1
	M10 (ACP-5461B)	536	1	NC1	NC2	NC2	NA	NA
	M23 (ACP-5134)	646	2	2050	NC2	NC2	5.1	44.9
	M25	NA	NA	NA	NA	NA	NA	NA
	Acalabrutinib (parent)	1790	1	4570	5380	1.35 [c]	11.3	NA
	M27 (ACP‑5862)	3510	2	23300	40400	9.61	57.4	510
	Total ^{14}C in profile	8690	1	40600	47100	3.64 [c]	NA	888
Female *n* = 3	M1 (ACP-5197)	1700	0.25	2250	3150	1.14 [c]	4.2	37.1
	M5 (ACP-5530)	4050	1	6470	NC2	NC2	12.0	107
	M10 (ACP-5461B)	2140	2	3050	NC2	NC2	5.7	50.2
	M23 (ACP-5134)	759	2	NC1	NC2	NC2	NC1	NC1
	M25	277	1	NC1	NC2	NC2	NA	NA

Acalabrutinib (parent)	4110	1	6070	11500	1.47 [c]	11.3	NA
M27 (ACP-5862)	3770	2	22600	NC2	NC2	42.1	372
Total ^{14}C in profile	17500	1	53700	57800	2.88 [c]	NA	885

Abbreviations: AUC_{0-t}, area under the concentration time curve from time 0 to the last quantifiable concentration (ng equivalent hours/g); $AUC_{0-\infty}$, area under the concentration time curve from time 0 to infinity (ng equivalent hours/g); C_{max}, maximum concentration (ng equivalent/g); NA, not applicable - entire profile not detectable; NC1, not calculated due to less than 3 available concentration values; NC2, not calculated due to the lack of a distinct elimination phase; T_{max}, time of maximum observed plasma concentration (ng equivalent/g) observed; $t_{1/2}$, terminal half-life.

[a] % of profile = (100/total ^{14}C in profile AUC_{0-t})•AUC_{0-t} of parent or metabolite.

[b] % of parent = (100/acalabrutinib AUC_{0-t})•AUC_{0-t} of metabolite or total ^{14}C in profile.

[c] C_{max} used in calculation; terminal profile may not be representative of true elimination phase.

Figure S1
Reconstructed ion chromatogram and radiochromatogram from analysis of a 1-hour pooled plasma sample obtained from male rats after a single oral administration of [^{14}C]ACP-196 (Group 1, 100 mg/kg)

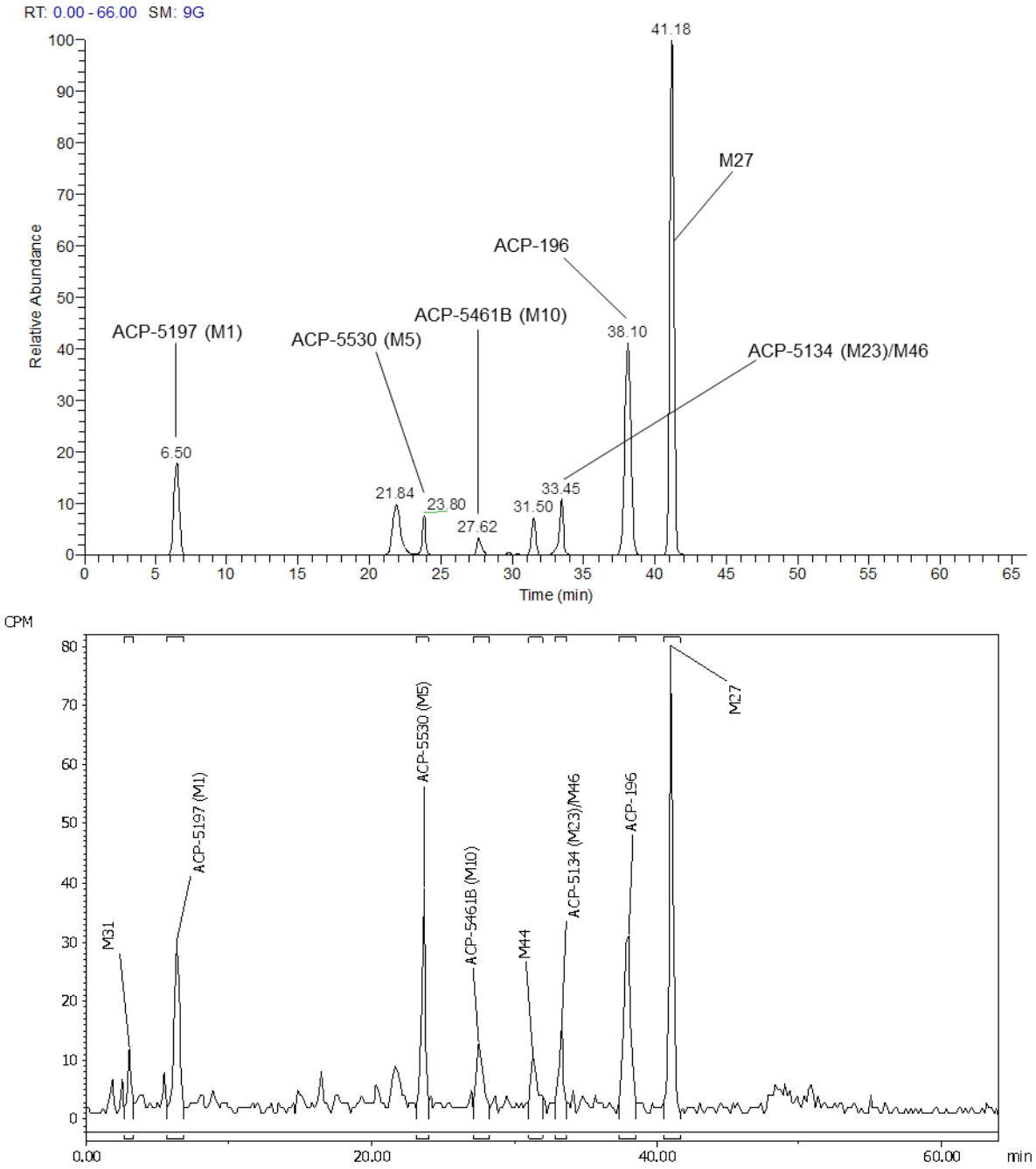

Table S2

Pharmacokinetic parameters for [^{14}C]acalabrutinib and metabolites in pooled plasma samples after a single oral dose of [^{14}C]acalabrutinib to dogs (30 mg/kg)

Sex	Component	C_{max} (ng eq/g)	T_{max} (h)	AUC_{0-t} (ng eq•h/g)	$AUC_{0-\infty}$ (ng eq•h/g)	$t_{1/2}$ (h)	% of Profile[a]	% of Parent[b]
Male	M1 (ACP-5197)	847	2	2230	4960	3.37 [c]	5.8	12.5
(*n* = 3)	M5 (ACP-5530)	644	2	1780	2400	1.59 [c]	4.6	10.0
	M7 (ACP-5531)/ M40	508	2	1580	4020	4.52 [c]	4.1	8.9
	M10 (ACP-5461B)	1890	4	7420	NC	NC	19.1	41.7
	M23 (ACP-5134)	NA	NA	NA	NA	NA	NA	NA
	M25	318	3	612	NC	NC	1.6	3.4
	Acalabrutinib (parent)	6830	1	17800	21500	1.35	45.9	NA
	M27 (ACP-5862)	797	2	2350	3620	2.13 [c]	6.1	13.2
	Total ^{14}C in profile	10400	1	38800	40000	0.92 [c]	NA	218
Female	M1 (ACP-5197)	1050	2	2720	4930 [d]	2.52 [c]	5.9	14.1
(*n* = 3)	M5 (ACP-5530)	991	1	1900	2770 [d]	1.52 [c]	4.1	9.8
	M7 (ACP-5531)/ M40	743	2	1930	2650	1.61 [c]	4.2	10.0
	M10 (ACP-5461B)	2530	3	9990	15000 [d]	2.79 [c]	21.7	51.8
	M23 (ACP-5134)	454	3	227	NC	NC	0.5	1.2
	M25	540	2	1160	NC	NC	2.5	6.0
	Acalabrutinib (parent)	8370	1	19300	21600	1.01	41.9	NA
	M27 (ACP-5862)	1310	1	3750	5780 [d]	2.10	8.1	19.4

Table S2

Pharmacokinetic parameters for [^{14}C]acalabrutinib and metabolites in pooled plasma samples after a single oral dose of [^{14}C]acalabrutinib to dogs (30 mg/kg)

Sex	Component	C_{max} (ng eq/g)	T_{max} (h)	AUC_{0-t} (ng eq•h/g)	$AUC_{0-\infty}$ (ng eq•h/g)	$t_{1/2}$ (h)	% of Profile[a]	% of Parent[b]
	Total ^{14}C in profile	13700	1	46100	48000	1.02	NA	239

Abbreviations: AUC_{0-t}, area under the concentration time curve from time 0 to the last quantifiable concentration (ng equivalent hours/g); $AUC_{0-\infty}$, area under the concentration time curve from time 0 to infinity (ng equivalent hours/g); C_{max}, maximum concentration (ng equivalent/g); NA, not applicable - entire profile not detectable; NC, not calculated due to the lack of a distinct elimination phase; T_{max}, time of maximum observed plasma concentration (ng equivalent/g) observed; $t_{1/2}$, terminal half-life.

[a] % of profile = (100/total ^{14}C in profile AUC_{0-t})•AUC_{0-t} of parent or metabolite.

[b] % of parent = (100/acalabrutinib AUC_{0-t})•AUC_{0-t} of metabolite or total ^{14}C in profile.

[c] C_{max} used in calculation; terminal profile may not be representative of true elimination phase.

[d] $AUC_{0-\infty}$% extrapolated >30%.

Figure S2
Reconstructed ion chromatogram and radiochromatogram from analysis of a 2-hour pooled plasma sample obtained from male dogs after a single oral administration of [^{14}C]ACP-196 (Group 1, 30 mg/kg)