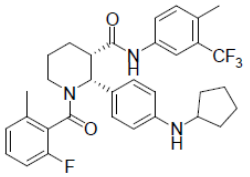
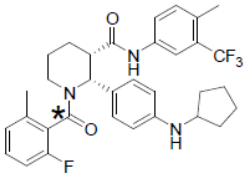
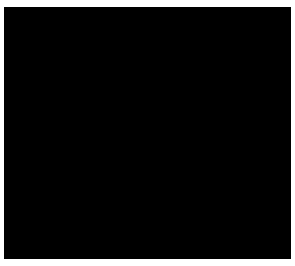
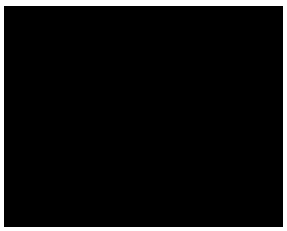
目次

2.6.4 薬物動態試験の概要文 7
2.6.4.1 まとめ 7
2.6.4.1.1 吸収 9
2.6.4.1.2 分布 10
2.6.4.1.3 代謝 10
2.6.4.1.4 排泄 10
2.6.4.1.5 薬物動態学的薬物相互作用 11
2.6.4.2 分析法 11
2.6.4.3 吸収 14
2.6.4.3.1 *In vitro* 膜透過性 14
2.6.4.3.2 *In vivo* 薬物動態試験 14
2.6.4.3.2.1 単回投与試験における薬物動態 14
2.6.4.3.2.2 単回又は反復投与試験におけるトキシコキネティクス 15
2.6.4.4 分布 16
2.6.4.4.1 血漿蛋白結合 16
2.6.4.4.2 血球移行性 17
2.6.4.4.3 組織分布 17
2.6.4.4.4 胎盤移行性 18
2.6.4.5 代謝 18
2.6.4.5.1 種差と代謝経路 18
2.6.4.6 排泄 19
2.6.4.6.1 マスバランス試験 19
2.6.4.6.2 乳汁中排泄 21
2.6.4.7 薬物動態学的薬物相互作用 21
2.6.4.7.1 CYP の阻害及び誘導能 21
2.6.4.7.2 薬物トランスポーターの阻害能及び基質性 23
2.6.4.7.3 その他の薬物相互作用 24
2.6.4.8 その他の薬物動態試験 24
2.6.4.9 考察及び結論 24
2.6.4.10 図表 25
2.6.4.11 参考文献 25

化合物一覧

略号・一般名	化学名	構造式	由来
CCX168	(2*R*,3*S*)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-*N*-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide		原薬
[^{14}C]CCX168		 ＊ signifies the position of radiolabel	[^{14}C]標識体
CCX168-M1		[redacted]	代謝物
CCX168-M3		[redacted]	代謝物
CCX168-M6		[redacted]	代謝物
CCX168-M8		[redacted]	代謝物

略号・一般名	化学名	構造式	由来
CCX168-M9			代謝物
CCX168-M10			代謝物
CCX168-M11			代謝物
CCX168-M12			代謝物
CCX168-M15			代謝物
CCX168-M16			代謝物

略号・一般名	化学名	構造式	由来
CCX168-M17			代謝物
CCX168-M18			代謝物
CCX168-M19			代謝物
CCX168-M22			代謝物
CCX168-M26			代謝物

略号一覧

略号	略していない表現	内容
[^{3}H]	Tritium labeled	水素 3 標識
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1	11β-水酸化ステロイド脱水素酵素 1 型
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2	11β-水酸化ステロイド脱水素酵素 2 型
[^{14}C]	Carbon 14 labeled	炭素 14 標識
ACE	Angiotensin converting enzyme	アンジオテンシン転換酵素
AAG	α_1-acid glycoprotein	α_1-酸性糖蛋白質
ANCA	Anti-neutrophil cytoplasmic antibody	抗好中球細胞質抗体
ARB	Angiotensin II receptor blocker	アンジオテンシン II 受容体遮断薬
AUC	Area under the curve	血漿中濃度–時間曲線下面積
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity	0 から無限大時間時間までの血漿中濃度–時間曲線下面積
(A-B)	Apical to basolateral	頂端側から側底側
(B-A)	Basolateral to apical	側底側から頂端側
BCRP	Breast cancer resistance protein	乳がん耐性蛋白質
b.i.d	Twice per day	1 日 2 回投与
BLQ	Below the limit of quantification	定量下限未満
Caco-2	human colorectal carcinoma cell line designation; used to assess membrane permeability *in vitro*	膜透過性試験に用いられるヒト結腸癌由来の細胞株
CL	Total body clearance	全身クリアランス
C_{max}	Maximum (maximal) plasma concentration	最大（最高）血漿中濃度
CYP	Cytochrome P450	シトクロム P450
DMSO	Dimethyl sulfoxide	ジメチルスルホキシド
FDA	Food and Drug Administration	米国食品医薬品局
F (%)	Bioavailability (systemic availability of the administered dose)	バイオアベイラビリティ
GLP	Good laboratory practices	医薬品の安全性に関する 非臨床試験の実施の基準
HLM	Human liver microsomes	ヒト肝ミクロソーム
H_t	Hematocrit	ヘマトクリット
HPMC	Hydroxypropyl methylcellulose	ヒドロキシプロピルメチルセルロース
hr	Hour	時間
IC_{50}	Concentration associated with 50% inhibition	50%阻害濃度
IV	Intravenous(ly); also expressed as i.v.	静脈内投与
kg	Kilogram	キログラム
$K_{B/PL}$	Whole blood-to-plasma ratio	血液/血漿比
K_I	Concentration at 50% k_{inact}	阻害定数（k_{inact} が 50%となる濃度）
k_{inact}	Rate of maximal inactivation	最大不活性化速度定数
$K_{RBC/PL}$	Red blood cell-to-plasma ratio	赤血球/血漿比
LE	Long Evans	—
LC-MS/MS	Liquid chromatography/tandem mass spectrometry	液体クロマトグラフィータンデム質量分析法
mg	Milligram	ミリグラム
mL	Milliliter	ミリリットル
MATE1	Multidrug and toxin extrusion 1	多剤及び毒素排出トランスポーター1
MATE2-K	Multidrug and toxin extrusion 2-K	多剤及び毒素排出トランスポーター2-K
min^{-1}	Per minute	毎分
MRT	Mean residence time	平均滞留時間
ng	Nanogram	ナノグラム
OAT1	Organic anion transporter 1	有機アニオントランスポーター1
OAT3	Organic anion transporter 3	有機アニオントランスポーター3
OATP1B1	Organic anion transporting polypeptide 1B1	有機アニオン輸送ポリペプチド 1B1
OATP1B3	Organic anion transporting polypeptide 1B3	有機アニオン輸送ポリペプチド 1B3

略号	略していない表現	内容
OCT2	Organic cation transporter 2	有機カチオントランスポーター2
P_{app}	Apparent permeability coefficient	見かけの透過係数
PEG-400	Polyethylene glycol 400	ポリエチレングリコール 400
MDR1/P-gp	P-glycoprotein	P-糖蛋白質
PO	Per os (orally); also expressed as p.o.	経口投与
q.d.	Once per day	1 日 1 回投与
SD	Sprague-Dawley	—
$t_{1/2}$	Elimination half-life	消失半減期
T_{max}	Time to maximum (maximal) concentration	最大血漿中濃度到達時間
TK	Toxicokinetic(s)	トキシコキネティクス
V_{ss}	Volume of distribution at steady state	定常状態の分布容積

2.6.4 薬物動態試験の概要文

2.6.4.1 まとめ

CCX168 の非臨床薬物動態（吸収、分布、代謝及び排泄）について、マウス、ラット、ハムスター、ウサギ、イヌ及びサルを用いた試験により評価した。多くの知見は CCX168 を単回又は反復経口投与した試験から得られており、投与量は反復投与毒性試験で用いられた用量範囲内であった。主な投与経路は CCX168 の臨床投与経路である経口投与であるが、静脈内投与時の薬物動態及びバイオアベイラビリティを求めるために静脈内投与も実施した。CCX168 のヒト血漿蛋白質への結合、代謝、経細胞輸送、シトクロム P450（CYP）酵素又は薬物トランスポーターが関与する薬物相互作用を評価するため、*in vitro* 試験を実施した。

非臨床薬物動態試験で用いた動物種は、マウス（CD-1）、ラット（SD 及び LE）、ハムスター（ゴールデンシリアン）、ウサギ（ニュージーランドホワイト）、イヌ（ビーグル）及びサル（カニクイ）であり、これらは毒性試験で用いた動物種であった。高用量の CCX168 を投与した血中動態試験及び排泄試験には、薬理試験及び毒性試験に用いた媒体と同一又は同様な媒体を用いた。

CCX168 及び放射性同位体標識の CCX168（[^{14}C]CCX168 又は[^{3}H]CCX168）、並びにヒト主要代謝物である CCX168-M1 の非臨床薬物動態試験概略を表 2.6.4.1-1 及び表 2.6.4.1-2 に示す。

表 2.6.4.1-1　　CCX168 の非臨床薬物動態試験

試験の種類	試験系	投与方法	投与量又は濃度	記載箇所
吸収				
In vitro 透過性	Caco-2 細胞単層膜	*In vitro*	5 µmol/L	4.2.2.2.1 PC0361_168_a
血中動態	マウス/CD-1/雌	経口 静脈内	2, 30 mg/kg 0.5 mg/kg	4.2.2.2.2 PC0366_168
	ラット/ SD/雄	経口 静脈内 経口	2, 3, 30, 100, 200, 300 mg/kg 0.5 mg/kg 500, 1000, 2000　mg/kg × 2　日	4.2.2.2.3 PC0365_168_a 4.2.2.2.4 PC0482_168 4.2.2.2.5 PC0637_168
	ラット/SD/雄及び雌	経口	100, 300 mg/kg q.d. × 7　日 50, 100, 300 mg/kg b.i.d. × 7　日	4.2.2.2.6 PC0639_168
	ハムスター/ゴールデンシリアン/雄及び雌	経口	50, 100, 300 mg/kg q.d. 50, 100 mg/kg b.i.d.	4.2.2.2.8 PC0648_168
	ウサギ/ニュージーランドホワイト/雌	経口 経口	50, 100, 200, 300, 1000 mg/kg 100 mg/kg q.d.又は 50, 100 mg/kg b.i.d.	4.2.2.2.9 PC0203_168 4.2.2.2.10 PC0658_168
	イヌ/ビーグル/雄	静脈内	0.5 mg/kg	4.2.2.2.11 PC0367_168
	サル/カニクイ/雄及び雌	経口 経鼻胃内 サル/カニクイ/雄	3～120 mg/kg 15 mg/kg q.d.又は b.i.d. 15 mg/kg	4.2.2.2.4 PC0482_168 4.2.2.2.12 PC0647_168 4.2.2.2.13 PC0653_168
		経口又は経鼻胃内		

試験の種類	試験系	投与方法	投与量又は濃度	記載箇所
分布				
蛋白結合	マウス、ラット、ハムスター、ウサギ、イヌ、サル及びヒト血漿 ヒトアルブミン ヒト AAG	*In vitro*	2.5～50 µmol/L 5, 10 µmol/L 5, 10 µmol/L	4.2.2.3.1 PC0632_168 4.2.2.3.2 PC0681_168 4.2.2.3.3 PC0685_168
組織分布	ラット/SD 及び LE/雄及び雌	経口	[^{14}C]CCX168 15 mg/kg 300 µCi/kg	4.2.2.3.4 PC0641_168
血球移行性	マウス、ラット、イヌ及びヒト血液	*In vitro*	5 µmol/L	4.2.2.3.5 PC0364_168_a
代謝				
In vitro 代謝	凍結マウス、ラット、イヌ、サル及びヒト肝細胞	*In vitro*	0.2 µmol/L	4.2.2.4.1 PC0370_168
	凍結ラット、ウサギ、イヌ、サル及びヒト肝細胞、並びにラット、ハムスター、ウサギ、サル及びヒト肝ミクロソーム（HLM）	*In vitro*	20 µmol/L [^{3}H]CCX168 1 µmol/L	4.2.2.4.2 PC0369_168 4.2.2.4.3 PC0623_168_a
	HLM 及び組換えヒト CYP	*In vitro*	1, 2 µmol/L	4.2.2.4.4 PC0373_168 4.2.2.4.5 PC0711_168
In vivo 代謝	ラット/SD/雄及び雌/無処置及び胆管カニューレ処置（BDC）	経口	[^{14}C]CCX168 15 mg/kg 300 µCi/kg	4.2.2.4.6 PC0641_168_a
	サル/カニクイ/雄及び雌	経口	[^{14}C]CCX168 15 mg/kg 100 µCi/kg	4.2.2.4.7 PC0645_168_a
排泄				
マスバランス	ラット/SD/雄及び雌/無処置及び胆管カニューレ処置（BDC）	経口	[^{14}C]CCX168 15 mg/kg 300 µCi/kg	4.2.2.3.4 PC0641_168
	サル/カニクイ/雄及び雌	経口	[^{14}C]CCX168 15 mg/kg 100 µCi/kg	4.2.2.5.1 PC0645_168
薬物相互作用				
CYP 阻害試験（競合阻害）	HLM	*In vitro*	0.04～30 µmol/L	4.2.2.6.1 PC0360_168
CYP 阻害試験（時間依存的阻害）	HLM	*In vitro*	0.025～25 µmol/L	4.2.2.6.3 PC0710_168
	HLM	*In vitro*	0.1～10 µmol/L	4.2.2.6.5 PC0622_168
CYP 誘導試験	凍結ヒト肝細胞	*In vitro*	0.03～30 µmol/L	4.2.2.6.6 PC0635_168_a
薬物トランスポーターに関する相互作用試験	薬物トランスポーターを安定発現した細胞株	*In vitro*	0.027～25 µmol/L	4.2.2.6.8 PC0712_168
11β-HSD に関する相互作用試験	HLM（11β-HSD1）及びヒト腎ミクロソーム（11β-HSD2）	*In vitro*	0.01～10 µmol/L	4.2.1.2.5 PC0469_168
プレドニゾン又はプレドニゾロンの血漿蛋白結合へ及ぼす影響	ヒト血漿	*In vitro*	1 µmol/L	4.2.2.6.9 PC0466_168

表 2.6.4.1-2　　CCX168-M1 の非臨床薬物動態試験

試験の種類	試験系	投与方法	投与量又は濃度	記載箇所
吸収				
血中動態	ラット/SD/雄	経口 静脈内	2 mg/kg 0.5 mg/kg	4.2.2.2.7 PC0633_168
分布				
蛋白結合	マウス、ラット、ハムスター、ウサギ、イヌ、サル及びヒト血漿 ヒトアルブミン ヒト AAG	*In vitro*	2.5～50 µmol/L 5, 10 µmol/L 5, 10 µmol/L	4.2.2.3.1 PC0632_168 4.2.2.3.2 PC0681_168 4.2.2.3.3 PC0685_168
血球移行率	ラット、イヌ及びヒト血液	*In vitro*	5 µmol/L	4.2.2.3.5 PC0364_168_a
代謝				
In vitro 代謝	HLM 及び組換えヒト CYP 分子種	*In vitro*	1, 2 µmol/L	4.2.2.4.5 PC0711_168
薬物相互作用				
CYP 阻害（競合）	HLM	*In vitro*	0.412～30 µmol/L	4.2.2.6.2 PC0489_168
CYP 阻害（時間依存的阻害）	HLM	*In vitro*	0.025～25 µmol/L	4.2.2.6.3 PC0710_168
	HLM	*In vitro*	1～50 µmol/L	4.2.2.6.4 PC0634_168
CYP 誘導	凍結ヒト肝細胞	*In vitro*	10 µmol/L	4.2.2.6.7 PC0491_168
薬物トランスポーターに関する相互作用試験	薬物トランスポーターを安定発現した細胞株	*In vitro*	0.0027～2 µmol/L	4.2.2.6.8 PC0712_168
11β-HSD に関する相互作用試験	HLM（11β-HSD1）及びヒト腎ミクロソーム（11β-HSD2）	*In vitro*	0.01～10 µmol/L	4.2.1.2.5 PC0469_168

2.6.4.1.1 吸収

CCX168 は、Caco-2 細胞単層膜において頂端側から側底側へ高い透過性（$P_{app(A-B)}$：25.2×10^{-6} cm/s）を示し、顕著な排出（側底側から頂端側への透過）は認められなかった。

1%ヒドロキシプロピルメチルセルロース（HPMC）を媒体とした懸濁製剤を用いて CCX168（フリー体結晶）を 2 mg/kg で単回経口投与したとき、マウス及びラットにおいて CCX168 は速やかに吸収され（T_{max}: 1 時間）、バイオアベイラビリティは低かった（それぞれ 17%及び 27%）。

一方、PEG-400/Kolliphor HS-15（PEG-400/Solutol HS-15）（[redacted], v/v）を媒体とした溶液製剤で CCX168（100 mg/kg まで）をラットに経口投与したとき、CCX168 のバイオアベイラビリティは約 50%～100%であった。

経口投与に用いる媒体を検討するため、PEG-400、Kolliphor HS-15、トウモロコシ油及びゴマ油等について、ラット、ハムスター、ウサギ及びサルの血中動態を指標に複数用量で評価した。その結果、PEG-400/Kolliphor HS-15（[redacted], v/v）を媒体とした溶液製剤を用いて CCX168 を単回又は反復経口投与したとき、最大の曝露が確認された。

長期毒性試験（13～44 週間）における CCX168 のトキシコキネティクスの結果は、ラット

を用いた短期毒性試験（1～4 週間）の結果とおおむね一致した。しかしながら、長期毒性試験の曝露量は、ハムスター（1 週間）及びカニクイザル（4 週間まで）における短期毒性試験の曝露量に比し高かった。各動物種に投与された最高用量は、ラットで 200 mg/kg/日、ハムスターで 1000 mg/kg/日、ウサギで 200 mg/kg/日、サルで 45 mg/kg/日であった。

ラット、ハムスター及びサルに CCX168 を反復経口投与したとき、C_{max} 及び AUC は投与量に比例して増加せず（曝露量の増加は投与量の増加比を下回った）、とくに 30 mg/kg/日を超える用量においては顕著であった。

ラット、ハムスター及びサルに CCX168 を反復投与したとき、全身曝露に顕著な性差は認められなかった。

2.6.4.1.2 分布

CCX168 及びヒト主要代謝物 CCX168-M1 は、マウス、ラット、ハムスター、ウサギ、イヌ、サル及びヒト血漿において 2.5～50 μmol/L の濃度範囲で可逆的に蛋白結合し（結合率：99.9%以上）、ラット、イヌ及びヒト赤血球への移行性は認められなかった。

CCX168 は可逆的にヒトアルブミン及び α_1-酸性糖蛋白質（AAG）に結合した（結合率：99.9%以上）。また、CCX168-M1 も可逆的にヒトアルブミン（結合率：99.9%）及び AAG（結合率：約 99%）に結合した。

ラットに[^{14}C]CCX168 を単回経口投与したときの組織分布から、放射能は速やかに吸収され、脂肪組織及び肝臓等に広範に分布することが示された。アルビノ（SD）及び有色（LE）ラットにおける[^{14}C]CCX168 の組織分布は、ほぼ同様であった。

2.6.4.1.3 代謝

凍結マウス、ラット、イヌ、サル及びヒト肝細胞において、CCX168 の代謝クリアランスは低～中等度であった。

CCX168 をラット、ハムスター、ウサギ、イヌ、サル及びヒトの肝細胞又は肝ミクロソームとインキュベートしたとき、主に第一相反応により生成された CCX168 の酸化代謝物が複数認められた。

ラット、サル及びヒトに[^{14}C]CCX168 を経口投与したときの代謝物検索において、CCX168 及び代謝物の CCX168-M1（一水酸化代謝物）は、いずれの動物種においても血漿中に最も多く存在した。CCX168-M1 はヒト循環血中において唯一の主要代謝物（薬物関連物質の総曝露量に対し 10%超）であったが、ラット、ハムスター及びサルの毒性試験において十分な曝露量が確認された。

ヒト肝ミクロソーム及び組換えヒト CYP を用いた代謝酵素同定試験の結果、CYP3A4 が CCX168 の代謝クリアランス及び CCX168-M1 生成に主に寄与していると考えられた。

2.6.4.1.4 排泄

ラット、サル及びヒトに[^{14}C]CCX168 を経口投与し、マスバランス（物質収支）を評価した。ラット及びヒトにおける投与放射能の回収率はそれぞれ約 97%～98%及び約 87%であったが、サルにおける回収率は投与媒体の構成成分である PEG-400 により下痢が生じたため約 71%～72%であった。いずれの動物種においても、放射能の大部分は主に第一相反応による代謝物として糞中に回収されたが、尿中排泄はわずかであった。これらの結果から、CCX168 は良好に

吸収され、CCX168 の主な消失経路は第一相反応による酸化代謝とそれに続く代謝物の胆汁排泄であると考えられた。

2.6.4.1.5 薬物動態学的薬物相互作用

In vitro 試験の結果から CCX168 及び CCX168-M1 は、低～中等度の時間依存的な CYP3A4 阻害作用又は中等度の CYP3A4 誘導能を有するため、CYP に関連した薬物相互作用を惹起する可能性があると考えられた。

臨床薬物相互作用試験（CL008_168、2.7.2）において、CCX168 及び CCX168-M1 は、併用薬物の曝露量を顕著に変化させるような CYP の阻害又は誘導に起因した薬物相互作用を惹起しなかった。一方、CCX168 及び CCX168-M1 の血中曝露量は、強い CYP3A4 誘導薬との併用により減少し、強い CYP3A4 阻害薬との併用により程度は低いが増加した。

CCX168 はヒト MDR1/P-gp 及び BCRP の基質ではなかった。CCX168-M1 は BCRP の基質ではなかったが、MDR1/P-gp の基質であった。CCX168 及び CCX168-M1 は、肝トランスポーターである OATP1B1 又は OATP1B3 の基質ではなかった。

In vitro 薬物トランスポーター阻害試験の結果から、CCX168 及び CCX168-M1 は重要な薬物トランスポーターの典型基質輸送に影響を与えず、薬物相互作用の可能性は低いと考えられた。

2.6.4.2 分析法

純度 98%以上の CCX168、純度 99%超の代謝物 CCX168-M1 及び CCX168-[redacted]、並びに純度 99%超の重水素標識の内標準物質（CCX168-d4）を、濃度分析法バリデーション試験又は生体内試料の測定に用いた。

CCX168 及び代謝物の血中動態を評価するため、放射能測定の場合を除き液体クロマトグラフィータンデム型質量分析法（LC-MS/MS）により、CCX168 及び代謝物の血漿中濃度を測定した。薬理試験、薬物動態試験、GLP 非適用のトキシコキネティクス試験及び *in vitro* 薬物動態試験では、LC-MS/MS 法を用いた濃度分析を行った。

ラット、ハムスター、ウサギ及びサルを用いた各種 GLP 毒性試験において、CCX168、CCX168-M1 及び CCX168-[redacted] の曝露量評価では、血漿試料を除蛋白質処理し LC-MS/MS による濃度分析を行った（表 2.6.4.2-1）。これらの濃度分析法については信頼性が検証されており、検量線範囲は、CCX168 では 1～1000 ng/mL 又は 2～2000 ng/mL、CCX168-M1 及び CCX168-[redacted] では 1～1000 ng/mL であった。検証されたすべての CCX168 及び CCX168-M1 の濃度分析法では、生体試料中濃度分析法に関する FDA ガイダンス [1)]に従った精度及び真度が確認されている。検量線及び既知濃度試料（QC）の分析結果は良好であった。また、すべての濃度分析法において、明らかな分析への妨害は認められず良好な選択性が確認され、かつ試料調製中及び保管条件における分析対象物質の安定性が確認されている。加えて、これらの濃度分析法には、実試料の再測定（ISR）を行った結果からも再現性が確認されている。各分析法の詳細は、2.6.5　表 2.6.5.2.1～2.6.5.2.7 に記載した。

[^{14}C]CCX168 を投与し採取した生体試料及び組織中の放射能は、必要に応じて試料の燃焼処理を行い、液体シンチレーションカウンターを用いて測定した。[^{14}C]CCX168 又は[^{3}H]CCX168 を用いた CCX168 の代謝物検索では、放射能検出器付き HPLC を用いて試料の分析を行った。

表 2.6.4.2-1　　生体試料濃度分析法のバリデーション試験及びその測定法を用いた毒性試験の一覧

Method Validation Report		[redacted]	Type of Method	Species/Sample Matrix	Analytes	Quantification Range	Location or Toxicology/TK Reports Using the Method**	Type of Toxicology Study	Treatment Duration (Days/Weeks)
Location or ChemoCentryx Report No.*	CRO-[redacted] Study ID	Method ID							
4.2.2.1.1 PC0362_168 PC0362_168_a	[redacted]223	[redacted]	LC-MS/MS	Rat/plasma	CCX168	1–1000 ng/mL	4.2.3.2.1 PC0384_168 4.2.3.2.2 PC0356_168	Repeat-Dose Toxicity	13 Weeks 4 Weeks
4.2.2.1.2 PC0650_168	[redacted]655	[redacted]	LC-MS/MS	Rat/plasma	CCX168, CCX168-M1 and CCX168-[redacted]	2–2000 ng/mL (CCX168); 1–1000 ng/mL (CCX168-M1 and CCX168-[redacted])	4.2.3.2.3 PC0655_168	Repeat-Dose Toxicity	26 Weeks
4.2.2.1.3 PC0652_168 PC0652_168_a	[redacted]719	[redacted]	LC-MS/MS	Hamster/plasma	CCX168, CCX168-M1 and CCX168-[redacted]	2–2000 ng/mL (CCX168); 1–1000 ng/mL (CCX168-M1 and CCX168-[redacted])	4.2.3.5.2.4 PC0667_168 4.2.3.5.2.1 PC0671_168 4.2.3.5.3.1 PC0673_168	Reproductive & Developmental Toxicity	GD 6 through 12 GD 6 through 12 GD 6 through Day 20 Postpartum
							4.2.3.2.4 PC0677_168 PC0677_168_a	Repeat-Dose Toxicity	13 Weeks
4.2.2.1.4 PC0651_168 PC0651_168_a	[redacted]721	[redacted]	LC-MS/MS	Rabbit/plasma	CCX168, CCX168-M1 and CCX168-[redacted]	1–1000 ng/mL	4.2.3.5.2.5 PC0666_168 4.2.3.5.2.2 PC0672_168	Reproductive & Developmental Toxicity	Dose Range-Finding GD 6 through 18 (Segment II)

Method Validation Report		[redacted] Method ID	Type of Method	Species/Sample Matrix	Analytes	Quantification Range	Location or Toxicology/TK Reports Using the Method**	Type of Toxicology Study	Treatment Duration (Days/Weeks)
Location or ChemoCentryx Report No.*	CRO-[redacted] Study ID								
4.2.2.1.5 PC0363_168 PC0363_168_a	[redacted]220	[redacted]	LC-MS/MS	Cynomolgus monkey/plasma	CCX168	1–1000 ng/mL	4.2.3.2.6 PC0357_168 PC0357_168_a 4.2.3.2.5 PC0385_168	Repeat-Dose Toxicity	20 Weeks 4 Weeks
4.2.2.1.6 PC0649_168 PC0649_168_a	[redacted]009	[redacted]	LC-MS/MS	Cynomolgus monkey/plasma	CCX168, CCX168-M1 and CCX168-[redacted]	1–1000 ng/mL	4.2.3.2.7 PC0654_168	Repeat-Dose Toxicity	44 Weeks

*「_a」が付されている試験番号は、試験報告書の追補であることを示す。
**「_a」が付されている試験番号は、試験報告書の訂正版（TK データを含む）であることを示す。
GD：妊娠日数；Location：記載箇所

2.6.4.3 吸収

CCX168 の吸収は、Caco-2 細胞単層膜を用いた *in vitro* 試験並びにマウス、ラット、ハムスター、ウサギ及びサルにおける *in vivo* 試験で評価した。CCX168 は、Caco-2 細胞単層膜において頂端側から側底側へ高い透過性（$P_{app(A-B)}$：25.2 × 10^{-6} cm/s）を示し、排出トランスポーターの基質ではないと考えられた（表 2.6.4.3.1-1）。動物において、懸濁製剤として経口投与した場合には CCX168 のバイオアベイラビリティは低かったが（17%～27%、表 2.6.4.3.2.1-1）、PEG-400/Kolliphor HS-15（[redacted], v/v）を媒体とした溶液製剤を 100 mg/kg までの用量でラットに経口投与したときにはバイオアベイラビリティは高かった（約 50%～100%、PC0365_168_a）。ラット排泄試験の結果から（尿及び糞中に排泄された総放射能から糞中への未変化体排泄量を減じた）、[^{14}C]CCX168（15 mg/kg）を単回経口投与したときのラットにおける放射能の吸収率を約 80%と推察した（PC0641_168_a）。CCX168 を反復投与したときの血中動態は、ラット、ハムスター、ウサギ及びサルを用いた毒性試験において評価した。毒性試験から得られた反復投与時のトキシコキネティクス（TK）の要約を 2.6.7 に示す。

2.6.4.3.1 *In vitro* 膜透過性

添付資料 4.2.2.2.1

Caco-2 細胞単層膜における CCX168（最終濃度 5 μmol/L）の膜透過性について、37°C で保温した緩衝液（pH 7.4）中で、頂端側から側底側（A-B）方向及び側底側から頂端側（B-A）方向の透過性を評価した（PC0361_168_a）。CCX168 の見かけの透過係数（P_{app}）を対照物質（アンチピリン及びロペラミド）の P_{app} と比較した（表 2.6.4.3.1-1）。CCX168 は、Caco-2 細胞単層膜において高い透過性（$P_{app\,(A-B)}$：25.2 × 10^{-6} cm/s；$P_{app\,(B-A)}$：27.3 × 10^{-6} cm/s）を示し、その排出比（1.08）から排出トランスポーターの基質ではないと考えられた。

表 2.6.4.3.1-1　　Caco-2 細胞単層膜における CCX168 の透過性

	CCX168	Antipyrine	Loperamide
$P_{app\,(A-B)}$ (× 10^{-6} cm/s)	25.2	50.4	11.4
$P_{app\,(B-A)}$ (× 10^{-6} cm/s)	27.3	24.0	33.2
Efflux ratio (B-A / A-B)	1.08	0.48	2.91

試験番号：PC0361_168_a

2.6.4.3.2 *In vivo* 薬物動態試験

2.6.4.3.2.1 単回投与試験における薬物動態

添付資料 4.2.2.2.2、4.2.2.2.3、4.2.2.2.4、4.2.2.2.9、4.2.2.2.11、4.2.2.2.13

CCX168 の薬物動態を明らかにするため、雌マウス（PC0366_168）、雄 SD ラット（PC0365_168_a）、雄イヌ（PC0367_168）及び雄ザル（PC0653_168）に CCX168 を単回経口及び静脈内投与した。各動物種及び投与経路における薬物動態パラメータを表 2.6.4.3.2.1-1 に示す。

表 2.6.4.3.2.1-1　マウス、ラット、イヌ及びサルに CCX168 を単回投与したときの薬物動態パラメータ

Parameter	Mouse (PC0366_168)	Rat (PC0365_168_a*)	Dog (PC0367_168)	Monkey (PC0653_168)
IV dose (mg/kg)	0.5[a]	0.5[b]	0.5[c]	ND
N	9[d]	2[e]	3[e]	—
AUC (ng•hr/mL)	343	397	711	—
MRT (hr)	0.9	1.4	6.4	—
CL (mL/min/kg)	26.6	21.2	11.9	—
$t_{1/2}$ (hr)	1.8	1.9	14.2	—
Vd_{ss} (L/kg)	1.5	1.8	4.7	—
PO dose (mg/kg)	2[f]	2[f]	ND	15[g]
N	9[d]	2[e]	—	3[e]
C_{max} (ng/mL)	75	152	—	815
$AUC_{0-\infty}$ (ng•hr/mL)	240	434	—	8840
MRT (hr)	4.0	2.7	—	7.5
$t_{1/2}$ (hr)	2.9	2.3	—	4.5
T_{max} (hr)	1.0	1.0	—	5.3
F (%)	17	27	—	—

[a] 投与製剤：0.1 mg/mL CCX168（フリー体結晶）；投与媒体 N,N-ジメチルアセタミド/エタノール/ポリエチレングリコール/0.9% 生理食塩液（[redacted], v/v/v/v）
[b] 投与製剤：0.5 mg/mL CCX168（フリー体結晶）；投与媒体 N,N-ジメチルアセタミド/エタノール/ポリエチレングリコール（[redacted], v/v/v）
[c] 投与製剤：0.5 mg/mL CCX168（フリー体結晶）；投与媒体 N,N-ジメチルアセタミド/水/プロピレングリコール（[redacted], v/v/v）
[d] 各時点の採血は 9 例中 3 例ずつ交代で行われ、各時点の平均濃度を一連の血中動態とした。
[e] PK parameters reported as the group means.
[f] 投与製剤：0.4 mg/mL CCX168（フリー体結晶）；投与媒体 1%ヒドロキシプロピルメチルセルロース水溶液
[g] 投与製剤：15 mg/mL CCX168（フリー体結晶）；投与媒体 PEG-400/Kolliphor HS-15 ([redacted], v/v).
*「_a」が付されている試験番号は、試験報告書の訂正版であることを示す。
ND：未実施

マウス、ラット及びイヌに単回静脈内投与したとき、CCX168 の全身クリアランスは中等度（肝血流量の 41%～59%、PC0364_168）であり、分布容積は大きかった（1.5～4.7 L/kg；表 2.6.4.3.2.1-1）。消失半減期は、マウス及びラットでは短く（約 2 時間）、イヌでは長かった（14.2 時間）。CCX168（フリー体結晶）を HPMC 水溶液に懸濁し 2 mg/kg の用量で経口投与したとき、CCX168 はマウス及びラットにおいて速やかに吸収され（T_{max}：1 時間）、バイオアベイラビリティは低かった（それぞれ 17%及び 27%）。PEG-400/Kolliphor HS-15（[redacted], v/v）を媒体とし CCX168 溶液として経口投与したとき、ラットにおいて 100 mg/kg までの用量でバイオアベイラビリティ（約 60%～100%）は良好であった（PC0365_168_a）。経口投与に用いる媒体を探索するため、PEG-400、Kolliphor HS-15、トウモロコシ油及びゴマ油等を媒体として用い、複数用量でラット及びサルの血中動態を評価した。経口投与における CCX168 の最大曝露は、PEG-400/Kolliphor HS-15（[redacted], v/v）を媒体とし溶液製剤としたときに確認された（PC0482_168）。ウサギにおいても 100 mg/kg の CCX168 を PEG-400/Kolliphor HS-15（[redacted], v/v）の溶液製剤として経口投与したときに最大曝露量（AUC：4300 ng•hr/mL、C_{max}：727 ng/mL）が確認された（PC0203_168）。

2.6.4.3.2.2 単回又は反復投与試験におけるトキシコキネティクス

添付資料 4.2.2.2.6、4.2.2.2.8、4.2.2.2.12、4.2.3.2.7

毒性試験の投与量を設定するために、SD ラット、ハムスター、ウサギ及びサルを用いた単回又は反復投与試験を実施した（表 2.6.4.1-1）。CCX168 を PEG-400/Kolliphor HS-15

([redacted], v/v）の溶液製剤として、ラットに 100 mg/kg を 1 日 2 回反復経口投与したとき、7 日目に CCX168 及び CCX168-M1 の最大曝露（$AUC_{0\text{-}24hr}$：それぞれ 122000 及び 17500 ng•hr/mL）が認められた（PC0639_168）。ハムスターに CCX168 を PEG-400/Kolliphor HS-15（[redacted], v/v）の溶液製剤として、100 mg/kg（100 mg/kg を 1 日 1 回又は 50 mg/kg を 1 日 2 回）を経口投与したとき、CCX168 の最大曝露（100 mg/kg q.d.：$AUC_{0\text{-}24hr}$ 39900 ng•hr/mL、C_{max} 4490 ng/mL；50 mg/kg b.i.d.：$AUC_{0\text{-}24hr}$ 42700 ng•hr/mL、C_{max} 5600 ng/mL）が認められた（PC0648_168）。ウサギに 100 mg/kg を経口投与したとき（上記と同じ溶液製剤を用いて 100 mg/kg を 1 日 1 回又は 50 mg/kg を 1 日 2 回）、CCX168、CCX168-M1 及び CCX168-[redacted] の最大曝露が認められた（PC0658_168）。また、CCX168 を PEG-400/Kolliphor HS-15（[redacted], v/v）の溶液製剤として、サルに 15 mg/kg を 1 日 2 回投与したときの CCX168 及び CCX168-M1 の曝露量（AUC）は、同用量を 1 日 1 回投与したときと比較して高値であった。反復投与毒性試験におけるサルの最大曝露量は、CCX168 を 1 mL/kg の溶液製剤として 15/22.5 mg/kg の用量で 1 日 2 回投与したときに認められた（PC0647_168 及び PC0654_168）。

ラット、ハムスター、ウサギ及びサルにおける TK 試験及びその TK パラメータの概要を 2.6.7 に示した。曝露量、用量依存性、投与期間における蓄積性及び性差については、2.6.6 に記載した。ラット、ハムスター及びサルを用いた反復投与毒性試験における無毒性量での代表的な TK データの概要を、2.6.5.4 に示した。

ラットにおける長期毒性試験（13 週間以上）で得られた TK 成績（平均の C_{max} 及び AUC）は、同様の投与量での短期毒性試験（4 週間以下）の成績とおおむね一致した（2 倍以内）。ハムスター及びサルでは、長期毒性試験における平均の C_{max} 及び AUC は、同様の投与量での短期毒性試験と比較し 3～10 倍高かった。

各動物種を用いた反復投与毒性試験における最高用量は、ラットでは 200 mg/kg/日、ハムスターでは 1000 mg/kg/日、ウサギでは 200 mg/kg/日及びサルでは 45 mg/kg/日であった。

ラット、ハムスター及びサルに CCX168 を反復経口投与したとき、CCX168 の C_{max} 及び AUC の増加は投与量に比例せず（曝露量の増加は投与量の増加比を下回った）、特に 30 mg/kg/日を超える投与量では顕著であった。また、CCX168-M1 についても同様の傾向が認められた。

ラット、ハムスター及びサルに CCX168 を反復経口投与したとき、CCX168 の全身曝露量に顕著な性差は認められなかった。また、CCX168-M1 についても同様の傾向が認められた。

2.6.4.4 分布

2.6.4.4.1 血漿蛋白結合

添付資料 4.2.2.3.1、4.2.2.3.2、4.2.2.3.3

CCX168 及びヒト主要代謝物である CCX168-M1 の血漿蛋白結合率を、マウス、ラット、ハムスター、ウサギ、イヌ、サル及びヒト血漿を用いて平衡透析法により求めた（PC0632_168）。評価した 7 動物種すべての血漿において、CCX168 及び CCX168-M1 はいずれも、2.5～50 µmol/L の濃度範囲で可逆的に蛋白結合した（結合率：99.9%以上）。また、非結合形分率は 0.1%未満であった（PC0632_168）。ヒトアルブミン及び α_1-酸性糖蛋白質（AAG）に対し CCX168（5 及び 10 µmol/L）は可逆的に結合し、いずれも結合率は 99.9%超であった。また、

CCX168-M1（5 及び 10 µmol/L）もヒトアルブミン及び AAG に対して可逆的に結合し、それぞれ結合率は 99.9%及び約 99%であった（PC0681_168 及び PC0685_168)。

2.6.4.4.2 血球移行性

添付資料 4.2.2.3.5

CCX168 及びヒト主要代謝物である CCX168-M1 の赤血球への移行性を、マウス（CCX168 のみ）、ラット、イヌ及びヒト血液及び血漿を用いて評価した（PC0364_168_a）。赤血球/血漿（$K_{RBC/PL}$）比及び血液/血漿（$K_{B/PL}$）比を表 2.6.4.4.2-1 に示した。いずれの動物種においても、CCX168 及び CCX168-M1 の赤血球へ移行はわずかであったことから、CCX168 及び CCX168-M1 は赤血球へほぼ移行しないと考えられた。

表 2.6.4.4.2-1　CCX168 及び CCX168-M1 の赤血球/血漿比（$K_{RBC/PL}$）及び血液/血漿比（$K_{B/PL}$）

CCX168			
	H_t (Hematocrit)	$K_{RBC/PL}$	$K_{B/PL}$
Mouse	0.51	0.45	0.72
Rat	0.55	0.60	0.78
Dog	0.47	0.27	0.66
Human	0.52	0.42	0.70
CCX168-M1			
	H_t (Hematocrit)	$K_{RBC/PL}$	$K_{B/PL}$
Rat	0.30	0.76	0.93
Dog	0.48	0.37	0.70
Human	0.47	0.30	0.67

試験番号：PC0364_168_a

2.6.4.4.3 組織分布

添付資料 4.2.2.3.4

CCX168 の組織分布をラットにおいて評価した。組織分布の概要は 2.6.5（表 2.6.5.5.1～2.6.5.5.4）に示した。ラットに 15 mg/kg の[^{14}C]CCX168 を単回経口投与したとき、放射能は速やかに大部分の組織及び臓器に広範に分布した（PC0641_168)。アルビノ（SD）ラット及び有色（LE）ラットにおける組織分布は、ほぼ同様であった。

雌雄のアルビノラットにおいて放射能が高濃度に分布した組織は、褐色脂肪、肝臓、白色脂肪、副腎、膀胱（雄)、ハーダー腺（雄)、包皮腺（雄)、膵臓（雌)、心筋（雌）及び唾液腺（雌）であった。雌雄の有色ラットにおいて放射能が高濃度に分布した組織は、褐色脂肪、肝臓、白色脂肪、副腎、ハーダー腺、膵臓、腎臓及び腎臓髄質/皮質（雄)、盲腸（雌）及び小腸（雌）であった。

雌雄有色ラットでは、ほとんどの組織において放射能濃度は投与後 4 又は 8 時間に最高値に達し、ほぼ同様に投与後 336 時間までに定量下限未満（BLQ）に低下した。投与後 336 時間に低濃度の放射能が検出された組織は、副腎、血液、ブドウ膜、脂肪、腎臓、肝臓、包皮腺、脾臓、皮膚（有色及び非有色)、小腸、子宮及び心筋であった。また、投与後 336 時間におけるこれら組織の放射能濃度は、T_{max} における放射能と比較して明らかに低かった。投与後 8～336 時間では、白色脂肪における[^{14}C]CCX168 の放射能濃度は、その他多くの組織に比べて高かった。

脳及び脊髄に低い放射能が検出されたが、投与後 24～72 時間までに BLQ に低下したことから、中枢神経系組織への分布は限定的であると考えられた。雄のアルビノ及び有色ラットの精巣においても低い放射能が検出され、投与後 24～72 時間までに BLQ に低下した。雌のアルビノ及び有色ラットの卵巣及び子宮において低～中等度の放射能が検出され、投与後 3 日では約 1/4～1/2 に減少した。その後、有色ラットにおいては、これら 2 つの臓器の放射能はさらに減少した（約 1/25～1/10 未満）。有色組織であるブドウ膜への分布傾向から、[^{14}C]CCX168 由来の放射能が眼のメラニン含有組織への親和性を有することが示唆された。この分布は緩徐であり可逆的であると考えられた。また、放射能の総曝露量は、他の非メラニン含有組織と比較して低～中等度であった。アルビノラット及び有色ラットの皮膚における放射能分布は同程度であり、それぞれ投与後 72 時間及び 336 時間までは測定可能であった。ただし、雄有色ラットでは投与後 336 時間の放射能は BLQ であった。皮膚における放射能の総曝露量は、他の非メラニン含有組織と比較して中等度であった。有色ラットにおいて、有色及び非有色皮膚からの放射能の消失は同程度であり、[^{14}C]CCX168 由来の放射能は外皮メラニンに対し親和性を示さないと考えられた。

2.6.4.4.4 胎盤移行性

添付資料 4.2.3.5.2.1、4.2.3.5.2.2

CCX168 の胎盤移行性については評価していない。しかしながら、ハムスター及びウサギを用いた胚・胎児発生に関する試験において、催奇形性は認められなかった（PC0671_168 及び PC0672_168）。

2.6.4.5 代謝

2.6.4.5.1 種差と代謝経路

添付資料 4.2.1.1.5、4.2.2.4.1、4.2.2.4.2、4.2.2.4.3、4.2.2.4.4、4.2.2.4.5、4.2.2.4.6、4.2.2.4.7、4.2.3.2.3、4.2.3.2.4、4.2.3.2.7、4.2.3.5.2.4、4.2.3.5.2.1、4.2.3.5.3.1、4.2.3.5.2.5

CCX168 を凍結保存したマウス、ラット、イヌ、サル及びヒト肝細胞とインキュベートしたとき、CCX168 の代謝クリアランスは、低～中等度（10.9～45.3 μL/10^{6}cells/min）であった（PC0370_168）。

ラット、ハムスター、ウサギ、イヌ、サル及びヒトから調製された肝細胞又は肝ミクロソームと CCX168 をインキュベートしたとき、CCX168 の代謝物が複数生成し、それらは主に第一相反応による代謝物であった（PC0369_168 及び PC0623_168_a）。最も多く生成した代謝物の 1 つは、CCX168 のメチル基が水酸化された CCX168-M1 であった（PC0623_168_a）。

ラット（PC0641_168_a）、サル（PC0645_168_a）及びヒト（CL004_168_MetID）に[^{14}C]CCX168 を経口投与し代謝物検索を行った結果、いずれの動物種においても血漿中で最も CCX168 及び CCX168-M1 が多かった。CCX168-M1 は、ヒト循環血中において唯一の主要代謝物（薬物関連物質の総曝露量に対し 10%超）であった。CCX168-M1 はヒト C5a 受容体に対し CCX168 とほぼ同等の薬理作用を有するが（PC0463_168_a）、ラット、ハムスター及びサルの毒性試験において十分な曝露が確認されている（2.6.7）。認められたほとんどの代謝物（CCX168-M1 を含む）は、CCX168 の酸化代謝物であった。

CCX168-[redacted] はヒトでは[redacted]代謝物であるが、原薬に含まれる[redacted]不純

物であるため、反復投与毒性試験（SD ラット：PC0655_168、ハムスター：PC0677_168、サル：PC0654_168）及び生殖発生毒性試験（ハムスター：PC0667_168、PC0671_168 及び PC0673_168、ウサギ：PC0666_168）等の非臨床毒性試験で評価された。CCX168-[redacted] の安全性評価の詳細については、2.6.6 に示した。

CCX168 から CCX168-M1 生成までの代謝経路について、ヒト肝ミクロソーム及び組換えヒト CYP 分子種を用いて検討した結果、CCX168-M1 生成に CYP3A4 が主に関与し、次いで CYP2D6 及び CYP2C19 も寄与する可能性があると考えられた（図 2.6.4.5.1-1、PC0373_168 及び PC0711_168）。

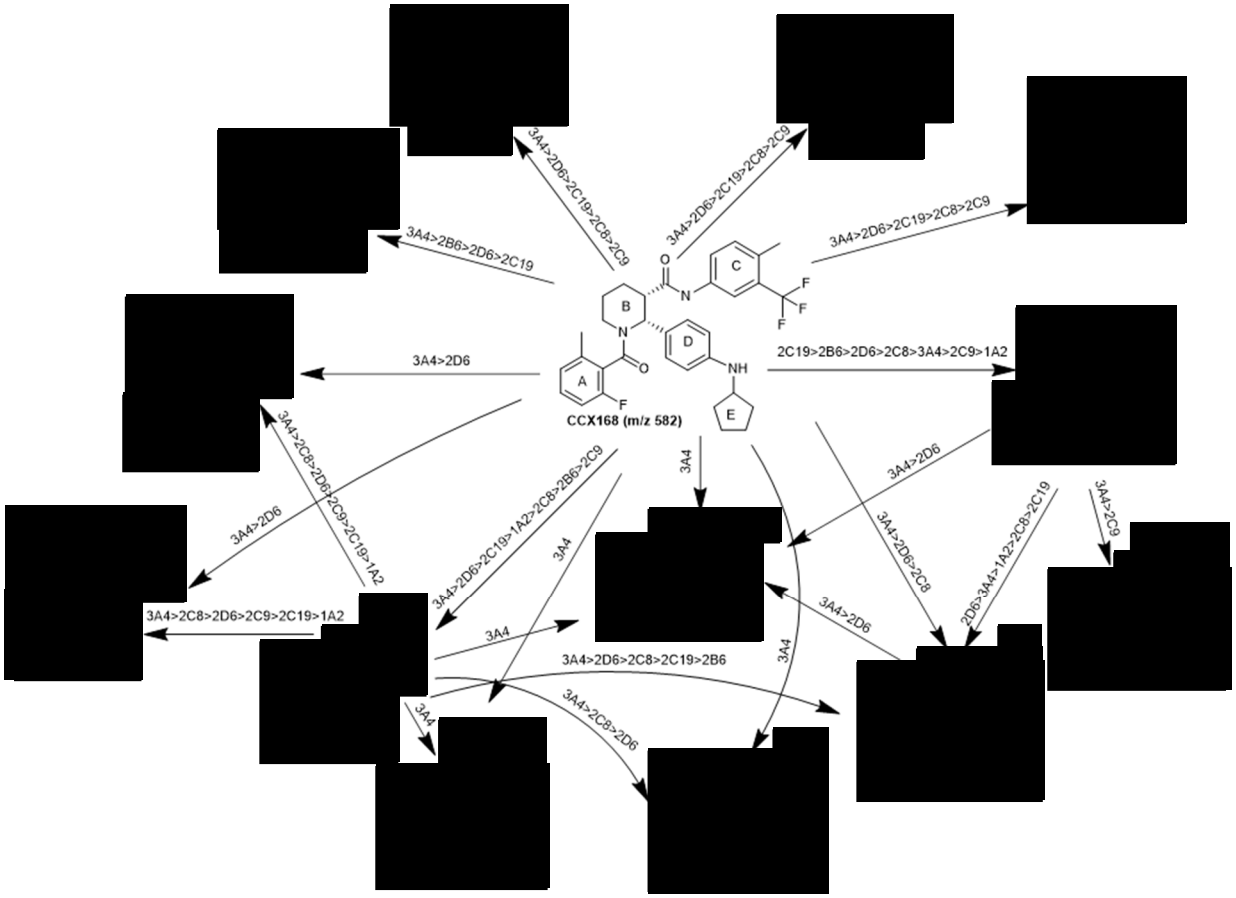


図 2.6.4.5.1-1　　CCX168 の推定代謝経路

[redacted]

2.6.4.6 排泄

2.6.4.6.1 マスバランス試験

添付資料 4.2.2.3.4、4.2.2.5.1、

SD ラット（PC0641_168）、サル（PC0645_168）及びヒト（CL004_168）に、それぞれ 15 mg/kg、15 mg/kg 及び 100 mg の[^{14}C]CCX168 を単回経口投与したときのマスバランス（物質収支）及び排泄を評価し、これらの結果を表 2.6.4.6.1-1 に示した。これらの動物種において、排泄物中に約 71%～98%の投与放射能が回収され、ほとんどの放射能が糞中に回収された。

ラットのマスバランス試験（PC0641_168）において、[^{14}C]CCX168 を経口投与し投与後 168 時間までに排泄された放射能の回収率は、雄ラットでは 97.1%であり、雌ラットでは 97.7%であった。投与した放射能の主な排泄経路は糞中排泄であり、雄及び雌ラットでそれぞれ投与量の 92.6%及び 96.1%が糞中に排泄された。投与した放射能の尿中排泄率はわずかであり、投与量の 2.71%（雄ラット）及び 1.05%（雌ラット）が尿へ排泄された。ラットの尿糞及び胆汁試料を用いた代謝物検索試験の結果から、未変化体 CCX168 の尿又は胆汁中への排泄はわずか（2%未満）であった。

サルのマスバランス試験（PC0645_168）では、すべての試料から収集した投与放射能の回収率は、雄ザルで 71.0%、雌ザルで 72.1%であった。投与媒体中の PEG-400 に起因する下痢により、ケージのすすぎ液、残屑、洗浄液及び拭取り中に、投与した放射能が異常に高い割合で回収された（雄ザル：38.1%、雌ザル：35.5%）。下痢により代謝ケージ及び動物被毛に放射能が付着し回収不足となった可能性が高いため、実際の放射能の回収率は観察された約 71%～72%よりも高いと考えられた。糞中排泄率は、投与放射能の 29.1%（雄ザル）及び 24.8%（雌ザル）であった。ケージ内で回収された放射能（約 36%～38%）は液状便由来であると考えられ、実際の糞中排泄率は高く、投与放射能の 60%超であったと推察された。尿中排泄率は投与放射能の 3.78%（雄ザル）及び 4.31%（雌ザル）であり、わずかであった。

健康成人に[^{14}C]CCX168 を経口投与したときのマスバランス試験（CL004_168）では、ほぼすべての投与放射能が回収された（86.7%）。投与放射能のほとんどが糞中に排泄され（77.2%）、尿中への排泄はわずかであった（9.5%）。排泄物中の放射能はほとんどが代謝物であり、未変化体 CCX168 の排泄はわずかであった。ヒト排泄物試料の代謝物検索の結果から、未変化体 CCX168 の尿又は胆汁中への排泄はわずかであること（10%未満）が示された（CL004_168_MetID）。

いずれの動物種においても投与された放射能の大部分は糞中に排泄され、尿中排泄率はわずかであった。代謝物検索試験の結果から、吸収された CCX168 の主要な消失経路は第一相反応による代謝とそれに続く胆汁排泄であり、未変化体 CCX168 の胆汁及び尿中排泄は寄与の小さい消失経路であると考えられた。

表 2.6.4.6.1-1　ラット、サル及びヒトにおける[^{14}C]CCX168 のマスバランス試験（排泄物における投与放射能の回収率）

Route	Intact Rats (PC0641_168)		Bile Duct-Cannulated Rats (PC0641_168)		Cynomolgus Monkey (PC0645_168)		Human (CL004_168)
	Male (N=3)	Female (N=3)	Male (N=3)	Female (N=3)	Male (N=3)	Female (N=3)	Male (N=6)
Urine	2.71	1.05	0.940	1.04	3.78	4.31[a]	9.5
Feces	92.6	96.1	62.7	70.9	29.1	24.8	77.2
Bile	—	—	27.2	24.6	—	—	—
Recovered in Cage[b]	1.83	0.588	2.73	0.615	38.1	35.5	—
Total Eliminated Radioactivity[c]	97.1	97.7	93.9	97.3	71.0	72.1	86.7

[a] 2 例の平均値；下痢により 1 例は外れ値（26.9%）とした。なお、この外れ値は総放射能排泄率の算出に含めた。
[b] カニクイザルは投与媒体成分の PEG-400 により下痢を呈したため、多くの放射能が代謝ケージから回収された。代謝ケージから回収された放射能を、総放射能排泄率の算出に含めた。
[c] 動物：尿、糞、（胆汁）、呼気及びケージからの回収率；ヒト：尿及び糞からの回収率

2.6.4.6.2 乳汁中排泄

添付資料 4.2.3.5.3.1

CCX168 の乳汁中への排泄は評価していない。しかしながら、ハムスターにおける生殖発生毒性試験において、CCX168 を経口投与した分娩後 15 日目の母動物及びその出生児の血漿中 CCX168 濃度を測定した結果、いずれの血漿中にも CCX168 の存在が確認された。したがって、CCX168 は授乳ハムスターの乳汁中へ移行する可能性が高いと考えられた（PC0673_168）。

2.6.4.7 薬物動態学的薬物相互作用

2.6.4.7.1 CYP の阻害及び誘導能

添付資料 4.2.2.4.4、4.2.2.4.5、4.2.2.6.1、4.2.2.6.2、4.2.2.6.3、4.2.2.6.4、4.2.2.6.5、4.2.2.6.6、4.2.2.6.7

CCX168 及び CCX168-M1 の CYP 活性に対する直接阻害作用を評価するため、ヒト肝ミクロソームを用いて各 CYP 分子種（CYP1A2、2B6、2C8、2C9、2C19、2D6 及び 3A4）の典型基質代謝の阻害を定量評価した（PC0360_168 及び PC0489_168）。CCX168 及び CCX168-M1 の CYP 活性に対する直接阻害作用（IC_{50} 値）を、表 2.6.4.7.1-1 に示した。CCX168 は各 CYP 活性を、ほぼ阻害しなかった。CCX168-M1 は CYP2C9 活性を阻害したものの（IC_{50} 値：4.7 μmol/L）、その他の CYP 活性はほぼ阻害しなかった。

ヒト肝ミクロソームを用いて CCX168 及び CCX168-M1 の時間依存的阻害（TDI）作用を評価した。CYP1A2、2B6、2C8、2C9、2C19 及び 2D6 活性に対し、NADPH 存在下及び非存在下のプレインキュベーション処理において CCX168 及び CCX168-M1 の IC_{50} 値にはいずれも明らかな違いは認められず、これらの CYP 活性に対し TDI 作用は示さないと考えられた（PC0710_168）。しかしながら、CCX168 及び CCX168-M1 は、いずれも CYP3A4 活性に対し TDI 作用を示した（PC0622_168 及び PC0634_168）。CCX168 及び CCX168-M1 の CYP3A4 活性に対する TDI パラメータを、表 2.6.4.7.1-2 に示した。

CCX168 の CYP 誘導能を、ヒト肝細胞を用いた酵素誘導試験により評価した（PC0635_168_a）。オメプラゾール、フェノバルビタール及びリファンピンをそれぞれ CYP1A2、CYP2B6 及び CYP3A4 誘導の陽性対照とし、CCX168 曝露による mRNA 発現量及び CYP 活性の上昇を定量した。mRNA 発現量を指標としたとき、CYP1A2 及び CYP2B6 の誘導はほぼ認められなかったが（陽性対照のそれぞれ 4%未満及び 24%未満）、CYP3A4 mRNA 発現量は最大 7.51 倍に上昇し誘導作用が認められた（陽性対照のリファンピンの約 30%～40%、表 2.6.4.7.1-3）。CYP 活性を指標としたとき、CYP3A4 活性は CCX168 濃度の上昇に伴って低下した。この結果は、前述の CCX168 が CYP3A4 の TDI 作用を有することに起因すると考えられた。また、CCX168-M1 も、ヒト肝細胞を用いて CYP 活性を指標として酵素誘導能を評価したとき、CCX168 と同様に CYP3A4 活性は低下した（PC0491_168）。

臨床薬物相互作用試験の結果、CCX168 及び CCX168-M1 は CYP3A4 及び CYP2C9 の弱い阻害能を有すると考えられ、併用した基質薬の血中曝露上昇は 2 倍未満であった（CL008_168）。一方、CCX168 及び CCX168-M1 はいずれも主に CYP3A4 により代謝されるため、CCX168 及び CCX168-M1 の血中曝露量は強い CYP3A4 誘導薬の併用により低下し、強い CYP3A4 阻害薬の併用により程度は低いが上昇した（PC0373_168 及び PC0711_168、2.7.2）。

表 2.6.4.7.1-1　　CCX168 及び CCX168-M1 の CYP 活性に対する直接阻害作用

CCX168 (PC0360_168)			
		IC_{50} (μmol/L)	Positive Control: IC_{50} (μmol/L)
CYP1A2		No inhibition	Furafylline: 2.1
CYP2B6		No inhibition	Thiotepa: 7.78
CYP2C8		No inhibition	Quercetin: 2.29
CYP2C9		No inhibition	Sulfaphenazole: 0.43
CYP2C19		No inhibition	Tranylcypromine: 4.67
CYP2D6		No inhibition	Quinidine: 0.05
CYP3A4	Midazolam	>30	Ketoconazole: 0.02
CYP3A4	Testosterone	No inhibition	Ketoconazole: 0.02
CCX168-M1 (PC0489_168)			
		IC_{50} (μmol/L)	Positive Control: IC_{50} (μmol/L)
CYP1A2		No inhibition	Furafylline: 1.8
CYP2B6		No inhibition	Thiotepa: 8.2
CYP2C8		>10	Quercetin: 1.9
CYP2C9		4.7	Sulfaphenazole: 0.36
CYP2C19		>10	Tranylcypromine: 15.7
CYP2D6		No inhibition	Quinidine: 0.04
CYP3A4	Midazolam	>10	Ketoconazole: 0.01
CYP3A4	Testosterone	>10	Ketoconazole: 0.02

表 2.6.4.7.1-2　　ヒト肝ミクロソームにおける CCX168 及び CCX168-M1 の CYP3A4 活性に対する時間依存的阻害作用

CCX168 (PC0622_168)			
Probe Substrate	Inhibitor	k_{inact} (min^{-1})	K_I (μmol/L)
Midazolam	CCX168	0.0659	4.47
Midazolam	Positive Control (Troleandomycin)	0.0656	0.81
CCX168-M1 (PC0634_168)			
Probe Substrate	Inhibitor	k_{inact} (min^{-1})	K_I (μmol/L)
Midazolam	CCX168-M1	0.0402	11.7
Midazolam	Positive Control (Troleandomycin)	0.0488	0. 511

表 2.6.4.7.1-3　　ヒト肝細胞における CCX168 の CYP3A4 誘導能

Treatment	Fold Induction in Gene Expression			Fold Induction in Activity		
	Donor 1	Donor 2	Donor 3	Donor 1	Donor 2	Donor 3
Solvent Control for Test Article (0.1% DMSO)	1.00 ± 0.16	1.00 ± 0.05	1.00 ± 0.13	1.00 ± 0.20	1.00 ± 0.19	1.00 ± 0.29
CCX168　0.03 μmol/L	1.20 ± 0.10	1.11 ± 0.10	1.31 ± 0.21	0.93 ± 0.10	0.85 ± 0.11	0.74 ± 0.09
CCX168　0.1 μmol/L	1.33 ± 0.27	1.24 ± 0.18	1.66 ± 0.22	0.78 ± 0.13	0.63 ± 0.10	0.51 ± 0.16
CCX168　0.3 μmol/L	2.10 ± 0.30	1.48 ± 0.17	2.21 ± 0.25	0.55 ± 0.10	0.44 ± 0.10	0.44 ± 0.07
CCX168　1 μmol/L	4.07 ± 0.54	2.14 ± 0.24	4.43 ± 0.20	0.54 ± 0.10	0.34 ± 0.05	0.38 ± 0.04
CCX168　3 μmol/L	7.51 ± 0.19	3.42 ± 0.31	5.38 ± 0.13	0.67 ± 0.17	0.27 ± 0.06	0.33 ± 0.03
CCX168　10 μmol/L	6.56 ± 0.37	4.18 ± 0.26	5.15 ± 0.92	0.59 ± 0.11	0.31 ± 0.03	0.36 ± 0.09
CCX168　30 μmol/L	4.39 ± 0.28	3.33 ± 0.24	3.44 ± 0.25	0.44 ± 0.05	0.23 ± 0.05	0.29 ± 0.02
Solvent Control for Positive Controls (0.1% DMSO)	1.00 ± 0.12	1.00 ± 0.34	1.00 ± 0.20	1.00 ± 0.13	1.00 ± 0.13	1.00 ± 0.25
Rifampin　10 μmol/L	17.83 ± 5.42	12.58 ± 1.59	13.25 ± 1.93	18.87 ± 3.96	8.13 ± 0.79	7.4 ± 1.20

試験番号 PC0635_168_a

2.6.4.7.2 薬物トランスポーターの阻害能及び基質性

添付資料 4.2.2.6.8

In vitro の薬物相互作用試験に関する FDA ガイダンス（2020 年 1 月）[2)]に従って、*in vitro* において薬物トランスポーター相互作用試験を実施し、CCX168 及び CCX168-M1 が薬物トランスポーターの阻害薬及び基質となる可能性について評価した（PC0712_168、表 2.6.4.7.2-1）。CCX168 及び CCX168-M1 の薬物トランスポーター（BCRP、MDR1/P-gp、MATE1、MATE2-K、OAT1、OAT3、OATP1B1、OATP1B3 及び OCT2）に対する阻害能、並びに肝取込みトランスポーター（OATP1B1 及び OATP1B3）及び排出トランスポーター（MDR1/P-gp 及び BCRP）に対する基質性を検討した。なお、CCX168 及び CCX168-M1 の尿中排泄は消失への寄与が小さいため、尿中排泄に関与する薬物トランスポーター（MATE1、MATE2-K、OAT1、OAT3 及び OCT2）に対する CCX168 及び CCX168-M1 の基質性は評価しなかった。

CCX168 及び CCX168-M1 は、いずれの薬物トランスポーターによる輸送も明らかに阻害しなかった。CCX168 は OATP1B1、OATP1B3、MDR1/P-gp 及び BCRP の基質ではなかった。CCX168-M1 は OATP1B1、OATP1B3 及び BCRP の基質ではなかったが、MDR1/P-gp の基質であった。ヒト代謝物検索試験（CL004_168-MetID）、*in vitro* 代謝試験（PC0711_168）及びイトラコナゾール併用臨床薬物相互作用試験（CL008_168）の結果に基づいて、CCX168-M1 は胆汁排泄ではなく主に代謝により消失するため、MDR1/P-gp は CCX168-M1 の消失に大きく寄与していないと考えられた。

結論として、重要な薬物トランスポーターに対する CCX168 及び CCX168-M1 の阻害能及び基質性に起因した薬物相互作用が生じる可能性は低いと考えられた。

表 2.6.4.7.2-1　　CCX168 及び CCX168-M1 の薬物トランスポーター阻害能及び基質性評価

Test Article	Transporter and assay type	Inhibition results	Substrate results	
		Maximum inhibition (% Inhibition)	Maximum net ER or fold accumulation	Substrate
CCX168	BCRP ML	NIO	< 2	No
	MDR1/P-gp ML	NIO	< 2	No
	MATE1 UPT	NIO	NT	—
	MATE2-K UPT	NIO	NT	—
	OAT1 UPT	21%	NT	—
	OAT3 UPT	NIO	NT	—
	OATP1B1 UPT	25%	< 2	No
	OATP1B3 UPT	NIO	< 2	No
	OCT2 UPT	NIO	NT	—
CCX168-M1	BCRP ML	NIO	< 2	No
	MDR1/P-gp ML	NIO	52.77	Yes
	MATE1 UPT	NIO	NT	—
	MATE2-K UPT	NIO	NT	—
	OAT1 UPT	NIO	NT	—
	OAT3 UPT	NIO	NT	—
	OATP1B1 UPT	NIO	< 2	No
	OATP1B3 UPT	NIO	< 2	No
	OCT2 UPT	NIO	NT	—

net ER：net efflux ratio（正味排出比）；ML：細胞単層膜を用いた試験；UPT：取込み試験；NIO：阻害なし（20%未満の阻害）；NT：未実施
試験番号 PC0712_168

2.6.4.7.3 その他の薬物相互作用

添付資料 4.2.1.2.4、4.2.1.2.5、4.2.2.6.9

ステロイド代謝酵素の 11β-水酸化ステロイド脱水素酵素 1 型（11β-HSD1）及び 2 型（11β-HSD2）はグルココルチコイドの代謝に関与することが知られている [3]。プレドニゾンは、CCX168 の適応症である ANCA 関連血管炎の治療において一般的に処方される薬物であるため、11β-HSD1 及び 11β-HSD2 活性に対する CCX168 及び CCX168-M1 の阻害作用を評価した。CCX168 及び CCX168-M1 は、いずれもこれらの代謝酵素に対し阻害作用を示さなかった（PC0469_168）。また、CCX168 はヒト血漿中のプレドニゾン及びプレドニゾロンの非結合形濃度に影響を及ぼさなかった（PC0466_168）。

同様に、ANCA 関連血管炎の治療において処方されるシクロホスファミドは CYP 活性による活性代謝物へ変換が必要であるが、*in vitro* 試験において CCX168 及び CCX168-M1 はシクロホスファミドの抗増殖作用を抑制しなかった（PC0465_168）。また、臨床試験結果（CL002_168 及び CL003_168）から、ANCA 関連血管炎患者において CCX168 とプレドニゾン、シクロホスファミド及びリツキシマブの併用には顕著な薬物相互作用は想定されなかった（CL002_168_PK Report 及び CL003_168_PK Report）。したがって、CCX168 はシクロホスファミド又はグルココルチコイドの薬効に影響を及ぼす可能性は低いと考えられる。

ANCA 関連血管炎患者に使用される他の併用薬であるアザチオプリン及びミコフェノール酸は、前者はチオプリン S-メチルトランスフェラーゼ及びキサンチンオキシダーゼにより、また後者はウリジン二リン酸グルクロノシルトランスフェラーゼにより代謝される。いずれも CYP 以外の代謝酵素により代謝されるため、CCX168 と薬物相互作用を惹き起こす可能性は低いと考えられる [4), 5)]。

アンジオテンシン変換酵素（ACE）阻害薬又はアンジオテンシン II 受容体遮断薬（ARB）は主に尿中排泄及び胆汁排泄により消失するため、CCX168 はこれら薬物の排泄を阻害する可能性は低いと考えられる。また、CYP はこれら薬物の主要な代謝酵素ではないことが報告されている [6), 7)]。

CCX168 は CYP 阻害及び誘導作用が弱いことから、消失又は活性化に CYP による代謝を必要とする薬物と相互作用する可能性は低い（例として、ロサルタンは CYP2C9 により活性代謝物に変換される [8)]）。

2.6.4.8 その他の薬物動態試験

その他の薬物動態試験は実施していない。

2.6.4.9 考察及び結論

CCX168 は Caco-2 細胞単層膜において透過性が高く、排出トランスポーターの基質ではないことが示された。動物における CCX168 の全身クリアランスは中等度であり、消失半減期は最長で 14.2 時間であった。CCX168 のバイオアベイラビリティは溶解性に依存し水溶性の媒体では低かったが、PEG-400/Kolliphor HS-15 ([redacted], v/v）を投与媒体としてラットに 100 mg/kg までの用量を投与したとき、バイオアベイラビリティは約 4 倍向上した。ラット、ハムスター及びサルに CCX168 を反復経口投与したとき、30 mg/kg/日を超える投与量において C_{max} 及び AUC の増加は投与量に比例しなかった。ラット、ハムスター及びサルにおける CCX168 の全

身曝露量には、顕著な性差は認められなかった。

CCX168 及び CCX168-M1 は、いずれの動物種の血漿においても 99.9%以上の血漿蛋白結合率を示し、可逆的に結合したと考えられた。また、CCX168 及び CCX168-M1 はヒトアルブミン及び AAG に対し高い結合率を示したが、可逆的な結合と考えられた。[^{14}C]CCX168 の単回経口投与によるラット組織分布試験の結果、放射能は速やかに大部分の組織及び臓器へ広範に分布した。アルビノ及び有色ラットの組織分布は、ほぼ同様であった。

[^{14}C]CCX168 を経口投与したマスバランス試験において、ラット及びヒト（CL004_168）では投与放射能の回収率は高かったが（ラット：約 97%～98%、ヒト：約 87%）、サルでは回収率は約 71%～72%であった。サルにおいて回収率が低くなった原因は、投与媒体成分の PEG-400 に起因した下痢である可能性が最も高いと考えられた。放射能の大部分は、酸化代謝物として糞中に回収された。CCX168 を溶液として経口投与したとき、ラット及びヒトの吸収率は、糞中の未吸収量（未変化体の存在量）に基づいてそれぞれ約 80%及び約 93%と推定された。CCX168 が吸収された後、第一相反応により代謝され、それらの代謝物が胆汁排泄される経路が CCX168 の主要消失経路であり、未変化体の胆汁及び尿中排泄量はわずかであった（ラット及びヒトともに 10%未満）。活性代謝物である CCX168-M1 は、ヒト循環血中において唯一の主要代謝物（薬物関連物質の総曝露量に対し 10%超）であったが、ラット及びサルの毒性試験における曝露量はヒトの曝露量より十分に高かった。CCX168-M1 及びその他多くの代謝物は、CCX168 の酸化代謝物であった。

CYP3A4 は、CCX168 の代謝、並びに CCX168-M1 の生成及び代謝に寄与する重要な代謝酵素であった。*In vitro* において、CCX168 及び CCX168-M1 の CYP3A4 に対する時間依存的阻害作用（k_{inact}/K_I 比：0.003～0.015）は、強力な時間依存的阻害薬であるトロレアンドマイシン（k_{inact}/K_I 比：約 0.1）と比較して、低～中等度であった。臨床薬物相互作用試験（CL008_168）結果から、CCX168 及び CCX168-M1 には、CYP の阻害又は誘導に起因した併用薬の顕著な曝露量変動を惹起する薬物相互作用の懸念はないことが考えられた。CCX168 及び CCX168-M1 は CYP3A4 の基質であることから、リファンピシンのように強い CYP3A4 誘導薬との併用により曝露量が減少し、イトラコナゾールのように強い CYP3A4 阻害薬の併用により程度は低いが曝露量は増加する可能性が考えられた。しかしながら、CCX168 は、ANCA 関連血管炎患者で一般的に使用される薬物、すなわち、プレドニゾン、シクロホスファミド、リツキシマブ、アザチオプリン、ミコフェノール酸、ACE 阻害薬又は ARB との併用においては薬物相互作用を惹起する可能性は低いと考えられた。

2.6.4.10 図表

図表は、本文中の適切な箇所に記載した。

2.6.4.11 参考文献

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目次

2.6.5 薬物動態試験概要表 5
2.6.5.1 薬物動態試験：一覧表 5
2.6.5.2 分析方法及びバリデーション試験 8
2.6.5.2.1 分析方法、バリデーション試験及び分析方法が用いられた毒性試験 8
2.6.5.2.2 濃度分析法概要（[redacted]：PC0362_168 及び PC0362_168_a） 9
2.6.5.2.3 濃度分析法概要（[redacted]：PC0363_168 及び PC0363_168_a） 12
2.6.5.2.4 濃度分析法概要（[redacted]：PC0649_168 及び PC0649_168_a） 15
2.6.5.2.5 濃度分析法概要（[redacted]：PC0650_168） 20
2.6.5.2.6 濃度分析法概要（[redacted]：PC0651_168 及び PC0651_168_a） 25
2.6.5.2.7 濃度分析法概要（[redacted]：PC0652_168 及び PC0652_168_a） 31
2.6.5.3 薬物動態試験：単回投与後の吸収 43
2.6.5.3.1 Caco-2 細胞単層膜における透過性 43
2.6.5.3.2 マウス、ラット及びサルに単回経口投与したときの薬物動態パラメータ 44
2.6.5.4 薬物動態試験：反復投与後の吸収 45
2.6.5.4.1 ラットに反復経口投与したときの薬物動態パラメータ 45
2.6.5.4.2 ハムスター及びサルに反復経口投与したときの薬物動態パラメータ 46
2.6.5.4.3 サルに反復投与したときの薬物動態パラメータ 47
2.6.5.5 薬物動態試験：分布 48
2.6.5.5.1 雄アルビノ（SD）ラットにおける組織分布 48
2.6.5.5.2 雌アルビノ（SD）ラットにおける組織分布 50
2.6.5.5.3 雄有色（LE）ラットにおける組織分布 52
2.6.5.5.4 雌有色（LE）ラットにおける組織分布 54
2.6.5.6 薬物動態試験：蛋白結合 56
2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験 57
2.6.5.7.1 妊娠動物（ハムスター）における試験 57
2.6.5.7.2 妊娠動物（ウサギ）における試験 58
2.6.5.7.3 授乳動物（ハムスター）における試験 59
2.6.5.8 薬物動態試験：その他の分布試験 60
2.6.5.8.1 血球移行性 60
2.6.5.9 薬物動態試験：代謝：*In Vivo* 61
2.6.5.9.1 ラットにおける代謝物検索 61
2.6.5.9.2 サルにおける代謝物検索 62
2.6.5.10 薬物動態試験：代謝：*In Vitro* 63
2.6.5.10.1 肝細胞における代謝安定性 63

2.6.5.10.2 肝ミクロソーム及び肝細胞を用いた代謝物検索 64
2.6.5.11 薬物動態試験：推定代謝経路 65
2.6.5.11.1 CCX168 及び CCX168-M1 の代謝酵素の同定（選択的阻害薬による同定） 65
2.6.5.11.2 CCX168 の代謝酵素の同定（組換え CYP による同定） 66
2.6.5.11.3 CCX168-M1 の代謝酵素の同定（組換え CYP による同定） 67
2.6.5.12 薬物動態試験：薬物代謝酵素の誘導／阻害 68
2.6.5.13 薬物動態試験：排泄 69
2.6.5.14 薬物動態試験：排泄：胆汁中 70
2.6.5.15 薬物動態試験：薬物相互作用 71
2.6.5.15.1 CYP 阻害（ヒト肝ミクロソーム） 71
2.6.5.15.2 時間依存的 CYP 阻害（ヒト肝ミクロソーム） 72
2.6.5.15.3 時間依存的 CYP3A4 阻害（ヒト肝ミクロソーム） 73
2.6.5.15.4 CYP 誘導（ヒト肝細胞） 74
2.6.5.15.5 薬物トランスポーターの阻害 75
2.6.5.15.6 薬物トランスポーターに対する基質性 76
2.6.5.15.7 ステロイド代謝酵素（11β-HSD1 及び 11β-HSD2）の阻害 77
2.6.5.15.8 プレドニゾン又はプレドニゾロンの血漿蛋白結合へ及ぼす影響 78
2.6.5.16 薬物動態試験：その他 79

略号一覧

略号	略していない表現	内容
[^{3}H]	Tritium labeled	水素 3 標識
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1	11β-水酸化ステロイド脱水素酵素 1 型
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2	11β-水酸化ステロイド脱水素酵素 2 型
[^{14}C]	Carbon 14 labeled	炭素 14 標識
ACE	Angiotensin converting enzyme	アンジオテンシン転換酵素
AAG	α_1-acid glycoprotein	α_1-酸性糖蛋白質
ANCA	Anti-neutrophil cytoplasmic antibody	抗好中球細胞質抗体
ARB	Angiotensin II receptor blocker	アンジオテンシン II 受容体遮断薬
AUC	Area under the curve	血漿中濃度-時間曲線下面積
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity	0 から無限大時間時間までの血漿中濃度-時間曲線下面積
(A-B)	Apical to basolateral	頂端側から側底側
(B-A)	Basolateral to apical	側底側から頂端側
BCRP	Breast cancer resistance protein	乳がん耐性蛋白質
b.i.d	Twice per day	1 日 2 回投与
BLQ	Below the limit of quantification	定量下限未満
Caco-2	human colorectal carcinoma cell line designation; used to assess membrane permeability *in vitro*	膜透過性試験に用いられるヒト結腸癌由来の細胞株
CL	Total body clearance	総クリアランス
C_{max}	Maximum (maximal) plasma concentration	最大（最高）血漿中濃度
CV	Coefficient of variance	精度
CYP	Cytochrome P450	シトクロム P450
DMSO	Dimethyl sulfoxide	ジメチルスルホキシド
EC_{50}	Concentration associated with 50% effect	50%有効濃度
E_{max}	Maximum effect	最大効果
ER	Efflux ratio	排出比
FDA	Food and Drug Administration	米国食品医薬品局
F (%)	Bioavailability (systemic availability of the administered dose)	バイオアベイラビリティ
HEK	human embryonic kidney cells	ヒト胎児腎細胞
H_t	Hematocrit	ヘマトクリット
HPMC	Hydroxypropyl methylcellulose	ヒドロキシプロピルメチルセルロース
hr	Hour	時間
IC_{50}	Concentration associated with 50% inhibition	50%阻害濃度
IV	Intravenous(ly); also expressed as i.v.	静脈内投与
ISR	Incurred sample reanalysis	—
kg	Kilogram	キログラム
$K_{B/PL}$	Whole blood-to-plasma ratio	血液/血漿比
K_I	Concentration at 50% k_{inact}	阻害定数（k_{inact} が 50%となる濃度）
k_{inact}	Rate of maximal inactivation	最大不活性化速度定数
$K_{RBC/PL}$	Red blood cell-to-plasma ratio	赤血球/血漿比
LE	Long Evans	—
LC-MS/MS	Liquid chromatography/tandem mass spectrometry	液体クロマトグラフタンデム質量分析法
LLOQ	Low limit of quantification	定量下限
mg	Milligram	ミリグラム
mL	Milliliter	ミリリットル
MATE1	Multidrug and toxin extrusion 1	多剤及び毒素排出トランスポーター1
MATE2-K	Multidrug and toxin extrusion 2-K	多剤及び毒素排出トランスポーター2-K
min^{-1}	Per minute	毎分
MRT	Mean residence time	平均滞留時間
NADPH	β-Nicotinamide adenine dinucleotide 2'-phosphate reduced	還元型 β-ニコチンアミドアデニンジヌクレオチド 2'-リン酸
NOAEL	No observable adverse effect level	無毒性量

略号	略していない表現	内容
ng	Nanogram	ナノグラム
OAT1	Organic anion transporter 1	有機アニオントランスポーター1
OAT3	Organic anion transporter 3	有機アニオントランスポーター3
OATP1B1	Organic anion transporting polypeptide 1B1	有機アニオン輸送ポリペプチド 1B1
OATP1B3	Organic anion transporting polypeptide 1B3	有機アニオン輸送ポリペプチド 1B3
OCT2	Organic cation transporter 2	有機カチオントランスポーター2
P_{app}	Apparent permeability coefficient	見かけの透過係数
PEG-400	Polyethylene glycol 400	ポリエチレングリコール 400
MDR1/P-gp	P-glycoprotein	P-糖蛋白質
PO	Per os (orally); also expressed as p.o.	経口投与
QC	Quality control	—
q.d.	Once per day	1 日 1 回投与
SD	Sprague-Dawley	—
$t_{1/2}$	Elimination half-life	消失半減期
t_{max}	Time to maximum (maximal) concentration	最大血漿中濃度到達時間
TK	Toxicokinetic(s)	トキシコキネティクス
ULOQ	Upper limit of quantification	定量上限
V_{ss}	Volume of distribution at steady state	定常状態の分布容積

2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験：一覧表

Pharmacokinetics Overview			Test Article: CCX168, [^{3}H]CCX168, [^{14}C]CCX168, or CCX168-M1		
Type of Study	Test System	Method of Administration	Testing Facility	Report Number	Location
Absorption	Caco-2 cell monolayer	CCX168 solution	[redacted] (UK)	PC0361_168_a	4.2.2.2.1
	Mouse	Intravenous and oral dosing of CCX168 in solution or suspension	ChemoCentryx	PC0366_168	4.2.2.2.2
	Rat	Intravenous and oral dosing of CCX168 in solution or suspension	ChemoCentryx	PC0365_168_a	4.2.2.2.3
	Rat and Monkey	Oral dosing of CCX168 in solution formulations	ChemoCentryx; [redacted]	PC0482_168	4.2.2.2.4
	Rat	Oral dosing of CCX168 in solution	ChemoCentryx	PC0637_168	4.2.2.2.5
	Rat	Oral dosing of CCX168 in solution or suspension	ChemoCentryx	PC0639_168	4.2.2.2.6
	Rat	Intravenous and oral dosing of CCX168-M1 in solution or suspension	ChemoCentryx	PC0633_168	4.2.2.2.7
	Hamster	Oral dosing of CCX168 in solution or suspension	[redacted]; ChemoCentryx	PC0648_168	4.2.2.2.8
	Rabbit	Oral dosing of CCX168 suspension or solution	[redacted]; ChemoCentryx	PC0203_168	4.2.2.2.9
	Rabbit	Oral dosing of CCX168 in solution	[redacted]; ChemoCentryx	PC0658_168	4.2.2.2.10
	Dog	Intravenous dosing of CCX168 in solution	[redacted]; ChemoCentryx	PC0367_168	4.2.2.2.11
	Monkey	Nasogastric dosing of CCX168 in solution	[redacted]; ChemoCentryx	PC0647_168	4.2.2.2.12
	Monkey	Nasogastric and oral dosing of CCX168 in solution	[redacted]; ChemoCentryx	PC0653_168	4.2.2.2.13
	Monkey	Oral dosing of CCX168 in solution	[redacted]	PC0654_168	4.2.3.2.7
	Monkey	Oral dosing of CCX168 in solution or suspension	[redacted]; ChemoCentryx	PC0368_168	4.2.2.2.14
Distribution	Protein binding in plasma from several species	CCX168 or CCX168-M1 solution	ChemoCentryx	PC0632_168	4.2.2.3.1
	Protein binding to human albumin	CCX168 or CCX168-M1 solution	ChemoCentryx	PC0681_168	4.2.2.3.2
	Protein binding to human α_1-acid glycoprotein (AAG)	CCX168 or CCX168-M1 solution	ChemoCentryx	PC0685_168	4.2.2.3.3

Pharmacokinetics Overview			Test Article: CCX168, [^{3}H]CCX168, [^{14}C]CCX168, or CCX168-M1		
Type of Study	Test System	Method of Administration	Testing Facility	Report Number	Location
	Rat	Oral dosing of [^{14}C]CCX168 solution	[redacted]	PC0641_168	4.2.2.3.4
	Blood/plasma partitioning using whole blood and plasma from several species	CCX168 or Metabolite CCX168-M1 solution	ChemoCentryx	PC0364_168_a	4.2.2.3.5
Metabolism	Metabolic stability and metabolite identification using hepatocyte suspension or liver microsomes of multiple species	CCX168 solution; [^{3}H]CCX168 solution	ChemoCentryx	PC0370_168 PC0369_168 PC0623_168_a	4.2.2.4.1 4.2.2.4.2 4.2.2.4.3
	CYP reaction phenotyping using human liver microsomes and recombinant CYP enzymes	CCX168 solution	ChemoCentryx	PC0373_168	4.2.2.4.4
	Characterization of metabolic pathways of CCX168 and CCX168-M1 using human liver microsomes and recombinant CYP enzymes	CCX168 and CCX168-M1 solution	ChemoCentryx	PC0711_168	4.2.2.4.5
	Rat, Bile Duct Canulated Rat, and Cynomolgus monkey	Oral dosing of [^{14}C]CCX168 solution	ChemoCentryx	PC0641_168_a PC0645_168_a	4.2.2.4.6 4.2.2.4.7
	Evaluation of steady state plasma levels of CCX168 metabolites in various species following oral administration of CCX168	Oral dosing of CCX168 solution	ChemoCentryx	PC0487_168_a	4.2.2.4.8
Excretion	Rat, Bile Duct Cannulated Rat, and Cynomolgus monkey	Oral dosing of [^{14}C]CCX168 solution	[redacted]	PC0641_168 PC0645_168	4.2.2.3.4 4.2.2.5.1
Pharmacokinetic Drug Interactions	CYP direct inhibition in human liver microsomes	CCX168 solution	ChemoCentryx	PC0360_168	4.2.2.6.1

Pharmacokinetics Overview			Test Article: CCX168, [^{3}H]CCX168, [^{14}C]CCX168, or CCX168-M1		
Type of Study	Test System	Method of Administration	Testing Facility	Report Number	Location
	CYP direct inhibition in human liver microsomes	CCX168-M1 solution	ChemoCentryx	PC0489_168	4.2.2.6.2
	CYP inhibition (time-dependent) in human liver microsomes	CCX168 and CCX168-M1 solution	[redacted]	PC0710_168	4.2.2.6.3
	CYP inhibition (time-dependent) in human microsomes	CCX168-M1 solution	ChemoCentryx	PC0634_168	4.2.2.6.4
	CYP inhibition (time-dependent) in human liver microsomes	CCX168 solution	[redacted]	PC0622_168	4.2.2.6.5
	CYP induction in human hepatocytes (EC_{50} and E_{max})	CCX168 solution	[redacted]	PC0635_168_a	4.2.2.6.6
	CYP induction in human hepatocytes	CCX168-M1 solution	ChemoCentryx	PC0491_168	4.2.2.6.7
	Interaction with hepatic, renal and intestinal drug transporters	CCX168 or CCX168-M1 solution	[redacted]	PC0712_168	4.2.2.6.8
	Interaction with prednisone and prednisolone in human plasma	CCX168 solution	ChemoCentryx	PC0466_168	4.2.2.6.9
	Inhibition of 11β-hydroxysteroid dehydrogenases in human liver microsomes or human kidney microsomes	CCX168 or CCX168-M1 solution	ChemoCentryx	PC0469_168	4.2.1.2.5
Other	None				

2.6.5.2 分析方法及びバリデーション試験

2.6.5.2.1 分析方法、バリデーション試験及び分析方法が用いられた毒性試験

Method Validation Report									
Location or ChemoCentryx Report No.*	CRO-[redacted] Study ID	[redacted] Method ID	Type of Method	Species/ Sample Matrix	Analytes	Quantification Range	Location or Toxicology/TK Reports Using the Method**	Type of Toxicology Study	Treatment Duration (Days/Weeks)
4.2.2.1.1 PC0362_168 PC0362_168_a	[redacted]223	[redacted]	LC-MS/MS	Rat / plasma	CCX168	1 – 1000 ng/mL	4.2.3.2.1 PC0384_168 4.2.3.2.2 PC0356_168	Repeat Dose Toxicity	13 Weeks 4 Weeks
4.2.2.1.2 PC0650_168	[redacted]655	[redacted]	LC-MS/MS	Rat / plasma	CCX168, CCX168-M1 and CCX168-[redacted]	2 – 2000 ng/mL (CCX168); 1 – 1000 ng/mL (CCX168-M1 and CCX168-[redacted])	4.2.3.2.3 PC0655_168	Repeat Dose Toxicity	26 Weeks
4.2.2.1.3 PC0652_168 PC0652_168_a	[redacted]719	[redacted]	LC-MS/MS	Hamster / plasma	CCX168, CCX168-M1 and CCX168-[redacted]	2 – 2000 ng/mL (CCX168); 1 – 1000 ng/mL (CCX168-M1 and CCX168-[redacted])	4.2.3.5.2.4 PC0667_168 4.2.3.5.2.1 PC0671_168 4.2.3.5.3.1 PC0673_168	Reproductive & Developmental Toxicity	GD 6 through 12 GD 6 through 12 GD 6 through Day 20 Postpartum
							4.2.3.2.4 PC0677_168 PC0677_168_a	Repeat Dose Toxicity	13 Weeks
4.2.2.1.4 PC0651_168 PC0651_168_a	[redacted]721	[redacted]	LC-MS/MS	Rabbit / plasma	CCX168, CCX168-M1 and CCX168-[redacted]	1 – 1000 ng/mL	4.2.3.5.2.5 PC0666_168 4.2.3.5.2.2 PC0672_168	Reproductive & Developmental Toxicity	Dose Range Finding GD 6 through 18
4.2.2.1.5 PC0363_168 PC0363_168_a	[redacted]220	[redacted]	LC-MS/MS	Cynomolgus monkey / plasma	CCX168	1 – 1000 ng/mL	4.2.3.2.6 PC0357_168 PC0357_168_a 4.2.3.2.5 PC0385_168	Repeat Dose Toxicity	20 Weeks 4 Weeks
4.2.2.1.6 PC0649_168 PC0649_168_a	[redacted]009	[redacted]	LC-MS/MS	Cynomolgus monkey / plasma	CCX168, CCX168-M1 and CCX168-[redacted]	1 – 1000 ng/mL	4.2.3.2.7 PC0654_168	Repeat Dose Toxicity	44 Weeks

*For report numbers listed in this column, the suffix "_a" denotes an addendum to the original report.
**For report number listed in this column, the suffix "_a" denotes an auxiliary report containing the TK data.
GD = Gestation Day.

2.6.5.2.2 濃度分析法概要（[redacted]：PC0362_168 及び PC0362_168_a）

Summary of Method Performance for [redacted] Method [redacted]			
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of CCX168 in Rat Plasma by HPLC with MS/MS Detection (ChemoCentryx Doc ID. PC0362_168) Validation of a Method for the Determination of CCX168 in Rat Plasma by HPLC with MS/MS Detection, Addendum No. 1 (ChemoCentryx Doc ID. PC0362_168_a) [[redacted] Method ID [redacted]]		
Method description	CCX168 and the internal standard (ISTD), CCX168-d4, were extracted from rat plasma by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS).		
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] and [redacted] [Primary Stock concentration 200 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rat plasma		
Validated assay range	1.00 to 1000 ng/mL		
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] and [redacted] [Primary Stock concentration 200 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rat plasma		
Minimum required dilutions (MRDs)	n/a		
Source and lot of reagents	No special reagents were used		
Regression model and weighting	Weighted ($1/x^2$) linear least-squares regression		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8	Table 5 of PC0362_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	−3.4% to 3.0% (values derived from %Accuracy data that were presented in the report)	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.7%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for CCX168: 1.00, 3.00, 75.0 and 750 ng/mL	−2.2% to 1.1% (derived from overall %Accuracy data that were presented in the report)	Tables 6 and 7 of PC0362_168
	Inter-batch %CV QCs for CCX168: 1.00, 3.00, 75.0 and 750 ng/mL	≤5.7%	Tables 6 and 7 of PC0362_168
	Total error (TE)	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]			
Selectivity & matrix effect	Aliquots of blank rat plasma from six different lots were tested for endogenous interferences. In all cases, the CCX168 and CCX168-d4 regions were free from significant interference (<20.0% of the mean utilized LLOQ and <5.0% of internal standard response in the control zero sample). Aliquots of these lots were spiked with 75.0 ng/mL of CCX168 and with internal standard. Selectivity data for CCX168 and CCX168-d4 failed in analysis group 003 with a high bias, but passed when the test was repeated in analysis group 005. There is no obvious reason for the failure in analysis group 003. The overall mean concentration of the spiked samples had a percent Relative Standard Deviation (RSD) of ≤15.0% and overall mean accuracy within the range of 85.0% to 115.0%. In all cases where one blank matrix sample was spiked with ISTD only (control zero), or spiked with CCX168 only (at the ULOQ concentration), the CCX168 and CCX168-d4 chromatograms showed no significant interference (<20.0% of the mean utilized LLOQ and <5.0% of the ISTD response in the control zero sample). There is >60% suppression of the signal but this matrix effect did not significantly impact assay performance.		Table 2, Table 3 and Figures B1 and B2 of PC0362_168
Interference and specificity	n/a		n/a
Hemolysis effect	n/a		n/a
Lipemic effect	n/a		n/a
Dilution linearity & hook effect	Tested at 3750 ng/mL using a 10-fold dilution (% bias ranged from −4.0% to 1.6%) Tested at 3750 ng/mL using a 20-fold dilution (% bias ranged from −0.8% to 3.5%)		Table 8 of PC0362_168 Table 3 of PC0362_168_a
Bench-top/process stability	CCX168 is stable in rat plasma at room temperature for 24 hr		Table 14 of PC0362_168
Freeze-thaw stability	CCX168 is stable in rat plasma after 3 freeze-thaw cycles at −60°C to −80°C		Table 14 of PC0362_168
Long-term stability	CCX168 is stable in rat plasma after 404 days at −60°C to −80°C		Table 2 of PC0362_168_a
Parallelism	n/a		n/a
Carry over	Carry over was tested by injecting an extract of blank matrix in duplicate immediately following the highest calibration standard and immediately following the HQC sample; at least one evaluation was positioned early in the batch and at least one evaluation was positioned towards the end of the batch. The extracts of blank matrix demonstrated a lack of significant carry over in the chromatographic regions of interest for CCX168 (<20.0% of the mean utilized LLOQ) and CCX168-d4 (<5.0% of the internal standard response in the control zero sample).		Figure B3 of PC0362_168
Method Performance in Study PC0384_168 (4-Week Repeat-Dose Toxicity in Rats)			
Assay passing rate	Include incurred sample re-analysis passing rate.	100% assay passing rate (8 out of 8 analytical runs)	Results section of Bioanalytical contributing report for PC0384_168
Standard curve performance	Cumulative bias range: x to y%	−4.7% to 6.0% (values derived from %Accuracy data that were presented in the report)	Table 4 of Bioanalytical contributing report for PC0384_168

Summary of Method Performance for [redacted] Method [redacted]			
	Cumulative precision: ≤x% CV	≤2.2%	
QC performance	Cumulative bias range: x to y%	−4.3% to 0.0% (values derived from %Accuracy data that were presented in the report)	Table 5 of Bioanalytical contributing report for PC0384_168
	Cumulative precision: ≤x% CV	≤3.8%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was performed in 8% of study samples (24 out of 300 samples), and 95.8% of the samples met the pre-specified criteria	Table 7 of Bioanalytical contributing report for PC0384_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	Length of storage stability to cover samples: 28 days at −60°C to −80°C required; stability for 404 days at −60°C to −80°C has been established	Results section of Bioanalytical contributing report for PC0384_168 and Table 2 of PC0362_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	8 out of 8 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 50.0, 200, 500, 800, 1000 ng/mL	Table 4 of Bioanalytical contributing report for PC0384_168
Method Performance in Study PC0356_168 (13-Week Repeat-Dose Toxicity in Rats)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (7 out of 7 analytical runs)	Table 1 of Appendix L of PC0356_168
Standard curve performance	Cumulative bias range: x to y%	−4.2% to 5.5%	Table 4 of Appendix L of PC0356_168
	Cumulative precision: ≤x% CV	≤6.2%	
QC performance	Cumulative bias range: x to y%	−5.1% to −3.0%	Table 5 of Appendix L of PC0356_168
	Cumulative precision: ≤x% CV	≤10.3%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was performed in 8% (24 out of 300 samples) of study samples, and 100% of the samples met the pre-specified criteria	Table 7 of Appendix L of PC0356_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	Length of storage stability to cover samples: 110 days at −60°C to −80°C required; stability for 404 days at −60°C to −80°C has been established	Results Section of Appendix L of PC0356_168 and Table 2 of PC0362_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	7 out of 7 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 50.0, 200, 500, 800, 1000 ng/mL; 6 out of 7 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 10.0 ng/mL	Table 4 of Appendix L of PC0356_168

2.6.5.2.3 濃度分析法概要（[redacted]：PC0363_168 及び PC0363_168_a）

Summary of Method Performance for [redacted] Method [redacted]			
Bioanalytical method validation report name, amendments, and hyperlinks	Partial Validation of a Method for the Determination of CCX168 in Monkey Plasma by HPLC with MS/MS Detection (ChemoCentryx Doc ID PC0363_168) Partial Validation of a Method for the Determination of CCX168 in Monkey Plasma by HPLC with MS/MS Detection, Addendum No. 1 (ChemoCentryx Doc ID PC0363_168_a) [[redacted] Method ID [redacted]]		
Method description	CCX168 and the internal standard (ISTD), CCX168-d4, were extracted from monkey plasma by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS).		
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] and [redacted] [Primary Stock concentration 200 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA cynomolgus monkey plasma		
Validated assay range	1.00 to 1000 ng/mL		
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] and [redacted] [Primary Stock concentration 200 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA cynomolgus monkey plasma		
Minimum required dilutions (MRDs)	n/a		
Source and lot of reagents	No special reagents were used		
Regression model and weighting	Weighted ($1/x^2$) linear least-squares regression		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8	Table 5 of PC0363_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	−6.0% to 11.0% (values derived from %Accuracy data that were presented in the report)	
	Cumulative precision (%CV) from LLOQ to ULOQ	n/a (number of standards <3)	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for CCX168: 1.00, 3.00, 75.0 and 750 ng/mL	−9.0% to 1.1% (derived from %Accuracy data that were presented in the report)	Tables 6 and 7 of PC0363_168
	Inter-batch %CV in 4 QCs QCs for CCX168: 1.00, 3.00, 75.0 and 750 ng/mL	≤3.2% (from Run 2 only; Run 3 only includes n = 2 QCs)	Tables 6 and 7 of PC0363_168
	Total Error (TE)	n/a	n/a
Interference and specificity	n/a		n/a

Summary of Method Performance for [redacted] Method [redacted]			
Selectivity & matrix effect	Aliquots of blank monkey plasma from six different lots were tested for endogenous interferences. In all cases, the CCX168 and CCX168-d4 regions were free from significant interference (<20.0% of the mean utilized LLOQ and <5.0% of internal standard response in the control zero sample). Aliquots of these lots were spiked with 75.0 ng/mL of CCX168 and with internal standard. The mean concentration of the spiked samples had a percent Relative Standard Deviation (RSD) of ≤15.0% and mean accuracy within the range of 85.0 to 115.0%. In all cases where one blank matrix sample was spiked with ISTD only (control zero), or spiked with CCX168 only (at the ULOQ concentration), the CCX168 and CCX168-d4 chromatograms showed no significant interference (i.e., <20.0% of the mean utilized LLOQ and <5.0% of the ISTD response in the control zero sample). There was significant suppression noted for both CCX168 and CCX168-d4. Since the matrix effect was the same for CCX168 and CCX168-d4, it did not significantly impact assay performance.		Table 2, Table 3 and Figures B1 and B2 of PC0363_168
Hemolysis effect	n/a		n/a
Lipemic effect	n/a		n/a
Dilution linearity & hook effect	Tested at 3750 ng/mL using a 10-fold dilution (%bias ranged from −3.5% to 0.8%)		Table 8 of PC0363_168
Bench-top/process stability	CCX168 is stable in monkey plasma at room temperature for 24 hr		Table 11 of PC0363_168
Freeze-Thaw stability	CCX168 is stable in monkey plasma after 5 freeze-thaw cycles at −60°C to −80°C		Table 11 of PC0363_168
Long-term stability	CCX168 is stable in monkey plasma after 137 days at −60°C to −80°C		Table 3 of PC0363_168_a
Parallelism	n/a		n/a
Carry over	Carry over was tested by injecting an extract of blank matrix in duplicate immediately following the highest calibration standard and immediately following the HQC sample; at least one evaluation was positioned early in the batch and at least one evaluation was positioned towards the end of the batch. The extracts of blank matrix demonstrated a lack of significant carry over in the chromatographic regions of interest for CCX168 (<20.0% of the mean utilized LLOQ) and CCX168-d4 (<5.0% of the internal standard response in the control zero sample).		Figure B3 of PC0363_168
Method Performance in Study PC0357_168 (20-Week Repeat-Dose Toxicity in Monkeys)			
Assay passing rate	Include incurred sample re-analysis passing rate	93.75% assay passing rate (15 out of 16 analytical runs)	Table 1 of Appendix M of PC0357_168
Standard curve performance	Cumulative bias range: x to y%	−3.1% to 3.0%	Table 4 of Appendix M of PC0357_168
	Cumulative precision: ≤x% CV	≤5.6%	
QC performance	Cumulative bias range: x to y%	−6.7% to −4.4%	Table 5 of Appendix M of PC0357_168
	Cumulative precision: ≤x% CV	≤6.0%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was performed in 6.8% of study samples (48 out of 708), and 100% of the samples met the pre-specified criteria	Table 7 of Appendix M of PC0357_168

Summary of Method Performance for [redacted] Method [redacted]			
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	Length of storage stability to cover samples: 125 days at −60°C to −80°C required; stability for 137 days at −60°C to −80°C has been established	Results section of Appendix M of PC0357_168 and Table 3 of PC0363_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	15 out of 15 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 50.0, 200, 500, 800, 1000 ng/mL	Table 4 of Appendix M of PC0357_168
Method Performance in Study PC0385_168 (4-Week Repeat-Dose Toxicity in Monkeys)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (9 out of 9 analytical runs)	Table 1 of Bioanalytical contributing report for PC0385_168
Standard curve performance	Cumulative bias range: x to y%	−4.0% to 4.0%	Table 4 of Bioanalytical contributing report for PC0385_168
	Cumulative precision: ≤x% CV	≤3.5%	
QC performance	Cumulative bias range: x to y%	−7.6% to −3.6%	Table 5 of Bioanalytical contributing report for PC0385_168
	Cumulative precision: ≤x% CV	≤3.1%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was performed in 6.6% of study samples (24 of out 366 samples), and 100% of the samples met the pre-specified criteria	Table 7 of Bioanalytical contributing report for PC0385_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	Length of storage stability to cover samples: 35 days at −60°C to −80°C required; stability for 137 days at −60°C to −80°C has been established	Results section of Bioanalytical contributing report for PC0385_168 and Table 3 of PC0363_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	9 out of 9 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 50.0, 200, 500, 800, 1000 ng/mL	Table 4 of Bioanalytical contributing report for PC0385_168

2.6.5.2.4 濃度分析法概要（[redacted]：PC0649_168 及び PC0649_168_a）

Summary of Method Performance for [redacted] Method [redacted]			
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168-[redacted] in Cynomolgus Monkey Plasma by HPLC with MS/MS Detection (ChemoCentryx Doc ID PC0649_168) [redacted] Method ID [redacted] Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168-[redacted] in Cynomolgus Monkey Plasma by HPLC with MS/MS Detection, Addendum No. 1 (ChemoCentryx Doc ID PC0649_168_a) [redacted] Method ID [redacted]		
Method description	CCX168, CCX168-M1, and CCX168-[redacted] and the internal standard (ISTD), CCX168-d4, were extracted from monkey plasma by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS)		
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA cynomolgus monkey plasma		
Validated assay range	1.00 to 1000 ng/mL for CCX168, CCX168-M1 and CCX168-[redacted]		
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA cynomolgus monkey plasma		
Minimum required dilutions (MRDs)	n/a		
Source and lot of reagents	No special reagents were used		
Regression model and weighting	CCX168, CCX168-M1 and CCX168-[redacted]: weighted ($1/x^2$) linear least-squares regression		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8 for CCX168, CCX168-M1 and CCX168-[redacted]	Tables 6.9 through 6.11 of PC0649_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	−3.7% to 2.4%	
	CCX168-M1	−2.6% to 3.8%	

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Summary of Method Performance for [redacted] Method [redacted]			
	CCX168-[redacted]	−2.3% to 3.4%	
	Cumulative precision (%CV) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	≤7.3%	
	CCX168-M1	≤5.5%	
	CCX168-[redacted]	≤8.6%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	The following values were manually calculated by combining the additional validation batches:	Tables 6.15 through 6.17 of PC0649_168
	QCs for CCX168: 1.00*, 3.00, 50.0 and 800 ng/mL	−3.2% to −0.6%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	−3.0% to 4.2%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	−1.3% to 0.3%	
	*only included in 3 out of 7 analytical runs		
	Inter-batch %CV	The following values were manually calculated by combining the additional validation batches:	
	QCs for CCX168: 1.00*, 3.00, 50.0 and 800 ng/mL	≤17.6%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	≤14.7%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	≤19.9%	
	*only included in 3 out of 7 analytical runs		
	Total Error (TE)	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]		
Selectivity & matrix effect	Aliquots of blank monkey plasma from six different lots were tested for endogenous interferences. There were no interference peaks (>20% of the LLOQ calibration standard response) detected in the six individual blank matrix samples or the validation run blank samples at the retention time of CCX168, CCX168-M1, and CCX168-[redacted]. Peaks (>20.0% of the LLOQ calibration standard for the batch) were detected in the CCX168-M1 and CCX168-[redacted] channels in the blank spiked at the ULOQ level of CCX168. There were also peaks detected in the CCX168 channel of the blank matrix sample spiked at the ULOQ level of CCX168-M1 as well as in the CCX168 channel of blank matrix spiked with ULOQ level of CCX168-[redacted]). In all cases, the peaks detected had less than 0.5% impact on calibration standard calculations when analytes were spiked at the same concentrations; therefore, there is no significant impact to the data. There were no interference peaks detected at the ISTD retention time (>5.0% of the internal standard peak response in the control zero sample) for the six individual blank matrix samples or validation run blank samples. The mean accuracy of each of the six spiked individual blank matrix samples was within the acceptance criteria stated in the protocol. The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria as stated in the protocol and the matrix factor was not considered to impact assay performance.	Figures 8.1 through 8.7; Tables 6.2 through 6.7 of PC0649_168
Interference and specificity	n/a	n/a
Hemolysis effect	Range of %bias: CCX168: 1.1% to 6.0% CCX168-M1: 4.9% to 8.0% CCX168-[redacted]: 3.4% to 13.3% The presence of hemolyzed red blood cells in the monkey plasma did not affect the quantification of CCX168, CCX168-M1, and CCX168-[redacted] in this assay.	Tables 6.52 through 6.54 of PC0649_168
Lipemic effect	n/a	n/a
Dilution linearity & hook effect	CCX168: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −9.2% to 7.0%) CCX168-M1: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −11.6% to 10.2%) CCX168-[redacted]: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −9.4% to 5.8%)	Tables 6.15 through 6.17 of PC0649_168
Bench-top/process stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in monkey plasma at room temperature for 24 hr. The stability of CCX168, CCX168-M1, and CCX168-[redacted] in the extracts was found to be acceptable. Stability was confirmed for 102 hr at 2 to 8°C.	Tables 6.43 through 6.45 of PC0649_168 Tables 6.34 through 6.36 of PC0649_168

Summary of Method Performance for [redacted] Method [redacted]			
Freeze-Thaw stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in monkey plasma after 4 freeze-thaw cycles at −60°C to −80°C		Tables 6.40 through 6.42 of PC0649_168
Long-term stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in monkey plasma after 634 days at −60°C to −80°C		Tables 7.11 through 7.13 of PC0649_168_a
Parallelism	n/a		n/a
Carry over	In each validation run containing a calibration curve, one blank matrix was analyzed immediately following each of the two highest calibration standards (one blank positioned early in the run and one positioned toward the end of the run). There was no evidence of carry over (>20.0% of the LLOQ calibration standard response) to the blank matrix extracts injected immediately after the two highest calibration standards for CCX168, CCX168-M1 or CCX168-[redacted]. There were no interference peaks detected at the ISTD retention time (>5.0% of the internal standard peak response in the control zero sample) of the ISTD peak area for the matrix blanks.		Figure 8.8 of PC0649_168
Method Performance in Study PC0654_168 (44-Week Repeat Dose Toxicity in Monkeys)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (25 out of 25 analytical runs for CCX168 and CCX168-[redacted]; 24 out of 24 analytical runs for CCX168-M1)	Table 6.1 of Bioanalytical Analysis Report within the Attachments for PC0654_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −2.7% to 3.3% CCX168-M1: −3.4% to 4.3% CCX168-[redacted]: −4.7% to 4.3%	Tables 6.15 to 6.17 of Bioanalytical Analysis Report within the Attachments for PC0654_168
	Cumulative precision: ≤x% CV	CCX168: ≤6.9% CCX168-M1: ≤7.9% CCX168-[redacted]: ≤6.4%	
QC performance	Cumulative bias range: x to y%	CCX168: −1.3% to 1.0%* CCX168-M1: 0.0% to 1.4%* CCX168-[redacted]: −1.1% to 1.6%* (*excluding outlier)	Table 6.9 to 6.11 of Bioanalytical Analysis Report within the Attachments for PC0654_168
	Cumulative precision: ≤x% CV	CCX168: ≤7.8 CCX168-M1: ≤9.3%* CCX168-[redacted]: ≤9.4%* (*excluding outlier)	

Summary of Method Performance for [redacted] Method [redacted]			
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	CCX168: ISR was performed in 9.8% of study samples (110 out of 1120), and 100% of the samples met the pre-specified criteria CCX168-M1: ISR was performed in 9.8% of study samples (110 out of 1120), and 100% of the samples met the pre-specified criteria CCX168-[redacted]: ISR was performed in 9.8% of study samples (110 out of 1120), and 85% of the samples met the pre-specified criteria	Tables 6.6 through 6.8 of Bioanalytical Analysis Report within the Attachments for PC0654_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All study samples were analyzed within the known stability period of 634 days when stored at −60°C to −80°C.	Section 3.2 of Bioanalytical Analysis Report within the Attachments for PC0654_168 and Tables 7.11 through 7.13 of PC0649_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 25 out of 25 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL; 23 out of 25 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL CCX168-M1: 24 out of 24 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL; 23 out of 24 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL CCX168-[redacted]: 25 out of 25 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL; 23 out of 25 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL	Tables 6.15 to 6.17 of Bioanalytical Analysis Report within the Attachments for PC0654_168

2.6.5.2.5 濃度分析法概要（[redacted]：PC0650_168）

Summary of Method Performance for [redacted] Method [redacted]			
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168-[redacted] in Rat Plasma by HPLC with MS/MS Detection (ChemoCentryx Doc ID PC0650_168) [redacted] Method ID [redacted]]		
Method description	CCX168, CCX168-M1, CCX168-[redacted] and the internal standard (ISTD), CCX168-d4, were extracted from rat plasma by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS)		
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rat plasma		
Validated assay range	2.00 to 2000 ng/mL for CCX168, 1.00 to 1000 ng/mL for CCX168-M1 and 1.00 to 1000 ng/mL for CCX168-[redacted]		
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rat plasma		
Minimum required dilutions (MRDs)	n/a		
Source and lot of reagents	No special reagents were used		
Regression model and weighting	CCX168, CCX168-M1 and CCX168-[redacted]: weighted ($1/x^2$) linear least-squares regression		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8 for each of the analytes: CCX168, CCX168-M1 and CCX168-[redacted]	Tables 6.9 through 6.11 of PC0650_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	−4.3% to 3.3%	
	CCX168-M1	−3.5% to 2.6%	
	CCX168-[redacted]	−4.3% to 5.3%	
	Cumulative precision (%CV) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	

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Summary of Method Performance for [redacted] Method [redacted]			
	CCX168	≤7.2%	
	CCX168-M1	≤7.4%	
	CCX168-[redacted]	≤6.8%	
Performance of QC during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	The following values were manually calculated by combining the additional validation batches:	Tables 6.15 through 6.20 of PC0650_168
	QCs for CCX168: 2.00* 6.00, 100 and 1600 ng/mL	−5.8% to 3.3%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	0.5% to 2.6%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	−4.3% to 5.0%	
	*only included in 4 out of 6 analytical runs		
	Inter-batch %CV	The following values were manually calculated by combining the additional validation batches:	
	QCs for CCX168: 2.00*, 6.00, 100.0 and 1600 ng/mL	≤10.7%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	≤19.9%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	≤7.9%	
	*only included in 4 out of 6 analytical runs		
	Total Error (TE)	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]		
Selectivity & matrix effect	Aliquots of blank rat plasma from six different lots were tested for endogenous interferences. There were no interference peaks (>20% of the LLOQ calibration standard response) detected in the six individual blank matrix samples at the retention time of CCX168, CCX168-M1, and CCX168-[redacted]. There were peaks observed in the ULOQ calibration injections of each analyte with an area >20.0% of the LLOQ. A peak was observed in the CCX168-[redacted] channel in the injections spiked with CCX168 and CCX168-M1 and a peak was observed in the CCX168 channel in the injection spiked with CCX168-[redacted]. It was determined that the peaks were the result of impurities in the reference standards and did not impact the results of this study. There were no interference peaks detected at the ISTD retention time (>5% of the internal standard peak response in the control zero sample) for the six individual blank matrix samples or validation run blank samples. The mean accuracy of each of the six spiked individual blank matrix samples was within the acceptance criteria stated in the protocol. The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria as stated in the protocol and the matrix factor was not considered to impact assay performance.	Figures 8.1 through 8.7, Tables 6.2 through 6.7 and Sections 4.3 through 4.4 of PC0650_168
Interference and specificity	n/a	n/a
Hemolysis effect	Range of %bias: CCX168: −3.1% to 3.8% CCX168-M1: −3.9% to 5.7% CCX168-[redacted]: −5.8% to 0.7% The presence of hemolyzed red blood cells in the rat plasma did not affect the quantification of CCX168, CCX168-M1 and CCX168-[redacted].	Tables 6.39 through 6.41 and Section 4.16 of PC0650_168
Lipemic effect	n/a	n/a
Dilution linearity & hook effect	CCX168: Tested at 5000 ng/mL using a 25-fold dilution (%bias ranged from −2.4% to 5.8%) CCX168-M1: Tested at 5000 ng/mL using a 25-fold dilution (%bias ranged from −6.4% to 5.2%) CCX168-[redacted]: Tested at 5000 ng/mL using a 25-fold dilution (%bias ranged from −5.0% to 5.8%)	Tables 6.15 through 6.17 of PC0650_168
Bench-top/process stability	CCX168 and CCX168-M1 are stable in rat plasma at room temperature for 4 hr and on wet ice for 4 hr CCX168-[redacted] is stable in rat plasma on wet ice for 4 hr. The stability of CCX168, CCX168-M1, and CCX168-[redacted] in the extracts was found to be acceptable. Stability was confirmed for 116 hr at 2 to 8°C.	Tables 6.33 through 6.35 of PC0650_168 Tables 6.24 through 6.26 of PC0650_168
Freeze-Thaw stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in rat plasma after 4 freeze-thaw cycles at −60°C to −80°C	Tables 6.30 through 6.32 of PC0650_168

Summary of Method Performance for [redacted] Method [redacted]			
Long-term stability	CCX168, CCX168-M1, and CCX168-[redacted] are stable in rat plasma for 85 days when stored in a freezer set to maintain −60°C to −80ºC.		Tables 6.36 through 6.38 of PC0650_168
Parallelism	n/a		n/a
Carry over	There was no evidence of carry over (>20% of the LLOQ calibration standard response) to the blank matrix extracts injected immediately after the two highest calibration standards for analytes CCX168 and CCX168-M1. Throughout the study, peaks with areas >20.0% of the LLOQ were observed in the channel for analyte CCX168-[redacted]; however, it was determined that these peaks did not impact the results of the study.		Figure 8.8 and Section 4.5 of PC0650_168
Method Performance in Study PC0655_168 (26-Week Repeat-Dose Toxicity in Rats)			
Assay passing rate	Include incurred sample re-analysis passing rate.	CCX168: 100% (12 out of 12 analytical runs) CCX168-M1: 91.7% (11 out of 12 analytical runs) CCX168-[redacted]: 91.7% (11 out of 12 analytical runs)	Table 6.1 and Section 4.1 in Bioanalytical Analysis Report within the Attachments for PC0655_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −4.0% to 3.8% CCX168-M1: −1.8% to 2.3% CCX168-[redacted]: −6.5% to 4.0%	Tables 6.15 through 6.17 in Bioanalytical Analysis Report within the Attachments for PC0655_168
	Cumulative precision: ≤x% CV	CCX168: ≤6.9% CCX168-M1: ≤7.6% CCX168-[redacted]: ≤7.1%	
QC performance	Cumulative bias range: x to y%	CCX168: −9.8% to 3.0% CCX168-M1: −11.4% to 4.6% CCX168-[redacted]: −8.4% to 7.2%	Tables 6.9 through 6.11 in Bioanalytical Analysis Report within the Attachments for PC0655_168
	Cumulative precision: ≤x% CV	CCX168: ≤15.0% CCX168-M1: ≤10.6% CCX168-[redacted]: ≤8.8%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	CCX168: ISR was performed in 10.0% of study samples (40 out of 399), and 100% of the samples met the pre-specified criteria CCX168-M1: ISR was performed in 10.0% of study samples (40 out of 399), and 95% of the samples met the pre-specified criteria CCX168-[redacted]: ISR was performed in 10.0% of study samples (40 out of 399), and 90% of the samples met the pre-specified criteria	Tables 6.6 through 6.8 in Bioanalytical Analysis Report within the Attachments for PC0655_168

Summary of Method Performance for [redacted] Method [redacted]			
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within the known stability period of 85 days when stored at −60°C to −80°C.	Section 3.2 in Bioanalytical Analysis Report within the Attachments for PC0655_168 and Tables 6.36 through 6.38 of PC0650_168
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 12 out of 12 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 4.00, 20.0, 400, 1000, 2000; 11 out of 12 calibrators at each of the following concentrations met the acceptance criteria: 80.0, 1700 ng/mL CCX168-M1: 11 out of 11 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 40.0, 200, 500, 1000 ng/mL; 10 out of 11 calibrators at the following concentration met the acceptance criteria: 850 ng/mL; 9 out of 11 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL CCX168-[redacted]: 11 out of 11 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 1000 ng/mL; 10 out of 11 calibrators at the following concentration met the acceptance criteria: 850 ng/mL	Tables 6.15 through 6.17 in Bioanalytical Analysis Report within the Attachments for PC0655_168

2.6.5.2.6 濃度分析法概要（[redacted]：PC0651_168 及び PC0651_168_a）

Summary of Method Performance for [redacted] Method [redacted]			
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168-[redacted] in Rabbit Plasma by HPLC with MS/MS Detection (ChemoCentryx Doc ID PC0651_168) [[redacted] Method ID [redacted]] Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168-[redacted] in Rabbit Plasma by HPLC with MS/MS Detection, Addendum 1 (ChemoCentryx Doc ID PC0651_168_a) [[redacted] Method ID [redacted]]		
Method description	CCX168, CCX168-M1 and CCX168-[redacted] and the internal standard (ISTD), CCX168-d4, were extracted from rabbit plasma by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS)		
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rabbit plasma		
Validated assay range	1.00 to 1000 ng/mL for CCX168, CCX168-M1 and CCX168-[redacted]		
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA rabbit plasma		
Minimum required dilutions (MRDs)	n/a		
Source and lot of reagents	No special reagents were used		
Regression model and weighting	CCX168, CCX168-M1 and CCX168-[redacted]: weighted ($1/x^2$) linear least-squares regression		
Validation parameters	Method Validation Summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8 for each of the analytes: CCX168, CCX168-M1 and CCX168-[redacted]	Tables 6.9 through 6.11 of PC0651_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	−2.8% to 6.0%	
	CCX168-M1	−3.0% to 5.0%	

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Summary of Method Performance for [redacted] Method [redacted]			
	CCX168-[redacted]	−4.0% to 5.3%	
	Cumulative precision (%CV) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	≤5.9%	
	CCX168-M1	≤8.4%	
	CCX168-[redacted]	≤6.1%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	The following values were manually calculated by combining the additional validation batches:	Tables 6.15 through 6.20 of PC0651_168
	QCs for CCX168: 1.00* 3.00, 50.0 and 800 ng/mL	−2.9% to 4.0%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	−4.1% to 5.0%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	−12.8% to 0.6%	
	*only included in 3 out of 6 analytical runs		
	Inter-batch %CV	The following values were manually calculated by combining the additional validation batches:	
	QCs for CCX168: 1.00*, 3.00, 50.0 and 800 ng/mL	≤10.1%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	≤12.9%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	≤12.4%	
	*only included in 3 out of 6 analytical runs		
	Total Error (TE)	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]		
Selectivity & matrix effect	Aliquots of blank rabbit plasma from six different lots were tested for endogenous interferences. There were no interference peaks (>20% of the LLOQ calibration standard response) detected in the six individual blank matrix samples or the validation run blank samples at the retention time of CCX168, CCX168-M1, and CCX168-[redacted]. A peak was observed in the CCX168 channel in the sample spiked with CCX168-[redacted]. There was a peak observed in the CCX168-M1 channel in the sample spiked with CCX168. There were peaks detected in the CCX168-[redacted] channel in the samples spiked with CCX168 and CCX168-M1. These peaks were determined to be the result of impurities in the reference standards and do not impact the data. There were no interference peaks detected at the ISTD retention time (>5.0% of the internal standard peak response in the control zero sample) for the six individual blank matrix samples or validation run blank samples. In Run 3, several individual lots of matrix showed unacceptable selectivity results for all analytes (i.e. not within the range of +15.0% of the nominal concentration). Therefore, the selectivity test was repeated with six new lots in Run 4. Again, the data was unacceptable and inconsistent in three lots for CCX168 and in one lot for CCX168-M1 and CCX168-[redacted]. The test was repeated in Run 8, this time using twelve separate lots from which small pools were prepared at the LQC level. The accuracy of eleven out of the twelve pools was within the acceptance criteria for CCX168 and CCX168-M1; the failed lot for both CCX168 and CCX168-M1 was within 20% of the nominal concentration. The accuracy of ten out of twelve pools was within the acceptance criteria for CCX168-[redacted]. It was concluded that the method demonstrated acceptable selectivity for the quantification of CCX168, CCX168-M1 and CCX168-[redacted] in rabbit plasma. The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria as stated in the protocol and the matrix factor was not considered to impact assay performance.	Figures 8.1 through 8.7 and Tables 6.2 through 6.8 of PC0651_168
Interference and specificity	n/a	n/a
Hemolysis effect	Range of %bias: CCX168: −0.5% to 7.7% CCX168-M1: −2.3% to 3.7% CCX168-[redacted]: −5.1% to 9.0% The presence of hemolyzed red blood cells in the rabbit plasma did not affect the quantification of CCX168, CCX168-M1, and CCX168-[redacted] in this assay.	Section 4.18 and Tables 6.40 through 6.42 of PC0651_168
Lipemic effect	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]			
Dilution linearity & hook effect	CCX168:Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −1.2% to 2.8%) CCX168-M1:Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −5.2% to 1.0%) CCX168-[redacted]:Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −1.4% to 2.2%)		Tables 6.15 through 6.17 of PC0651_168
Bench-top/process stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in rabbit plasma at room temperature for 4 hr and on wet ice for 4 hr The stability of CCX168, CCX168-M1, and CCX168-[redacted] in the extracts was found to be acceptable. Stability was confirmed for 115 hr at 2 to 8°C.		Tables 6.37 through 6.39 of PC0651_168 Tables 6.25 through 6.27 of PC0651_168
Freeze-Thaw stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in rabbit plasma after 4 freeze-thaw cycles at −10 to −30°C and −60 to −80°C		Tables 6.34 through 6.36 of PC0651_168
Long-term stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in rabbit plasma after 401 days at −10 to −30°C and at −60 to −80°C		Table 6.11, Table 6.13 and Table 6.15 of PC0651_168_a
Parallelism	n/a		n/a
Carry over	In Runs 2 through 8, in the CCX168-[redacted] channel, peaks (>20% of the LLOQ calibration standard response) were observed in the blank matrix extracts injected immediately after the two highest calibration standards and in the blank matrix extracts spiked with the internal standard only. These peaks were caused partially by carry over and partially by baseline noise included in peak integration. These peaks have been determined to not affect the study data. There were no interference peaks detected at the ISTD retention time (>5% of the internal standard peak response in the control zero sample) of the ISTD peak area for the matrix blanks.		Figure 8.8 of PC0651_168
Method Performance in Study PC0672_168 (Reproductive and Developmental Toxicity: Embryo-Fetal Toxicity in Rabbits)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (4 out of 4 analytical runs for CCX168, CCX168-M1 and CCX168-[redacted])	Table 8.1 of Appendix 17 for PC0672_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −3.5% to 3.0% CCX168-M1: −2.6% to 5.0% CCX168-[redacted]: −5.4% to 8.0%	Tables 8.5 through 8.7 of Appendix 17 for PC0672_168
	Cumulative precision: ≤x% CV	CCX168: ≤5.9% CCX168-M1: ≤9.0% CCX168-[redacted]: ≤5.7%	
QC performance	Cumulative bias range: x to y%	CCX168: −4.0% to −1.8% CCX168-M1: −4.2% to 0.1% CCX168-[redacted]: −2.8% to 8.3%	Tables 8.11 through 8.13 of Appendix 17 for PC0672_168
	Cumulative precision: ≤x% CV	CCX168: ≤5.9% CCX168-M1: ≤6.9% CCX168-[redacted]: ≤8.5%	

Summary of Method Performance for [redacted] Method [redacted]			
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	CCX168: ISR was performed in 16.7% of study samples (24 out of 144), and 87.5% of the samples met the pre-specified criteria CCX168-M1: ISR was performed in 16.7% of study samples (24 out of 144), and 83.3% of the samples met the pre-specified criteria CCX168-[redacted]: ISR was performed in 16.7% of study samples (24 out of 144), and 41.7% of the samples met the pre-specified criteria	Table 8.16 through Table 8.18 of Appendix 17 for PC0672_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within the known stability period of 401 days when stored at −60°C to −80°C.	Section 1 in Appendix 17 of PC0672_168 and Table 6.11, Table 6.13 and Table 6.15 of PC0651_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 4 out of 4 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-M1: 4 out of 4 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-[redacted]: 4 out of 4 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL	Tables 8.5 through 8.7 of Appendix 17 for PC0672_168
Method Performance in Study PC0666_168 (Reproductive and Developmental Toxicity: Dose Range-Finding Embryo-Fetal Toxicity in Rabbits)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (7 out of 7 analytical runs for CCX168, CCX168-M1 and CCX168-[redacted])	Table 6.1 of Appendix 16 for PC0666_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −4.8% to 3.3% CCX168-M1: −5.4% to 3.8% CCX168-[redacted]: −6.1% to 5.0%	Tables 6.15 through 6.17 of Appendix 16 for PC0666_168
	Cumulative precision: ≤x% CV	CCX168: ≤6.9% CCX168-M1: ≤8.4% CCX168-[redacted]: ≤9.6%	
QC performance	Cumulative bias range: x to y%	CCX168: −4.0% to −1.6% CCX168-M1: −1.0% to 0.2% CCX168-[redacted]: −4.0% to 2.5%	Tables 6.9 through 6.11 of Appendix 16 for PC0666_168

Summary of Method Performance for [redacted] Method [redacted]			
	Cumulative precision: ≤x% CV	CCX168: ≤9.5% CCX168-M1: ≤8.9% CCX168-[redacted]: ≤8.7%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	CCX168: ISR was performed in 13.2% of study samples (42 out of 317), and 69.0% of the samples met the pre-specified criteria CCX168-M1: ISR was performed in 13.2% of study samples (42 out of 317), and 69.0% of the samples met the pre-specified criteria CCX168-[redacted]: ISR was performed in 13.2% of study samples (42 out of 317), and 16.7% of the samples met the pre-specified criteria	Tables 6.6 through 6.8 of Appendix 16 for PC0666_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within the known stability period of 401 days when stored at −60°C to −80°C.	Section 3.2 in Appendix 16 of PC0666_168 and Table 6.11, Table 6.13 and Table 6.15 of PC0651_168_a
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 7 out of 7 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-M1: 7 out of 7 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-[redacted]: 7 out of 7 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850 ng/mL; 6 out of 7 calibrators at the following concentration met the acceptance criteria: 1000 ng/mL	Tables 6.15 through 6.17 of Appendix 16 for PC0666_168

2.6.5.2.7 濃度分析法概要（[redacted]：PC0652_168 及び PC0652_168_a）

Summary of Method Performance for [redacted] Method [redacted]		
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168[redacted] in Hamster Plasma (Golden Syrian) by HPLC with MS/MS Detection (ChemoCentryx Doc ID PC0652_168) [[redacted] Method ID [redacted]] Validation of a Method for the Determination of CCX168, CCX168-M1 and CCX168[redacted] in Hamster Plasma (Golden Syrian) by HPLC with MS/MS Detection, Addendum 1 (ChemoCentryx Doc ID PC0652_168_a) [[redacted] Method ID [redacted]]	
Method description	CCX168, CCX168-M1 and CCX168-[redacted] and the internal standard (ISTD), CCX168-d4, were extracted from hamster plasma (Golden Syrian) by protein precipitation. The supernatant was analyzed using liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS)	
Materials used for standard calibration curve and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL]; Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA hamster plasma (Golden Syrian)	
Validated assay range	2.00 to 2000 ng/mL for CCX168, 1.00 to 1000 ng/mL for CCX168-M1 and 1.00 to 1000 ng/mL for CCX168-[redacted] (PC0652_168). The same assay ranges were cross-validated for a different mass spectrometer instrument in PC0652_168_a. The method was revised to the following assay ranges on 04 Oct 2018, but was not used for any subsequent studies: 2.00 to 1000 ng/mL for CCX168, 1.00 to 500 ng/mL for CCX168-M1 and 1.00 to 500 for CCX168-[redacted] (PC0652_168_a).	
Materials used for quality controls (QCs) and concentration	CCX168, Lot No. [redacted] [Primary Stock concentration 200 µg/mL]; Lot No. [redacted] [Primary Stock concentration 200 µg/mL] CCX168-M1 (authentic compound [redacted]), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-[redacted] (authentic compound 不純物A*), Lot No. [redacted] [Primary Stock concentration 500 µg/mL]; Lot No. [redacted] [Primary Stock concentration 500 µg/mL] CCX168-d4 (also known as [redacted] [CCX168-ISTD] or CCX2140), Lot No. [redacted] (internal standard) [Primary Stock concentration 100 µg/mL] Blank K_2EDTA hamster plasma (Golden Syrian)	
Minimum required dilutions (MRDs)	n/a	
Source and lot of reagents	No special reagents were used	
Regression model and weighting	CCX168, CCX168-M1 and CCX168-[redacted]: weighted ($1/x^2$) linear least-squares regression	
Validation parameters	Method Validation Summary	Source location

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Summary of Method Performance for [redacted] Method [redacted]			
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	N = 8 for CCX168, CCX168-M1 and CCX168-[redacted]	Tables 6.15 through 6.17 of PC0652_168
	Cumulative accuracy (%bias) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	−4.1% to 2.7%	
	CCX168-M1	−4.0% to 2.9%	
	CCX168-[redacted]	−4.0% to 4.2%	
	Cumulative precision (%CV) from LLOQ to ULOQ	The following values were manually calculated by combining the additional validation batches:	
	CCX168	≤5.6%	
	CCX168-M1	≤6.1%	
	CCX168-[redacted]	≤5.1%	
Standard calibration curve performance during accuracy and precision runs (for cross-validated assay ranges; applicable to toxicology study PC0677_168 only)	Cumulative accuracy (%bias) from LLOQ to ULOQ	The values below were manually calculated by combining all validation batches for assay ranges: CCX168: 2.00 to 2000 ng/mL CCX168-M1: 1.00 to 1000 ng/mL CCX168-[redacted]: 1.00 to 1000 ng/mL	Tables 6.2 through 6.4 of PC0652_168_a
	CCX168	−6.5% to 4.3%	
	CCX168-M1	−10.8% to 5.0%	
	CCX168-[redacted]	−7.7% to 4.5%	
	Cumulative precision (%CV) from LLOQ to ULOQ	The values below were manually calculated by combining all validation batches for assay ranges: CCX168: 2.00 to 2000 ng/mL CCX168-M1: 1.00 to 1000 ng/mL CCX168-[redacted]: 1.00 to 1000 ng/mL	
	CCX168	≤8.7%	
	CCX168-M1	≤9.5%	
	CCX168-[redacted]	≤15.4%	
Standard calibration curve performance during accuracy and precision runs (For updated assay ranges on 04 Oct 2018; not applicable to any study)	Cumulative accuracy (%bias) from LLOQ to ULOQ	Assay ranges: CCX168: 2.00 to 1000 ng/mL CCX168-M1: 1.00 to 500 ng/mL CCX168-[redacted]: 1.00 to 500 ng/mL	Tables 6.2 through 6.4 of PC0652_168_a
	CCX168	−8.4% to 8.7%	
	CCX168-M1	−9.6% to 7.6%	
	CCX168-[redacted]	−9.2% to 12.4%	
	Cumulative precision (%CV) from LLOQ to ULOQ	Assay ranges: CCX168: 2.00 to 1000 ng/mL CCX168-M1: 1.00 to 500 ng/mL CCX168-[redacted]: 1.00 to 500 ng/mL	
		Not calculated; Run 12 only includes n = 1 calibration standards	

Summary of Method Performance for [redacted] Method [redacted]			
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	The following values were manually calculated by combining the additional validation batches:	Tables 6.21 through 6.26 of PC0652_168
	QCs for CCX168: 2.00* 6.00, 100 and 1600 ng/mL	−1.2% to 2.6%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	1.1% to 4.9%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	−0.58% to 4.2%	
	*only included in 4 out of 6 analytical runs		
	Inter-batch %CV	The following values were manually calculated by combining the additional validation batches:	
	QCs for CCX168: 2.00* 6.00, 100 and 1600 ng/mL	≤12.8%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800 ng/mL	≤18.1%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800 ng/mL	≤19.1%	
	*only included in 4 out of 6 analytical runs		
	Total Error (TE)	n/a	n/a
Performance of QCs during accuracy and precision runs (For cross-validated assay ranges; applicable to toxicology study PC0677_168 only)	Cumulative accuracy (%bias) in 4 QCs	The values below were manually calculated by combining all validation batches for assay ranges: CCX168: 2.00 to 2000 ng/mL CCX168-M1: 1.00 to 1000 ng/mL CCX168-[redacted]: 1.00 to 1000 ng/mL	Tables 6.8 through 6.10 of PC0652_168_a
	QCs for CCX168: 2.00* 6.00, 100 and 1600[1] ng/mL	−3.2% to 1.3%	
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800[2] ng/mL	−2.6% to 4.3%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800[2] ng/mL	−3.8% to 6.8%	
	*Only included in 2 out of 3 analytical runs [1]QC mistakenly prepared at 1580 ng/mL for Runs 9 and 10 [2]QC mistakenly prepared at 790 for Runs 9 and 10		
	Inter-batch %CV	The values below were manually calculated by combining all validation batches for assay ranges: CCX168: 2.00 to 2000 ng/mL CCX168-M1: 1.00 to 1000 ng/mL CCX168-[redacted]: 1.00 to 1000 ng/mL	
	QCs for CCX168: 2.00* 6.00, 100 and 1600[1] ng/mL	≤11.4%	

Summary of Method Performance for [redacted] Method [redacted]			
	QCs for CCX168-M1: 1.00*, 3.00, 50.0 and 800[2] ng/mL	≤13.0%	
	QCs for CCX168-[redacted]: 1.00*, 3.00, 50.0 and 800[2] ng/mL	≤12.4%	
	*only included in 2 out of 3 analytical runs [1]QC mistakenly prepared at 1580 ng/mL for Runs 9 and 10 [2]QC mistakenly prepared at 790 for Runs 9 and 10		
Performance of QCs during accuracy and precision runs (For updated assay ranges on 04 Oct 2018; not applicable to any study)	Cumulative accuracy (%bias) in 4 QCs	Assay ranges: CCX168: 2.00 to 1000 ng/mL CCX168-M1: 1.00 to 500 ng/mL CCX168-[redacted]: 1.00 to 500 ng/mL	Tables 6.8 through 6.10 of PC0652_168_a
	QCs for CCX168: 6.00, 100, 600 and 750 ng/mL	−1.8% to 10.7%	
	QCs for CCX168-M1: 3.00, 50.0, 300 and 375 ng/mL	−9.3% to 3.8%	
	QCs for CCX168-[redacted]: 3.00, 50.0, 300 and 375 ng/mL	−2.7% to 6.7%	
	Intra-batch %CV	Assay ranges: CCX168: 2.00 to 1000 ng/mL CCX168-M1: 1.00 to 500 ng/mL CCX168-[redacted]: 1.00 to 500 ng/mL	
	QCs for CCX168: 6.00, 100, 600 and 750 ng/mL	≤3.6%	
	QCs for CCX168-M1: 3.00, 50.0, 300 and 375 ng/mL	≤4.9%	
	QCs for CCX168-[redacted]: 3.00, 50.0, 300 and 375 ng/mL	≤4.6%	

Summary of Method Performance for [redacted] Method [redacted]		
Selectivity & matrix effect	There were no interference peaks (>20% of the LLOQ calibration standard response) detected in the six individual blank matrix samples or the validation run blank samples at the retention time of CCX168, CCX168-M1 and CCX168-[redacted]. There were peaks (>20% of the LLOQ calibration standard response) detected in the ULOQ samples without internal standard in each analyte channel. Peaks were observed in the CCX168-M1 and CCX168-[redacted] channels in the sample spiked with CCX168. Peaks were observed in the CCX168 and CCX168-[redacted] channels in the sample spiked with CCX168-M1. A peak was observed in the CCX168 channel in the sample spiked with CCX168-[redacted]. These peaks were determined to be the result of impurities in the reference standards and do not impact the data. There were no interference peaks detected at the ISTD retention time (>5% of the internal standard peak response in the control zero sample) for the six individual blank matrix samples or validation run blank samples. The mean accuracy of each of the twelve spiked individual blank matrix samples was within the acceptance criteria stated in the protocol for analyte CCX168. In Run 2, the mean accuracy of each of the six spiked individual blank matrix samples met acceptance criteria for analyte CCX168-M1. In Run 7, one of the six additional spiked individual blank matrix samples had a mean bias of 115.7% which is just outside the acceptance criteria. The overall selectivity of CCX168-M1 was considered acceptable based on these results. In Run 2, the mean accuracy of each of the six spiked individual blank matrix samples did not meet acceptance criteria for analyte CCX168-[redacted]. Selectivity was repeated with six additional individual blank matrix samples in Run 7 due to poor chromatography. In Run 7, the accuracy of four of six spiked individual blank matrix samples were within the acceptance criteria for analyte CCX168-[redacted]; however, the accuracy for two blank matrix samples did not meet acceptance criteria. It was therefore concluded that the method demonstrated acceptable selectivity for the quantification of CCX168 and CCX168-M1, but there is some individual variability for the selectivity of CCX168-[redacted] in hamster plasma. The precision of the matrix factor evaluation met the acceptance criteria as stated in the protocol and the matrix factor was not considered to impact assay performance.	Figures 8.1 through 8.6, Tables 6.2 through 6.13 and Section 4.3 and 4.4 of PC0652_168
Interference and specificity	n/a	n/a

Summary of Method Performance for [redacted] Method [redacted]		
Hemolysis effect	The data were within the acceptance criteria for analytes CCX168 and CCX168-M1 as stated in the protocol. In Runs 2 and 7, results from the hemolysis assessment did not meet acceptance criteria for analyte CCX168-[redacted]. The experiment was not repeated. It was demonstrated that the presence of hemolyzed red blood cells in the hamster plasma did not affect the quantification of CCX168 and CCX168-M1 in this assay, but did affect the results for CCX168-[redacted]. Range of %bias: CCX168: −12.0% to 6.2% CCX168-M1: −11.4% to 11.0% CCX168-[redacted]: 24.1% to 646.7% (Did not meet acceptance criteria)	Tables 6.48 through 6.50 and Section 4.17 of PC0652_168
Lipemic effect	n/a	n/a
Dilution linearity & hook effect	CCX168: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −5.2% to 33.6%) (Intra-run %bias: 4.7% for n = 12); 10 out of 12 replicates met acceptance criteria CCX168-M1: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −6.2% to 14.8%) (Intra-run %bias: 0.4% for n = 12); 12 out of 12 replicates met acceptance criteria CCX168-[redacted]: Tested at 5000 ng/mL using a 10-fold dilution (%bias ranged from −0.4% to 45.2%) (Intra-run %bias: 7.0% for n = 12); 11 out of 12 replicates met acceptance criteria	Tables 6.21 through 6.26 of PC0652_168
Dilution linearity & hook effect (For updated assay ranges on 04 Oct 2018; not applicable to any study)	CCX168: Tested at 5000 ng/mL using a 20-fold dilution (%bias ranged from −13.4% to −7.2%) (Intra-run %bias was manually calculated and was −10.2% for n = 6); 6 out of 6 replicates met acceptance criteria CCX168-M1: Tested at 5000 ng/mL using a 20-fold dilution (%bias ranged from −7.4% to −0.2%) (Intra-run %bias was manually calculated and was −3.2% for n = 6); 6 out of 6 replicates met acceptance criteria CCX168-[redacted]: Tested at 5000 ng/mL using a 20-fold dilution (%bias ranged from −3.0% to 2.2%) (Intra-run %bias was manually calculated and was 0.4% for n = 6); 6 out of 6 replicates met acceptance criteria	Tables 6.8 through 6.10 of PC0652_168_a
Bench-top/process stability	CCX168, CCX168-M1 and CCX168-[redacted] are stable in hamster plasma at room temperature and on wet ice for 4 hr The stability of CCX168 and CCX168-M1 in the extracts was found to be acceptable and stability was confirmed for 148 hr at 2 to 8°C.	Tables 6.42 through 6.44 and Section 4.15 of PC0652_168 Tables 6.30 through 6.32 and Section 4.15 of PC0652_168
Freeze-Thaw stability	CCX168, CCX168-M1, and CCX168-[redacted] are stable in hamster plasma after four freeze-thaw cycles at −60°C to −80°C and when thawed on wet ice.	Tables 6.39 through 6.41 and Section 4.14 of PC0652_168
Long-term stability	CCX168, CCX168-M1, and CCX168-[redacted] are stable in hamster plasma for 422 days when stored in a freezer set to maintain −60°C to −80°C.	Tables 6.45 through 6.47 and Section 4.16 of PC0652_168

Summary of Method Performance for [redacted] Method [redacted]			
Parallelism	n/a		n/a
Carry over	There was no evidence of carry over (>20% of the LLOQ calibration standard response) to the blank matrix extracts injected immediately after the two highest calibration standards in Runs 1 through 5. In Run 6, there was evidence of carry over in a blank matrix extract injected immediately after the two highest calibration standards for CCX168 and CCX168-[redacted]. This carry over did not impact the processed-sample viability experiment in Run 6. In Run 7, there was a peak observed in a blank matrix extract injected immediately after the two highest calibration standards for CCX168-[redacted]; the peak was determined to be caused in part from carry over and in part from baseline noise in the channel. There were no interference peaks detected at the ISTD retention time (>5% of the internal standard peak response in the control zero sample) of the ISTD peak area for the matrix blanks.		Figure 8.7 and Section 4.5 of PC0652_168
Method Performance in Study PC0673_168 (An Oral (Gavage) Pre-natal/Post-natal Developmental Toxicity Study of CCX168 in Hamsters, Including a Post-natal Behavioral/Functional Evaluation)			
Assay passing rate	Include incurred sample re-analysis passing rate	CCX168: 100% (6 out of 6 analytical runs) CCX168-M1: 100% (5 out of 5 analytical runs)	Table 8.1 and Section 4.2 in Appendix 42 of PC0673_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −5.5% to 5.3% CCX168-M1: −6.5% to 9.5%	Tables 8.3 through 8.4 in Appendix 42 of PC0673_168
	Cumulative precision: ≤x% CV	CCX168: ≤4.9% CCX168-M1: ≤4.8%	
QC performance	Cumulative bias range: x to y%	CCX168: −3.1% to 10.0% CCX168-M1: −4.1 to 12.6%	Tables 8.7 through 8.8 in Appendix 42 of PC0673_168
	Cumulative precision: ≤x% CV	CCX168: ≤7.0% CCX168-M1: ≤8.6%	
Method reproducibility	E.g. ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was not required for this study	n/a
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within the known stability period of 422 days when stored at −60°C to −80°C.	Section 1 in Appendix 42 of PC0673_168 and Tables 6.45 through 6.46 of PC0652_168

Summary of Method Performance for [redacted] Method [redacted]			
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 6 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 400, 1000, 1700, 2000 ng/mL; 5 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 20.0 and 80.0 ng/mL; 2 out of 6 calibrators at the following concentration met the acceptance criteria: 4.00 ng/mL CCX168-M1: 5 out of 5 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 200, 500, 850, 1000 ng/mL; 4 out of 5 calibrators at the following concentration met the acceptance criteria: 40.0 ng/mL; 3 out of 5 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL	Tables 8.3 through 8.4 in Appendix 42 of PC0673_168
Method Performance in Study PC0667_168 (A Dose Range-Finding Embryo-Fetal Development Study of CCX168 in Hamsters)			
Assay passing rate	Include incurred sample re-analysis passing rate	100% assay passing rate (6 out of 6 analytical runs for CCX168, CCX168-M1 and CCX168-[redacted])	Table 6.1 and Section 4.2 in Appendix 15 of PC0667_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −2.5% to 3.5% CCX168-M1: −2.0% to 3.0% CCX168-[redacted]: −2.8% to 2.5%	Tables 6.15 through 6.17 in Appendix 15 of PC0667_168
	Cumulative precision: ≤x% CV	CCX168: ≤8.9% CCX168-M1: ≤9.2% CCX168-[redacted]: ≤6.6%	
QC performance	Cumulative bias range: x to y%	CCX168: −9.2% to −4.1% CCX168-M1: −7.3% to −3.4% CCX168-[redacted]: −8.0% to −5.4%	Tables 6.9 through 6.11 in Appendix 15 of PC0667_168
	Cumulative precision: ≤x% CV	CCX168: ≤7.8% CCX168-M1: ≤10.2% CCX168-[redacted]: ≤10.5%	

Summary of Method Performance for [redacted] Method [redacted]			
Method reproducibility	E.g. ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	CCX168: ISR was performed in 10.6% of study samples (24 out of 227), and 92.7% of the samples met the pre-specified criteria CCX168-M1: ISR was performed in 10.6% of study samples (24 out of 227), and 85.4% of the samples met the pre-specified criteria CCX168-[redacted]: ISR was performed in 10.6% of study samples (24 out of 227), and 62.5% of the samples met the pre-specified criteria	Tables 6.6 through 6.8 and Section 4.4 in Appendix 15 of PC0667_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within the known stability period of 422 days when stored at −60°C to −80°C.	Section 3.2 in Appendix 15 of PC0667_168 and Tables 6.45 through 6.47 of PC0652_168
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 6 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 4.00, 20.0, 80.0, 400, 1000, 1700, 2000 ng/mL CCX168-M1: 6 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-[redacted]: 6 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 40.0, 200, 500, 850 ng/mL; 5 out of 6 calibrators at each of the following concentrations met the acceptance criteria: 10.0, 1000 ng/mL	Tables 6.15 through 6.17 in Appendix 15 of PC0667_168
Method Performance in Study PC0671_168 (An Embryo-Fetal Development Toxicity Study of CCX168 in Hamsters)			
Assay passing rate	Include incurred sample re-analysis passing rate	CCX168: 100% (5 out of 5 analytical runs) CCX168-M1: 100% (5 out of 5 analytical runs) CCX168-[redacted]: 100% (5 out of 5 analytical runs)	Tables 6.1 and Section 4.2 in Appendix 15 of PC0671_168
Standard curve performance	Cumulative bias range: x to y%	CCX168: −3.5% to 3.5% CCX168-M1: −3.6% to 3.5% CCX168-[redacted]: −7.0% to 5.4%	Tables 6.14 through Table 6.16 in in Appendix 15 of PC0671_168
	Cumulative precision: ≤x% RSD	CCX168: ≤6.5% CCX168-M1: ≤9.1% CCX168-[redacted]: ≤10.4%	

Summary of Method Performance for [redacted] Method [redacted]			
QC performance	Cumulative bias range: x to y%	CCX168: −3.1% to −1.8% CCX168-M1: −1.5% to 0.0% CCX168-[redacted]: −1.8% to 4.1%	Tables 6.8 through Table 6.10 in in Appendix 15 of PC0671_168
	Cumulative precision: ≤x% RSD	CCX168: ≤4.5% CCX168-M1: ≤5.7% CCX168-[redacted]: ≤13.0%	
Method reproducibility	E.g., ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was performed in 10.9% of study samples (24 out of 220) CCX168: 95.8% of the samples met the pre-specified criteria CCX168-M1: 95.8% of the samples met the pre-specified criteria CCX168-[redacted]: 87.5% of the samples met the pre-specified criteria	Tables 6.5 through Table 6.7 and Section 4.4 in in Appendix 15 of PC0671_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All study samples were analyzed within the known stability period of 422 days when stored at −60°C to −80°C.	Section 5 in Appendix 15 of PC0671_168 and Tables 6.45 through Table 6.47 of PC0652_168
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 5 out of 5 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 4.00, 20.0, 80.0, 400, 1000, 1700, 2000 ng/mL CCX168-M1: 5 out of 5 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL CCX168-[redacted]: 5 out of 5 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 10.0, 40.0, 200, 500, 850, 1000 ng/mL; 4 out of 5 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL	Tables 6.14 through Table 6.16 in in Appendix 15 of PC0671_168
Method Performance in Study PC0677_168 (A 13-Week Toxicity and Toxicokinetic Study of CCX168 in Hamsters with a 4-Week Recovery Period)			
Assay passing rate	Include incurred sample re-analysis passing rate	CCX168: 76.5% (13 out of 17 analytical runs) CCX168-M1: 84.6% (11 out of 13 analytical runs) CCX168-[redacted]: 75.0% (12 out of 16 analytical runs)	Table 8.1, Tables 8.3 through 8.5 in Appendix 18 of PC0677_168

Summary of Method Performance for [redacted] Method [redacted]			
Standard curve performance	Cumulative bias range: x to y%	CCX168: −9.5% to 6.0% CCX168-M1: −7.5% to 5.8% CCX168-[redacted]: −8.4% to 5.0%	Tables 8.3 through 8.5 in Appendix 18 of PC0677_168
	Cumulative precision: ≤x% CV	CCX168: ≤6.7% CCX168-M1: ≤9.0% CCX168-[redacted]: ≤8.5%	
QC performance	Cumulative bias range: x to y%	CCX168: −5.6% to 10.0% CCX168-M1: −5.1% to 8.8% CCX168-[redacted]: −4.8% to 7.2%	Tables 8.9 through 8.11 in Appendix 18 of PC0677_168
	Cumulative precision: ≤x% CV	CCX168: ≤9.6% CCX168-M1: ≤13.8% CCX168-[redacted]: ≤16.3%	
Method reproducibility	E.g. ISR was performed in x% of study samples, and x% of the samples met the pre-specified criteria	ISR was not required for this study	Section 1 in Appendix 18 of PC0677_168
Study sample analysis/stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	All samples were analyzed within 183 days of collection following storage at −60°C to −80°C. Long-term frozen matrix stability has been established for 422 days when stored at −60°C to −80°C.	Section 5.6 in Appendix 18 of PC0677_168 and Tables 6.45 through 6.47 of PC0652_168

Summary of Method Performance for [redacted] Method [redacted]			
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ	CCX168: 13 out of 13 calibrators at each of the following concentrations met the acceptance criteria: 2.00, 20.0, 400, 1000, 1700 ng/mL; 12 out of 13 calibrators at the following concentration met the acceptance criteria: 4.00 ng/mL; 11 out of 13 calibrators at each of the following concentrations met the acceptance criteria: 80.0, 2000 ng/mL CCX168-M1: 11 out of 11 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 200, 500, and 850 ng/mL; 10 out of 11 calibrators at each of the following concentrations met the acceptance criteria: 10.0, 40.0 ng/mL; 9 out of 11 calibrators at the following concentration met the acceptance criteria: 1000 ng/mL; 8 out of 11 calibrators at the following concentration met the acceptance criteria: 2.00 ng/mL CCX168-[redacted]: 12 out of 12 calibrators at each of the following concentrations met the acceptance criteria: 10.0, 200, 500 ng/mL; 11 out of 12 calibrators at each of the following concentrations met the acceptance criteria: 1.00, 2.00, 40.0, and 850 ng/mL; 10 out of 12 calibrators at the following concentration met the acceptance criteria: 1000 ng/mL	Tables 8.3 through 8.5 in Appendix 18 of PC0677_168

2.6.5.3 薬物動態試験：単回投与後の吸収

2.6.5.3.1 Caco-2 細胞単層膜における透過性

		Test Article: CCX168		
		Location in CTD: 4.2.2.2.1		
		Study No. PC0361_168_a		
Type of Study: *In Vitro* Permeability across the Caco-2 Cell Monolayers				
Method: The intestinal permeability of CCX168 across the Caco-2 cell monolayers was measured in the apical-to-basolateral (A-B) and basolateral-to-apical (B-A) directions at 37ºC with 5 µmol/L CCX168 in a buffer containing 5% bovine serum albumin at pH 7.4				
Tabulated Results:		CCX168	Control 1: Antipyrine	Control 2: Loperamide
	$P_{app\ (A-B)}$ ($\times 10^{-6}$ cm/s)	25.2	50.4	11.4
	$P_{app\ (B-A)}$ ($\times 10^{-6}$ cm/s)	27.3	24.0	33.2
	Efflux Index (B-A/A-B)	1.08	0.476	2.91
Additional Information: None				

2.6.5.3.2 マウス、ラット及びサルに単回経口投与したときの薬物動態パラメータ

			Test Article: CCX168	
			Location in CTD: See end of the table for each location.	
			Study No.: See end of the table for each study number.	
Species		Mice (CD-1)	Rat (Sprague-Dawley)	Monkey (Cynomolgus)
Gender (M/F)/Number of Animals:		F / 9	M / 2	M / 3
Feeding Condition:		Fed	Fasted	Fed
Vehicle/Formulation:		1% HPMC at 0.4 mg/mL	1% HPMC at 0.4 mg/mL	PEG-400/Kolliphor HS-15 ([redacted], v/v) at 15 mg/mL
Method of Administration:		Oral	Oral	Oral
Dose (mg/kg):		2	2	15
Sample (e.g., Whole Blood, Plasma, Serum):		Plasma	Plasma	Plasma
Analyte:		CCX168	CCX168	CCX168
Assay:		LC-MS/MS	LC-MS/MS	LC-MS/MS
PK Parameters (Mean):	C_{max} (ng/mL): $AUC_{0-\infty}$ (ng•hr/mL): $MRT_{0-\infty}$ (hr): $t_{1/2}$ (hr): T_{max} (hr): F (%):	75 240 4.0 2.9 1.0 17	152 434 2.7 2.3 1.0 27	815 8840 7.5 4.5 5.3 —
Location in CTD:		4.2.2.2.2	4.2.2.2.3	4.2.2.2.13
Study No.:		PC0366_168	PC0365_168_a	PC0653_168
Additional Information: None				

2.6.5.4 薬物動態試験：反復投与後の吸収

2.6.5.4.1 ラットに反復経口投与したときの薬物動態パラメータ

			Test Article: CCX168	
			Location in CTD: See end of the table for each location.	
			Study No.: See end of the table for each study number.	
Species	Rat (Sprague-Dawley)	Rat (Sprague-Dawley)	Rat (Sprague-Dawley)	Rat (Sprague-Dawley)
Gender (M/F) / Number of Animals:	M/F (9[a] per sex)	M/F (9[a] per sex)	M/F (9[a] per sex)	M/F (9[a] per sex)
Feeding Condition:	Fed	Fed	Fed	Fed
Vehicle/Formulation:	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)
Method of Administration:	Oral	Oral	Oral	Oral
Dose (mg/kg):	100 mg/kg q.d. × 4 weeks	100 mg/kg q.d. × 13 weeks	100 mg/kg b.i.d. × 26 weeks	100 mg/kg b.i.d. × 26 weeks
Sample:	Plasma	Plasma	Plasma	Plasma
Analyte:	CCX168	CCX168	CCX168	CCX168-M1
Assay:	LC-MS/MS (validated)	LC-MS/MS (validated)	LC-MS/MS (validated)	LC-MS/MS (validated)
PK Parameters (Mean): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL):	Male Week 4: 3830 1 50000 Female Week 4: 5090 4 67200	Male Week 13: 3870 1 56600 Female Week 13: 10100 2 114000	Male Week 26: 6100 2 82700 Female Week 26: 7370 1 106000	Male Week 26: 545 12 7090 Female Week 26: 214 12 3780
Location in CTD:	4.2.3.2.1	4.2.3.2.2	4.2.3.2.3	4.2.3.2.3
Study No.:	PC0384_168	PC0356_168	PC0655_168	PC0655_168
Additional Information: [a] In the rat studies, 10 animals per sex were used for the satellite TK arm and 9 animals were bled for sampling. Each sparse sampling time point used 3 animals to produce a composite TK profile. The TK data at the NOAEL dose is reported in this table.				

2.6.5.4.2 ハムスター及びサルに反復経口投与したときの薬物動態パラメータ

			Test Article: CCX168	
			Location in CTD: See end of the table for each location.	
			Study No.: See end of the table for each study number.	
Species	Hamster (Golden Syrian)	Hamster (Golden Syrian)	Monkey (Cynomolgus)	Monkey (Cynomolgus)
Gender (M/F)/Number of Animals:	M/F (12[a] per sex)	M/F (12[a] per sex)	M/F (5 per sex)	M/F (6 per sex)
Feeding Condition:	Fed	Fed	Fed	Fed
Vehicle/Formulation:	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)
Method of Administration:	Oral	Oral	Nasogastric	Oral
Dose (mg/kg):	500 mg/kg b.i.d. × 13 weeks	500 mg/kg b.i.d. × 13 weeks	50 mg/kg q.d. × 4 weeks	30 mg/kg q.d. × 20 weeks
Sample:	Plasma	Plasma	Plasma	Plasma
Analyte:	CCX168	CCX168-M1	CCX168	CCX168
Assay:	LC-MS/MS (validated)	LC-MS/MS (validated)	LC-MS/MS (validated)	LC-MS/MS (validated)
PK Parameters (Mean): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL):	Male Week 13: 1800 1 31700 Female Week 13: 1890 2 33400	Male Week 13: 133 4 2630 Female Week 13: 110 2 2240	Male Week 4: 682 3 6830 Female Week 4: 334 3 2540	Male Week 20: 1640 4 15500 Female Week 20: 1700 4 15200
Location in CTD:	4.2.3.2.4	4.2.3.2.4	4.2.3.2.5	4.2.3.2.6
Study No.:	PC0677_168_a	PC0677_168_a	PC0385_168	PC0357_168
Additional Information: [a] In the hamster studies, 12 animals per sex were used for the satellite TK arm and 12 animals were bled for sampling. Each sparse sampling time point used 3 animals to produce a composite TK profile. The TK data at the NOAEL dose is reported in this table.				

2.6.5.4.3 サルに反復投与したときの薬物動態パラメータ

			Test Article: CCX168	
			Location in CTD: See end of the table for each location.	
			Study No.: See end of the table for each study number.	
Species	Monkey (Cynomolgus)	Monkey (Cynomolgus)		
Gender (M/F)/Number of Animals:	M/F (6 per sex)	M/F (6 per sex)		
Feeding Condition:	Fed	Fed		
Vehicle/Formulation:	PEG-400/Kolliphor HS-15 ([redacted], v/v)	PEG-400/Kolliphor HS-15 ([redacted], v/v)		
Method of Administration:	Nasogastric (1-5 weeks) /oral (6-44 weeks)	Nasogastric (1-5 weeks) /oral (6-44 weeks)		
Dose (mg/kg):	15 (1-25 weeks) / 22.5 (26-44 weeks) mg/kg b.i.d.	15 (1-25 weeks) / 22.5 (26-44 weeks) mg/kg b.i.d.		
Sample:	Plasma	Plasma		
Analyte:	CCX168	CCX168-M1		
Assay:	LC-MS/MS (validated)	LC-MS/MS (validated)		
PK Parameters (Mean): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL): C_{max} (ng/mL): T_{max} (hr): $AUC_{0\text{-}24hr}$ (ng•hr/mL):	Male Week 42: 2200 11 26400 Female Week 42: 2470 8 32200	Male Week 42: 538 10 9330 Female Week 42: 548 9 9840		
Location in CTD:	4.2.3.2.7	4.2.3.2.7		
Study No.:	PC0654_168	PC0654_168		
Additional Information: The TK data at the NOAEL dose is reported in this table.				

2.6.5.5 薬物動態試験：分布

2.6.5.5.1 雄アルビノ（SD）ラットにおける組織分布

	Test Article: [^{14}C]CCX168					
	Location in CTD: 4.2.2.3.4					
	Study No.: PC0641_168					
Species: Rat (Sprague-Dawley)						
Gender (M/F)/Number of Animals: M/6 (used for different time points)						
Feeding Condition: Fed						
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)						
Method of Administration: Oral						
Dose (mg/kg): 15						
Radionuclide: ^{14}C						
Specific Activity: 59.2 mCi/mmol						
Assay: Quantitative whole body autoradiography						
Sampling Time: 1, 2, 4, 8, 24, and 72 hr						
	Concentration (ng Equivalents [^{14}C]CCX168/g)					
	Time Points					
Tissues/organs	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr
Adrenal gland(s)	5730[a]	7060	8170	9660[a]	851	369
Arterial wall	ND	ND	1580	2310	ND	ND
Bile	11100	28300	75200	47500	ND	ND
Blood	572	653	1660	1150	126	84.2
Bone	51.2	196	193	173	BLQ	ND
Bone marrow	818	1450	2360	2450	257	60.3
Brain cerebellum	BLQ	75.5	119	175	BLQ	ND
Brain cerebrum	BLQ	83.0	116	180	BLQ	ND
Brain choroid plexus	650	1000	1990	2050	296	ND
Brain medulla	BLQ	83.2	132	185	BLQ	ND
Brain olfactory lobe	BLQ	70.8	157	132	BLQ	ND
Bulbo-urethral gland	766	2160	3460	4390	ND	ND
Cecum	536	1030	ND[b]	3540	3440	126
Diaphragm	1220	2790	4550	5310	288	100
Epididymis	82.8	339	644	2040	157	BLQ
Esophagus	ND[b]	1320	1660	4370	92.9	BLQ
Exorbital lacrimal gland	769	2010	3180	5000	196	68.9
Eye lens	BLQ	BLQ	BLQ	BLQ	BLQ	ND
Eye uveal tract	118	449	2120	1060	93.0	ND
Eye(s)	BLQ	172	540	194	BLQ	ND

		Test Article: [^{14}C]CCX168				
		Location in CTD: 4.2.2.3.4				
		Study No.: PC0641_168				
	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr
Fat (abdominal)	239	816	1820	7560	4010	1920
Fat (brown)	3290	10100	20500	25700	2580	396
Fat (mesenteric)	393	1730	3210	10200	5640	3340
Fat (reproductive)	189	1210	1490	7700	3480	2080
Fat (subcutaneous)	250	1460	2660	10100	5510	2650
Harderian gland	283	1150	3020	8060	1580	122
Intra-orbital lacrimal gland	651	2150	2820	4880	167	57.0
Kidney cortex	1620	3560	4500	5860	440	228
Kidney medulla	1580	2870	3300	3990	291	120
Kidney(s)	1620	3520	4420	5660	432	223
Large intestine	177	568	1040	1470	210	87.0
Liver	5690	11300	16800	21600	3210	1960
Lung(s)	1200	2260	3030	2830	188	138
Lymph node(s)	415	937	1460	2520	193	52.9
Muscle	432	1000	1660	2520	78.2	BLQ
Myocardium	1830	2850	4050	4450	237	160
Nasal turbinates	158	660	988	1050	125	68.5
Pancreas	1640	3190	6050	6960	231	85.8
Pituitary gland	966	2010	3150	3650	144	49.7
Preputial gland	389[a]	932[a]	2070[a]	7770[a]	3440[a]	1050[a]
Prostate gland	334	967	1800	2870	102	BLQ
Salivary gland(s)	1030	2290	3640	4480	183	59.5
Seminal vesicle(s)	102	212	416	679	118	ND
Skin (nonpigmented)	201	665	819	3030	1080	232
Small intestine	847	1530	3700	4520	1630	394
Spinal cord	BLQ	92.9	128	200	BLQ	ND
Spleen	1040	1850	2470	2620	218	159
Stomach	535	2280	2260	1880	140	BLQ
Testis(es)	BLQ	110	297	671	53.7	BLQ
Thymus	265	760	1430	2340	84.7	BLQ
Thyroid	1310	2360	3340	3620	282	200
Urinary bladder	1020	507	8090	2090	927	ND
Urine	641	926	4990	7190	510	161

Additional Information:
BLQ: Below the limit of quantitation (< 49.2 ng equivalents [^{14}C]CCX168/g); ND: not detectable (sample shape not discernible from background or surrounding tissue).
[a] Tissue appears to be contaminated by liquefied fat; [b] Not detectable due to flare of gastrointestinal contents.

2.6.5.5.2 雌アルビノ（SD）ラットにおける組織分布

	Test Article: [^{14}C]CCX168					
	Location in CTD: 4.2.2.3.4					
	Study No.: PC0641_168					
Species: Rat (Sprague-Dawley)						
Gender (M/F)/Number of animals: F/6 (used for different time points)						
Feeding Condition: Fed						
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)						
Method of Administration: Oral						
Dose (mg/kg): 15						
Radionuclide: ^{14}C						
Specific Activity: 59.2 mCi/mmol						
Assay: Quantitative whole body autoradiography						
Sampling Time: 1, 2, 4, 8, 24, and 72 hr						
	Concentration (ng Equivalents [^{14}C]CCX168/g)					
	Time Points					
Tissues/organs	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr
Adrenal gland(s)	4650[a]	7590	19300[a]	5850	1300	477
Arterial wall	440	1970	2810	2260	ND	ND
Bile	ND	37200	31700	41500	9020	ND
Blood	463	832	1320	790	139	BLQ
Bone	BLQ	87.6	216	228	BLQ	BLQ
Bone marrow	1220	1840	6590	2670	417	105
Brain cerebellum	BLQ	70.2	209	83.5	BLQ	ND
Brain cerebrum	52.7	76.8	190	79.2	BLQ	ND
Brain choroid plexus	683	703	2760	946	116	ND
Brain medulla	63.8	71.4	232	94.7	BLQ	ND
Brain olfactory lobe	BLQ	82.1	194	73.1	BLQ	ND
Cecum	818	811	3250	1720	714	326
Diaphragm	1820	2980	7630	3470	437	57.0
Esophagus	947	1520	3360	1860	330	BLQ
Exorbital lacrimal gland	1200	2290	7350	3220	482	112
Eye lens	BLQ	BLQ	BLQ	BLQ	BLQ	ND
Eye uveal tract	90.0	312	1070	578	BLQ	ND
Eye(s)	BLQ	87.7	309	185	BLQ	ND
Fat (abdominal)	378	1350	4860	11000	9100	4660
Fat (brown)	4010	7340	49500	21000	6610	1210
Fat (mesenteric)	693	1910	4060	10100	8810	4800
Fat (reproductive)	297	763	3200	8660	6520	4450

	Test Article: [^{14}C]CCX168					
	Location in CTD: 4.2.2.3.4					
	Study No.: PC0641_168					
	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr
Fat (subcutaneous)	390	1260	5740	9640	8130	4450
Harderian gland	666	2050	8610	8070	2620	168
Intra-orbital lacrimal gland	1120	1900	6690	3190	539	92.2
Kidney cortex	2140	3390	7400	3790	702	113
Kidney medulla	2040	3040	6630	3420	613	78.8
Kidney(s)	2130	3300	7110	3710	691	105
Large intestine	300	661	1840	1130	577	BLQ
Liver	8330	11300	27300	15200	2920	831
Lung(s)	1740	1830	5070	2030	357	78.2
Lymph node(s)	575	1290[a]	3000	1890	307	58.2
Muscle	578	1050	3260	1860	201	BLQ
Myocardium	2780	3790	8670	2990	441	93.5
Nasal turbinates	232	353	1680	767	182	58.2
Ovary(ies)	1910[a]	2160[a]	6120[a]	5990[a]	8450[a]	3860[a]
Pancreas	2410	3960	10800	4410	535	96.8
Pituitary gland	1610	2900	6470	2770	286	67.9
Preputial gland	840[a]	1800[a]	5390[a]	5970[a]	4530[a]	1790[a]
Salivary gland(s)	1610	2760	7980	3530	444	77.0
Skin (nonpigmented)	211	715	2510	1930	1900	900
Small intestine	ND[b]	3190	ND[b]	ND[b]	1690	271
Spinal cord	BLQ	80.6	225	88.0	BLQ	ND
Spleen	1720	2130	4960	1920	309	128
Stomach	1490	1830	3870	1790	165	61.8
Thymus	424	1100	3150	1940	235	BLQ
Thyroid	1160	2510	6050	2130	369	102
Urinary bladder	522	1290	4100	3310	185	ND
Urine	133	891	1460	1120	NR	317
Uterus	418[a]	1070	2470[a]	1180	839[a]	1430[a]

Additional Information:
BLQ: Below the limit of quantitation (< 49.2 ng equivalents [^{14}C]CCX168/g); ND: Not detectable (sample shape not discernible from background or surrounding tissue); NR: Not represented.
[a] Tissue appears to be contaminated by liquefied fat; [b] Not detectable due to flare of gastrointestinal contents.

2.6.5.5.3 雄有色（LE）ラットにおける組織分布

	Test Article: [^{14}C]CCX168							
	Location in CTD: 4.2.2.3.4							
	Study No.: PC0641_168							
Species: Rat (Long Evans)								
Gender (M/F)/Number of animals: M/8 (used for different time points)								
Feeding Condition: Fed								
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)								
Method of Administration: Oral								
Dose (mg/kg): 15								
Radionuclide: ^{14}C								
Specific Activity: 59.2 mCi/mmol								
Assay: Quantitative whole body autoradiography								
Sampling Time: 1, 2, 4, 8, 24, 72, 168, and 336 hr								
	Concentration (ng Equivalents [^{14}C]CCX168/g)							
	Time Points							
Tissues/organs	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr
Adrenal gland(s)	4520	6700	7410	6640	582	358	153	117[a]
Arterial wall	ND	1290	2910	2460	ND	ND	ND	ND
Bile	14100	37200	49700	60800	ND	ND	ND	ND
Blood	978	2190	1340	991	148	87.0	77.8	52.4
Bone	68.5	110	127	96.1	BLQ	ND	ND	ND
Bone marrow	734	1910	2340	1540	126	BLQ	BLQ	ND
Brain cerebellum	BLQ	97.1	134	107	BLQ	ND	ND	ND
Brain cerebrum	BLQ	101	122	97.4	BLQ	ND	ND	ND
Brain choroid plexus	819	1310	1110	956	228	ND	ND	ND
Brain medulla	BLQ	88.0	134	125	BLQ	ND	ND	ND
Brain olfactory lobe	BLQ	87.6	122	88.0	BLQ	ND	ND	ND
Bulbo-urethral gland	872	1180	3250	2660	134	60.2	BLQ	ND
Cecum	522	1200	1490	ND[b]	1720	197	89.3	ND
Diaphragm	1470	3190	4040	2250	148	73.0	BLQ	BLQ
Epididymis	51.2[a]	416[a]	711	1170	95.9	1720[a]	ND	ND
Esophagus	868	2150	1640	1600	159	49.5	ND	ND
Exorbital lacrimal gland	559	2380	3600	3760	140	54.3	BLQ	ND
Eye lens	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND	ND
Eye uveal tract	304	959	1310	1110	251	237	124	121
Eye(s)	68.3	147	204	282	BLQ	BLQ	BLQ	BLQ
Fat (abdominal)	338	1950	2260	4120	2910	1880	951	383
Fat (brown)	3680	12900	16900	26200	1870	512	110	BLQ

	Test Article: [^{14}C]CCX168							
	Location in CTD: 4.2.2.3.4							
	Study No.: PC0641_168							
	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr
Fat (mesenteric)	267	1970	2570	4400	2740	2320	928	270
Fat (reproductive)	653	1030	1310	4100	2220	1750	873	379
Fat (subcutaneous)	214	1210	2070	6150	3310	2310	963	174
Harderian gland	364	1820	4020	6310	1030	122	ND	ND
Intra-orbital lacrimal gland	506	2180	3560	3710	127	58.6	ND	ND
Kidney cortex	1680	4020	4820	3860	457	266	104	57.9
Kidney medulla	1730	3930	5900	4300	216	124	BLQ	BLQ
Kidney(s)	1680	4040	5100	3970	426	249	97.8	54.7
Large intestine	500	1090	1130	958	204	94.4	ND	ND
Liver	6200	15500	18700	18300	3950	1550	670	231
Lung(s)	1920	2430	3050	1770	247	105	BLQ	BLQ
Lymph node(s)	446	1150	1860	1640	115	66.5	65.9	ND
Muscle	484	1320	1920	1560	57.7	BLQ	BLQ	BLQ
Myocardium	2030	3780	3880	2670	233	151	74.1	55.6
Nasal turbinates	233	603	1060	1280	152	52.3	ND	ND
Pancreas	1570	4540	3220	3960	200	73.3	BLQ	BLQ
Pituitary gland	1140	2560	3070	2430	124	85.3	BLQ	ND
Preputial gland	415[a]	1020[a]	2330[a]	3930[a]	2170[a]	1800[a]	565[a]	238[a]
Prostate gland	191	1280	1590	1900	58.0	BLQ	BLQ	BLQ
Salivary gland(s)	1040	3060	3940	3060	145	60.3	BLQ	ND
Seminal vesicle(s)	BLQ	290	299	2090	77.1	ND	ND	ND
Skin (nonpigmented)	184	1180[a]	1270	1820	676	499	52.3	ND
Skin (pigmented)	228	1260[a]	1950	3060	1120	530	85.8	BLQ
Small intestine	ND[b]	ND[b]	ND[b]	4470	548	165	ND	ND
Spinal cord	51.2	94.2	156	126	BLQ	ND	ND	ND
Spleen	1220	2410	2350	1580	240	126	99.5	87.4
Stomach	1070	2240	2680	1360	86.1	BLQ	ND	ND
Testis(es)	69.8	225	400	709	BLQ	ND	ND	ND
Thymus	313	1370	1790	1640	64.0	BLQ	BLQ	ND
Thyroid	1360	2750	3300	2200	326	169	103	BLQ
Urinary bladder	329	1330	1600	1510	209	77.7	ND	ND
Urine	7480	3660	3820	15600	531	137	BLQ	BLQ

Additional Information:
BLQ: Below the limit of quantitation (< 49.2 ng equivalents [^{14}C]CCX168/g); ND: Not detectable (sample shape not discernible from background or surrounding tissue).
[a] Tissue appears to be contaminated by liquefied fat; [b] Not detectable due to flare of gastrointestinal contents.

2.6.5.5.4 雌有色（LE）ラットにおける組織分布

	Test Article: [^{14}C]CCX168							
	Location in CTD: 4.2.2.3.4							
	Study No. PC0641_168							
Species: Rat (Long Evans)								
Gender (M/F)/Number of animals: F/8 (used for different time points)								
Feeding Condition: Fed								
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)								
Method of Administration: Oral								
Dose (mg/kg): 15								
Radionuclide: ^{14}C								
Specific Activity: 59.2 mCi/mmol								
Assay: Quantitative whole body autoradiography								
Sampling Time: 1, 2, 4, 8, 24, 72, 168, and 336 hr								
	Concentration (ng Equivalents [^{14}C]CCX168/g)							
	Time Points							
Tissues/organs	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr
Adrenal gland(s)	4640[a]	8810[a]	ND[b]	9610	711	333	1210[a]	225[a]
Arterial wall	ND	1950	3850	3120	482	ND	ND	ND
Bile	ND	40300	45400	59200	ND	ND	ND	ND
Blood	331	1190	1140	1370	142	BLQ	ND	ND
Bone	BLQ	148	82.7	185	BLQ	ND	ND	ND
Bone marrow	499	3110	3140	2410	561	BLQ	ND	ND
Brain cerebellum	BLQ	132	149	111	BLQ	ND	ND	ND
Brain cerebrum	BLQ	107	147	105	BLQ	ND	ND	ND
Brain choroid plexus	400	2220	2270	2530	ND	ND	ND	ND
Brain medulla	BLQ	111	160	122	BLQ	ND	ND	ND
Brain olfactory lobe	BLQ	114	137	75.1	BLQ	ND	ND	ND
Cecum	225	NR	5670[a]	7810[a]	3390	BLQ	1210[a]	ND
Diaphragm	756	5100	5720	4480	208	60.0	ND	ND
Esophagus	1130	2370	3480	2090	122	53.3	ND	ND
Exorbital lacrimal gland	508	4430	5590	4730	251	63.8	ND	ND
Eye lens	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND
Eye uveal tract	210	1230	1410	2240	726	225	199	189
Eye(s)	BLQ	253	285	408	162	BLQ	ND	ND
Fat (abdominal)	653	1440	3910	8880	3870	2810	1410	737
Fat (brown)	1350	16600	25000	33600	5450	853	357	79.5
Fat (mesenteric)	556	2200	6380	11800	3710	2320	1820	426
Fat (reproductive)	754	719	1790	5970	2630	1760	1110	395
Fat (subcutaneous)	160	1230	2630	7790	3250	2060	1640	406

		Test Article: [^{14}C]CCX168						
		Location in CTD: 4.2.2.3.4						
		Study No. PC0641_168						
	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr	168 hr	336 hr
Harderian gland	298	3970	6340	9060	1580	115	BLQ	ND
Intra-orbital lacrimal gland	405	4460	5160	5020	306	50.6	94.7	ND
Kidney cortex	1030	6250	5500	4430	389	143	ND	ND
Kidney medulla	1150	6290	4670	4410	259	120	ND	ND
Kidney(s)	1060	6260	5440	4410	353	139	BLQ	ND
Large intestine	212	1180	1480	1480	983	66.6	BLQ	ND
Liver	4640	21300	23100	20100	2100	825	378	136
Lung(s)	964	3880	3140	2840	209	BLQ	ND	ND
Lymph node(s)	269	1880	2690[a]	2210	154	BLQ	50.3	ND
Muscle	184	1730	2540	2140	87.1	BLQ	ND	ND
Myocardium	1240	6310	6080	4220	228	64.3	ND	ND
Nasal turbinates	152	666	1560	1650	264	69.4	ND	ND
Ovary(ies)	1120[a]	2830[a]	4480[a]	6260[a]	3660[a]	1530[a]	1030[a]	564[a]
Pancreas	1280	8550	7090	5410	226	79.9	ND	ND
Pituitary gland	737	5090	5410	3470	177	BLQ	ND	ND
Preputial gland	155[a]	1790[a]	3310[a]	6470[a]	2760[a]	2370[a]	1020[a]	352[a]
Salivary gland(s)	664	5380	6460	4570	240	64.4	ND	ND
Skin (nonpigmented)	72.9	1010	1370	3300	1820	877	278	82.9
Skin (pigmented)	143	1950	1830	3320	1970	1140	662	134
Small intestine	4650[a]	ND[b]	6160[a]	6510	1090	528	473	126
Spinal cord	BLQ	128	187	132	BLQ	ND	ND	ND
Spleen	933	3870	3900	2650	235	87.5	71.1	ND
Stomach	ND[b]	1410	3960	2120	124	BLQ	ND	ND
Thymus	212	2030	2760	2390	118	BLQ	ND	ND
Thyroid	879	4610	3870	3390	244	107	BLQ	BLQ
Urinary bladder	518	938[a]	1580	2120	173	ND	ND	ND
Urine	558	986	3640	4400	184	290	ND	ND
Uterus	272[a]	1260[a]	1970[a]	2400[a]	114	1010[a]	686[a]	89.3[a]

Additional Information:
BLQ: Below the limit of quantitation (< 49.2 ng equivalents [^{14}C]CCX168/g); ND: Not detectable (sample shape not discernible from background or surrounding tissue); NR: Not represented.
[a] Tissue appeared to be contaminated by liquefied fat; [b] Not detectable due to flare of gastrointestinal contents.

2.6.5.6 薬物動態試験：蛋白結合

	Test Article: CCX168 and CCX168-M1			
Type of study: *In vitro* Plasma Protein Binding				
Study System: Plasma of various species; human albumin; human α_1-acid glycoprotein				
Target Entity, Test System and Method: Rapid equilibrium dialysis (RED)				
Species	Conc. Tested	% Bound	Study No.	Location in CTD
Mouse (CD-1) plasma	2.5 – 50 µmol/L	>99.9%	PC0632_168	4.2.2.3.1
Rat (Sprague-Dawley) plasma	2.5 – 50 µmol/L	>99.9%		
Hamster (Golden Syrian) plasma	2.5 – 50 µmol/L	>99.9%		
Rabbit (New Zealand White) plasma	2.5 – 50 µmol/L	>99.9% (CCX168) 99.9% or >99.9% (CCX168-M1)		
Dog (Beagle) plasma	2.5 – 50 µmol/L	>99.9%		
Monkey (Cynomolgus) plasma	2.5 – 50 µmol/L	>99.9%		
Human plasma	2.5 – 50 µmol/L	>99.9%		
Human albumin	5, 10 µmol/L	>99.9% (CCX168) 99.9% (CCX168-M1)	PC0681_168	4.2.2.3.2
Human α_1-acid glycoprotein	5, 10 µmol/L	>99.9% (CCX168) 98.9 – 99.3% (CCX168-M1)	PC0685_168	4.2.2.3.3
Additional Information: None				

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

2.6.5.7.1 妊娠動物（ハムスター）における試験

							Test Article: CCX168		
							Location in CTD: 4.2.3.5.2.1		
							Study No. PC0671_168		
Type of Study: Embryo-Fetal Development Toxicity Study									
Species: Hamster (Golden Syrian)									
Gestation day (GD)/Number of Animals: GD12/12									
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)									
Method of Administration: Oral									
Dose (mg/kg): NOAEL 1000 mg/kg daily (500 mg/kg b.i.d.)									
Analyte: CCX168, CCX168-M1, and CCX168-[redacted]									
Assay: LC-MS/MS									
Time (hr)	0	1	2	4	8	9	10	12	24
Mean Concentration of CCX168 (ng/mL) Dam: Fetus: N/A	1020	1390	1650	1280	1320	1910	2150	1300	1870
Mean Concentration of CCX168-M1 (ng/mL) Dam: Fetus: N/A	35.0	46.2	61.0	54.7	57.7	65.1	77.2	67.7	98.0
Mean Concentration of CCX168-[redacted] (ng/mL) Dam: Fetus: N/A	52.7	64.2	88.0	81.4	64.1	81.2	92.0	68.1	66.3
Additional Information: CCX168: $AUC_{0\text{-}24hr}$ = 36400 ng•hr/mL, C_{max} = 2150 ng/mL; CCX168-M1: $AUC_{0\text{-}24hr}$ = 1680 ng•hr/mL, C_{max} = 98.0 ng/mL; CCX168-[redacted]: $AUC_{0\text{-}24hr}$ = 1690 ng•hr/mL, C_{max} = 92.0 ng/mL.									

2.6.5.7.2 妊娠動物（ウサギ）における試験

						Test Article: CCX168
						Location in CTD: 4.2.3.5.2.2
						Study No. PC0672_168
Type of Study: Embryo-Fetal Development Toxicity Study						
Species: Rabbit (New Zealand White)						
Gestation day (GD)/Number of Animals: GD18/3						
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)						
Method of Administration: Oral						
Dose (mg/kg): NOAEL (developmental) 200 mg/kg daily (PK data at this dose are shown below)						
Analyte: CCX168, CCX168-M1, and CCX168-[redacted]						
Assay: LC-MS/MS						
Time (hr)	0	1	2	4	8	24
Mean Concentration of CCX168 (ng/mL) Dam: Fetus: N/A	96.5	233	509	290	111	144
Mean Concentration of CCX168-M1 (ng/mL) Dam: Fetus: N/A	29.7	36.4	61.7	53.4	27.5	25.2
Additional Information: CCX168: $AUC_{0\text{-}24hr}$ = 4180 ng•hr/mL, C_{max} = 509 ng/mL; CCX168-M1: $AUC_{0\text{-}24hr}$ = 780 ng•hr/mL, C_{max} = 65.1 ng/mL						

2.6.5.7.3 授乳動物（ハムスター）における試験

					Test Article: CCX168
					Location in CTD: 4.2.3.5.3.1
					Study No. PC0673_168
Type of Study: Prenatal/Postnatal Developmental Toxicity Study					
Species: Hamster (Golden Syrian)					
Day of Lactation (LD) / Number of Animals: LD15 / 6					
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)					
Method of Administration: Oral					
Dose (mg/kg): NOAEL 1000 mg/kg daily (500 mg/kg b.i.d.)					
Analyte: CCX168 and CCX168-M1					
Assay: LC-MS/MS					
Time (hr)	0	1	2	4	10
Mean Concentration of CCX168 (ng/mL) Dam: Infant: 10 hr post dose	463	2400	1970	1270	1710 972
Mean Concentration of CCX168-M1 (ng/mL) Dam: Infant: 10 hr post dose	59.1	126	164	137	190 123
Additional Information: CCX168: $AUC_{0\text{-}24hr}$ = 30900 ng•hr/mL, C_{max} = 2400 ng/mL; CCX168-M1: $AUC_{0\text{-}24hr}$ = 3260 ng•hr/mL, C_{max} = 190 ng/mL					

2.6.5.8 薬物動態試験：その他の分布試験

2.6.5.8.1 血球移行性

	Test Article: CCX168 and CCX168-M1			
	Location in CTD: 4.2.2.3.5			
	Study No. PC0364_168_a			
Type of Study: *In Vitro* Whole Blood-to-Plasma Partitioning				
Method: For each species, duplicate aliquots of whole blood and reference plasma were incubated with 5 µmol/L CCX168 or CCX168-M1. Blood-to-plasma partitioning was calculated by taking into account the hematocrit, as well as the concentration of test compound in both the reference plasma and plasma obtained from whole blood samples.				
Tabulated Results:	CCX168			
	Species	H_t (Hematocrit)	$K_{RBC/PL}$	$K_{B/PL}$
	Mouse	0.51	0.45	0.72
	Rat	0.55	0.60	0.78
	Dog	0.47	0.27	0.66
	Human	0.52	0.42	0.70
	CCX168-M1			
	Species	H_t (Hematocrit)	$K_{RBC/PL}$	$K_{B/PL}$
	Rat	0.30	0.76	0.93
	Dog	0.48	0.37	0.70
	Human	0.47	0.30	0.67
Additional Information: None				

2.6.5.9 薬物動態試験：代謝：*In Vivo*

2.6.5.9.1 ラットにおける代謝物検索

										Test Article: [^{14}C]CCX168	
Species: Rat (Sprague-Dawley) Gender (M/F)/Number of animals: M/21; F/21										Study No.:	Location in CTD:
Feeding Condition: Fed										PC0641_168	4.2.2.3.4
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)										PC0641_168_a	4.2.2.4.6
Method of Administration: Oral											
Dose (mg/kg): 15											
Radionuclide: ^{14}C											
Specific Activity: 59.2 mCi/mmol											
Sample Type	% of Dose in Mass Balance Study (M/F) PC0641_168	Pooled Sample Range for Metabolite ID[b] PC0641_168_a	% of Identified Metabolite[c] in Pooled Sample (M/F)								
			Parent	CCX168-M1	CCX168-M2	CCX168-M3	CCX168-M5	CCX168-M6	CCX168-M15	CCX168-M24	CCX168-M25
Plasma	NA	0-168 hr	51.6/65.0	9.24/15.0	ND	5.18/9.07	ND	3.50/ 6.79	3.43/4.13	ND	ND
Urine	2.71/1.05	0-72 hr	ND	ND	ND	ND/10.0	ND	ND	ND/2.51	ND	ND
Bile[a]	27.2/24.6	0-48 hr	1.00/1.45	ND	12.8/32.3	7.82/5.69	5.89/6.92	1.64/1.83	ND	12.0/15.5	3.13/3.67
Feces	92.6/96.1	0-72 hr	21.5/19.5	1.78/3.22	ND	9.83/12.0	ND	0.56/ND	12.5/17.2	ND	7.62/6.08

NA = Not Applicable; ND = Not Detected.

[a] Bile duct-cannulated rats only. All other values are from intact rats.

[b] The sample ranges used for Metabolite ID accounted for >90% of the total radioactivity in each of the corresponding sample types.

[c] Additional unknown metabolites were observed in the HPLC trace. A complete summary of observed metabolites is in PC0641_168_a.

2.6.5.9.2 サルにおける代謝物検索

			Test Article: [^{14}C]CCX168						
Species: Monkey (Cynomolgus) Gender (M/F)/Number of animals: M/3; F/3			Study No.:				Location in CTD:		
Feeding Condition: Fed			PC0645_168				4.2.2.5.1		
Vehicle/Formulation: PEG-400/Kolliphor HS-15 ([redacted], v/v)			PC0645_168_a				4.2.2.4.7		
Method of Administration: Oral									
Dose (mg/kg): 15									
Radionuclide: ^{14}C									
Specific Activity: 59.2 mCi/mmol									
Sample Type	% of Dose in Mass Balance Study[a] (M/F) PC0645_168	Pooled Sample Range for Metabolite ID[b] PC0645_168_a	% of Identified Metabolite[c] in Pooled Sample (pooled gender)						
			Parent	CCX168-M1	CCX168-M9	CCX168-M10/M11	CCX168-M12	CCX168-M16	CCX168-M23
Plasma	NA	0-168 hr	12.7	12.8	ND	2.2	2.1	ND	ND
Urine	3.78/4.31[a]	0-120 hr	26[a]	3.7[a]	ND	2.1[a]	ND	1.6[a]	ND
Feces	29.1/24.8	0-96 hr	31.0[a]	14.6[a]	1.7[a]	9[a]	ND	3.3[a]	1.9[a]

NA = Not Applicable; ND = Not Detected

[a] Samples from one animal were excluded from the study due to cross-contamination between urine and fecal samples caused by diarrhea.

[b] The sample ranges used for Metabolite ID accounted for >90% of the total radioactivity in each of the corresponding sample types.

[c] Additional unknown metabolites were observed in the HPLC trace. A complete summary of observed metabolites is in PC0645_168_a.

2.6.5.10 薬物動態試験：代謝：*In Vitro*

2.6.5.10.1 肝細胞における代謝安定性

				Test Article: CCX168	
				Location in CTD: 4.2.2.4.1	
				Study No. PC0370_168	
Type of Study: *In Vitro* Metabolic Stability in Hepatocytes					
Method: For each species, cryopreserved hepatocytes (0.5×10^6 cells/mL) were incubated with 0.2 µmol/L CCX168 for up to 60 minutes with verapamil as a high clearance control. The intrinsic clearance was calculated from the rate of compound disappearance.					
		CCX168		Verapamil	
Tabulated Results:	Species	CL_{int} (µL/10^6 cells/min)	Clearance Classification	CL_{int} (µL/10^6 cells/min)	Clearance Classification
	Mouse	20.6 ± 1.7	Low to Moderate	132.6 ± 4.5	High
	Rat	45.3 ± 4.5	Moderate	145.1 ± 3.1	High
	Dog	36.0 ± 1.2	Moderate	59.3 ±1.8	High
	Monkey	33.4 ± 2.7	Low to Moderate	223.3 ± 2.9	High
	Human	10.9 ± 0.7	Low to Moderate	35.3 ± 1.8	Moderate to High
Additional Information: N = 4 for all species (N = 3 for dog hepatocytes)					

2.6.5.10.2 肝ミクロソーム及び肝細胞を用いた代謝物検索

				Test Article: [^{3}H]CCX168		
				Location in CTD: 4.2.2.4.3		
				Study No. PC0623_168_a		
Study System:	Rat Liver Microsomes	Monkey Liver Microsomes	Human Liver Microsomes	Rat Hepatocyte Suspension	Monkey Hepatocyte Suspension	Human Hepatocyte Suspension
Time:	4 hr	4 hr	4 hr	2 hr	2 hr	2 hr
Concentration:	1 µmol/L (25 µCi/mL)	1 µmol/L (25 µCi/mL)	1 µmol/L (25 µCi/mL)	1 µmol/L (25 µCi/mL)	1 µmol/L (25 µCi/mL)	1 µmol/L (25 µCi/mL)
Parent	16.9%	10.5%	39.9%	88.3%	76.9%	92.5%
CCX168-M1	20.4%	10.6%	17.7%	0.6%	5.1%	0.4%
CCX168-M3	8.8%	6.3%	2.2%	—	—	—
CCX168-M6	1.3%	—	0.4%	0.3%	2%	0.8%
CCX168-M8	0.7%	—	2.7%	—	—	—
CCX168-M9	—	—	1.2%	—	—	—
CCX168-M10	—	8.6%[a]	2.3%	—	—	—
CCX168-M11	—	8.6%[a]	2.8%	—	—	—
CCX168-M12	—	—	0.5%	—	—	—
CCX168-M13	—	5.1%	3.0%	—	—	—
CCX168-M14	—	9.2%	1.5%	—	—	—
CCX168-M15	30.7%	—	—	—	—	—
Additional Information: CCX168-M2, CCX168-M5 and CCX168-M7 were detected when CCX168 was incubated with rat hepatocytes while CCX168-M1, CCX168-M3 and CCX168-M6 were detected when CCX168 was incubated with dog hepatocytes (PC0369_168).						

[a] CCX168-M10 and CCX168-M11 overlapped in the HPLC traces and were combined to account for 8.6%.

2.6.5.11 薬物動態試験：推定代謝経路

2.6.5.11.1 CCX168 及び CCX168-M1 の代謝酵素の同定（選択的阻害薬による同定）

			Test Article: CCX168 and CCX168-M1						
			Location in CTD: 4.2.2.4.4 (for CCX168) and 4.2.2.4.5 (for CCX168-M1)						
			Study No. PC0373_168 (for CCX168) and PC0711_168 (for CCX168-M1)						
Type of Study: *In Vitro* Phenotyping of Drug Metabolizing Enzymes									
Method: CCX168 or CCX168-M1, with midazolam as a positive control, were incubated separately at 1 µmol/L with CYP isozyme-specific inhibitors in pooled human liver microsomes (0.5 mg/mL)									
Tabulated Results:	Incubation time	Turnover (mean)	% Inhibition (mean)						
Compound Incubated	min	%	3A4	2B6	2C8	1A2	2C9	2C19	2D6
CCX168	30	27.3	90.9	46.6	NI	NI	NI	NI	NI
Midazolam	5	63.3	97.3	40.3	25.6	4.8	4.9	NI	5.1
CCX168-M1	120	63.4	118	12.9	29.7	NI	2.4	7.3	1.2
Midazolam	5	66.1	90.6	6.1	18.0	NI	1.0	NI	NI
Additional Information: CYP isozyme-specific inhibitors used in the experiments: 1 µmol/L ketoconazole (3A4), 50 µmol/L thio-TEPA (2B6), 30 µmol/L quercetin (2C8), 20 µmol/L furafylline (1A2), 10 µmol/L sulfaphenazole (2C9), 15 µmol/L ticlopidine (2C19), 1 µmol/L quinidine (2D6). NI=No Inhibition									

2.6.5.11.2 CCX168 の代謝酵素の同定（組換え CYP による同定）

				Test Article: CCX168			
				Location in CTD: 4.2.2.4.5			
				Study No. PC0711_168			
Type of Study: *In Vitro* Phenotyping of Drug Metabolizing Enzymes							
Method: CCX168 was incubated at 2 µmol/L in duplicate with 20 pmol/mL of each of the following recombinant CYP isozymes.							
Tabulated Results:	% Contribution to Formation of Each Metabolite						
Metabolite Formed	3A4	1A2	2B6	2C9	2C19	2D6	2C8
CCX168-M1	68.9	2.5	0.2	0.1	9.0	17.6	1.7
CCX168-M3	84.3	0	0	0	0	13.8	1.9
CCX168-M6	9.5	3.2	19.5	3.3	30.6	17.7	16.1
CCX168-M26	100	0	0	0	0	0	0
CCX168-M8/M17/M18	90.8	0	0	0.4	2.6	4.4	1.9
CCX168-M9	92.0	0	3.0	0	2.3	2.8	0
CCX168-M10/M11	98.3	0	0	0	0	1.7	0
CCX168-M16	100	0	0	0	0	0	0
CCX168-M19	100	0	0	0	0	0	0
Additional Information: No formation of CCX168-M21, CCX168-M22 or CCX168-M23 from CCX168 with any of the CYP isozymes.							

2.6.5.11.3 CCX168-M1 の代謝酵素の同定（組換え CYP による同定）

				Test Article: CCX168-M1			
				Location in CTD: 4.2.2.4.5			
				Study No. PC0711_168			
Type of Study: *In Vitro* Phenotyping of Drug Metabolizing Enzymes							
Method: CCX168-M1 was incubated at 2 µmol/L in duplicate with 20 pmol/mL of each of the following recombinant CYP isozymes.							
Tabulated Results:	% Contribution to Formation of Each Metabolite						
Metabolite Formed	3A4	1A2	2B6	2C9	2C19	2D6	2C8
CCX168-M3	56.5	0	2.8	0	10.3	19.5	10.7
CCX168-M6	0	0	0	0	0	0	0
CCX168-M26	100	0	0	0	0	0	0
CCX168-M8/M17/M18	0	0	0	0	0	0	0
CCX168-M9	0	0	0	0	0	0	0
CCX168-M10/M11	92.7	0.1	0	0.5	0.2	2.5	3.9
CCX168-M16	92.2	0	0	0	0	1.7	6.1
CCX168-M19	100	0	0	0	0	0	0
Additional Information: No formation of CCX168-M21, CCX168-M22 or CCX168-M23 from CCX168-M1 with any of the CYP isozymes.							

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導／阻害

薬物代謝酵素の誘導／阻害は、2.6.5.15 項に記載した。

2.6.5.13 薬物動態試験：排泄

					Test Article: [^{14}C]CCX168			
Species:	Rat (Sprague-Dawley)				Monkey (Cynomolgus)			
Gender (M/F)/Number of Animals:	M/F (3/3)				M/F (3/3)			
Feeding Condition:	Fed				Fed			
Vehicle/Formulation:	PEG-400/Kolliphor HS-15 ([redacted], v/v)				PEG-400/Kolliphor HS-15 ([redacted], v/v)			
Method of Administration:	Oral				Oral (nasogastric)			
Dose (mg/kg):	15 mg/kg, 300 µCi/kg				15 mg/kg, 100 µCi/kg			
Analyte:	Total ^{14}C radioactivity				Total ^{14}C radioactivity			
Assay:	Liquid scintillation counting				Liquid scintillation counting			
Excretion Route:	Urine	Feces	Cage	Total	Urine	Feces	Cage	Total
	M: 2.71% F: 1.05%	M: 92.6% F: 96.1%	M: 1.828% F: 0.5875%	M: 98.9%[a] / 97.1%[b] F: 99.8%[a] / 97.7%[b]	M: 3.78% F: 4.31%[c]	M: 29.1% F: 24.8%	M: 38.1% F: 35.5%	M: 71.0% F: 72.1%
Time (0 – T hr)	0–168 hr	0–168 hr	0–168 hr	0–168 hr	0–168 hr	0–168 hr	0–168 hr	0–168 hr
Location in CTD:	4.2.2.3.4				4.2.2.5.1			
Study Number:	PC0641_168				PC0645_168			
Additional Information: Actual total recovery in monkey was likely higher due to complications from diarrhea attributed to PEG-400 dosing.								

[a] Total Excreted Radioactivity + Carcass (residual).
[b] Total Excreted Radioactivity.
[c] Samples from one animal were excluded from the study due to cross-contamination between urine and fecal samples caused by diarrhea.

2.6.5.14 薬物動態試験：排泄：胆汁中

					Test Article: [^{14}C]CCX168
					Location in CTD: 4.2.2.3.4
					Study No.: PC0641_168
Species:	Rat (Sprague-Dawley)				
Gender (M/F)/Number of Animals:	M/F (3/3)				
Feeding Condition:	Fed				
Vehicle/Formulation:	PEG-400/Kolliphor HS-15 ([redacted], v/v)				
Method of Administration:	Oral				
Dose (mg/kg):	15 mg/kg, 300 µCi/kg				
Analyte:	Total ^{14}C radioactivity				
Assay:	Liquid scintillation counting				
Excretion route:	Bile	Urine	Feces	Cage	Total
	M: 27.2% F: 24.6%	M: 0.940% F: 1.04%	M: 62.7% F: 70.9%	M: 2.733% F: 0.6154%	M: 94.7%[a] / 93.9%[b] F: 98.5%[a] / 97.3%[b]
Time (0 – T hr)	0–120 hr	0–120 hr	0–120 hr	0–120 hr	0–120 hr
Additional Information: None					

[a] Total Excreted Radioactivity + Carcass (residual).
[b] Total Excreted Radioactivity.

2.6.5.15 薬物動態試験：薬物相互作用

2.6.5.15.1 CYP 阻害（ヒト肝ミクロソーム）

		Test Article: CCX168 and CCX168-M1		
		Location in CTD: 4.2.2.6.1 (for CCX168); 4.2.2.6.2 (for CCX168-M1)		
		Study No.: PC0360_168 (for CCX168); PC0489_168 (for CCX168-M1)		
Type of Study: CYP Inhibition in Human Liver Microsomes				
Method: Appropriate probe substrates of CYP450s were incubated in human liver microsomes with NADPH in the presence of various concentrations of CCX168 (0.04 to 30 µmol/L) or CCX168-M1 (0.412 to 30 µmol/L). The marker metabolite of each probe substrate was measured by LC-MS/MS and the peak area responses of the marker metabolite at various CCX168 or CCX168-M1 concentrations were graphed for the calculation of the CYP IC_{50}.				
Tabulated Results:	CYP Isoform	CCX168 IC_{50} (µmol/L)	CCX168-M1 IC_{50} (µmol/L)	Positive Control IC_{50} (µmol/L)
	CYP1A2	NI	NI	Furafylline: 2.1, 1.8
	CYP2B6	NI	NI	Thiotepa: 7.78, 8.2
	CYP2C8	NI	>10	Quercetin: 2.29, 1.9
	CYP2C9	NI	4.7	Sulfaphenazole: 0.43, 0.36
	CYP2C19	NI	>10	Tranylcypromine: 4.67, 15.7
	CYP2D6	NI	NI	Quinidine: 0.05, 0.04
	CYP3A4 (Midazolam)	>30	>10	Ketoconazole: 0.02, 0.01
	CYP3A4 (Testosterone)	NI	>10	Ketoconazole: 0.02, 0.02
Additional Information: NI = No inhibition observed at the highest assay concentration (30 µmol/L) of CCX168 or CCX168-M1.				

2.6.5.15.2 時間依存的 CYP 阻害（ヒト肝ミクロソーム）

			Test Article: CCX168 and CCX168-M1			
			Location in CTD: 4.2.2.6.3			
			Study No.: PC0710_168			
Type of Study: Time-Dependent CYP Inhibition in Human Liver Microsomes						
Method: Fold IC_{50} shift = IC_{50} determined from a 30-minute pre-incubation with a test compound in the absence of NADPH divided by IC_{50} determined from a 30-minute pre-incubation with a test compound in the presence of NADPH. Following the pre-incubation period, the probe substrate specific for each CYP isoform and NADPH was added to determine the enzyme activity.						
Tabulated Results: Compound Tested	Fold IC_{50} Shift (Time-Dependent Inhibition)					
	1A2	2B6	2C8	2C9	2C19	2D6
Positive Control	60.4	30.0	8.04	10.8	2.95	12.8
CCX168	NC	NC	NC	NC	NC	NC
CCX168-M1	NC	NC	NC	1.05	0.91	NC
Additional Information: NC = not calculated due to IC_{50} being greater than the maximum tested concentration (>25 µmol/L). Positive controls are the following: furafylline (CYP1A2), ticlopidine (CYP2B6), gemfibrozil glucuronide (CYP2C8), tienilic acid (CYP2C9), fluoxetine (CYP2C19), paroxetine (CYP2D6).						

2.6.5.15.3 時間依存的 CYP3A4 阻害（ヒト肝ミクロソーム）

		Test Article: CCX168 and CCX168-M1		
		Location in CTD: 4.2.2.6.5 (for CCX168); 4.2.2.6.4 (for CCX168-M1)		
		Study No.: PC0622_168 (for CCX168); PC0634_168 (for CCX168-M1)		
Type of Study: Time-Dependent CYP3A4 Inhibition in Human Liver Microsomes				
Method: CCX168 or CCX168-M1 was pre-incubated at various concentrations in human liver microsomes in the presence of NADPH for various duration. Following pre-incubation, the enzyme activity was measured using midazolam as the probe substrate. Inhibition constants K_I and k_{inact} were derived.				
Tabulated Results:	Inhibition Kinetic Constant	CCX168	CCX168-M1	Positive Control (Troleandomycin)
	k_{inact} (min^{-1})	0.0659	0.0402	0.0656, 0.0488
	K_I (µmol/L)	4.47	11.7	0.81, 0.511
Additional Information: None				

2.6.5.15.4 CYP 誘導（ヒト肝細胞）

			Test Article: CCX168 and CCX168-M1	
			Location in CTD: 4.2.2.6.6 (for CCX168); 4.2.2.6.7 (for CCX168-M1)	
			Study No.: PC0635_168_a (for CCX168); PC0491_168 (for CCX168-M1)	
Type of Study: CYP Induction in Human Hepatocytes				
Method: CCX168 or the control inducers were incubated in the culture of plated human hepatocytes for 72 hr to induce expression of CYP450 enzymes. After the induction period, enzymatic activities and mRNA expression of CYP1A2, CYP2B6 and CYP3A4 were measured separately. Seven concentrations (30 µmol/L 10 µmol/L, 3 µmol/L, 1 µmol/L 0.3 µmol/L, 0.1 µmol/L and 0.03 µmol/L) of CCX168 were evaluated in hepatocytes from three human donors. Enzymatic activities were measured for CCX168-M1 at 10 µmol/L following incubation with human hepatocytes of a single donor for 52 hr. Positive controls were omeprazole, phenobarbital, and rifampin for CYP1A2, CYP2B6, and CYP3A4, respectively.				
Tabulated Results:	CYP Isoform	Mean Fold Induction in mRNA Expression CCX168 / Positive Control	Mean Fold Induction in Enzymatic Activity	
			CCX168 / Positive Control	CCX168-M1 / Positive Control
	CYP1A2	Donor 1: 1.06 – 3.59-fold / 90.85-fold (< 4% of positive control) Donor 2: 1.07 – 2.01-fold / 67.63-fold (< 3% of positive control) Donor 3: 1.14 – 1.89-fold / 66.15-fold (< 3% of positive control)	Donor 1: 1.13 – 2.13-fold / 50.89-fold (< 5% of positive control) Donor 2: 0.90 – 1.81-fold / 14.64-fold (< 13% of positive control) Donor 3: 1.29 – 1.76-fold / 12.92-fold (< 14% of positive control)	Donor 4: 3.0-fold / 17.4-fold (< 18% of positive control)
	CYP2B6	Donor 1: 1.04 – 2.07-fold / 8.95-fold (< 24% of positive control) Donor 2: 1.09 – 1.95-fold / 11.92-fold (< 17% of positive control) Donor 3: 1.04 – 1.55-fold / 7.36-fold (< 22% of positive control)	Donor 1: 1.04 – 1.3-fold / 3.88-fold (< 34% of positive control) Donor 2: 0.97 – 1.13-fold / 3.66-fold (< 31% of positive control) Donor 3: 0.94 – 1.15 fold / 2.34-fold (< 50% of positive control)	Donor 4: 2.0-fold / 36.5-fold (< 6% of positive control)
	CYP3A4	Donor 1: 1.20 – 7.51-fold / 17.83-fold (< 43% of positive control) E_{max}: 6.15; EC_{50}: 7.26 µmol/L Donor 2: 1.11 – 4.18-fold / 12.58-fold (< 34% of positive control) E_{max}: 3.66; EC_{50}: 13.6 µmol/L Donor 3: 1.31 – 5.38 fold / 13.25-fold (< 41% of positive control) E_{max}: 4.63; EC_{50}: 2.62 µmol/L	Donor 1: 0.44 – 0.93-fold / 18.87-fold (< 5% of positive control) Donor 2: 0.23 – 0.85-fold / 8.13-fold (< 11% of positive control) Donor 3: 0.29 – 0.74-fold / 7.4-fold (< 11% of positive control)	Donor 4: 0.4-fold / 22.7-fold (< 2% of positive control)
Additional Information: Unbound plasma C_{max} for CCX168 in ANCA-associated vasculitis patients at steady state following 30 mg b.i.d. administration is calculated to be 0.006 ± 0.003 µmol/L based on an estimated plasma steady-state C_{max} of 349 ± 169 ng/mL in population PK analysis (CMR_168_POP PK2) using 1% unbound fraction in plasma.				

2.6.5.15.5 薬物トランスポーターの阻害

			Test Article: CCX168 and CCX168-M1		
			Location in CTD: 4.2.2.6.8		
			Study No. PC0712_168		
Type of Study: *In Vitro* Evaluation of the Interaction Potential of CCX168 and Metabolite CCX168-M1 with Drug Transporters					
Method: Inhibition experiments were conducted for in transfected cell lines including: HEK293-OAT1, HEK293-OAT3, HEK293-OATP1B1, HEK293-OATP1B3, HEK293-OCT2, MDCKII-Fin-MATE1, MDCKII-Fin-MATE2-K, MDCKII-MDR1 and MDCKII-BCRP. CCX168 concentrations: 0.03-25 µmol/L for efflux transporter (BCRP and MDR1) inhibition test; 0.027-20 µmol/L for uptake transporter (OAT1/3, MATE1/2-K, OATP1B1/1B3, and OCT2) inhibition test. CCX168-M1 concentrations: 0.0027-2 µmol/L for all transporter inhibition test.					
Tabulated Results:	Transporters	Maximum inhibition (% Inhibition)		Positive Controls	% Inhibition with Positive Controls
		CCX168	CCX168-M1		
	BCRP	NIO	NIO	Ko143 (1 µmol/L)	98, 98
	MDR1	NIO	NIO	Valspodar (10 µmol/L)	98, 98
	OAT1	21	NIO	Probenecid (300 µmol/L)	97, 96
	OAT3	NIO	NIO	Probenecid (300 µmol/L)	94, 95
	MATE1	NIO	NIO	Pyrimethamine (1 µmol/L)	94, 94
	MATE2-K	NIO	NIO	Pyrimethamine (10 µmol/L)	94, 93
	OATP1B1	25	NIO	Rifampicin (50 µmol/L)	98, 99
	OATP1B3	NIO	NIO	Rifampicin (50 µmol/L)	79, 79
	OCT2	NIO	NIO	Verapamil (300 µmol/L)	80, 92
Additional Information: NIO = no inhibition observed (inhibition was less than 20%)					

2.6.5.15.6 薬物トランスポーターに対する基質性

			Test Article: [^{14}C]CCX168 and CCX168-M1		
			Location in CTD: 4.2.2.6.8		
			Study No.: PC0712_168		
Type of Study: *In Vitro* Evaluation of the Interaction Potential of CCX168 or Metabolite CCX168-M1 with Drug Transporters					
Tabulated Results:	Transporters	Cell Line	Method	Maximum net ER or fold accumulation	
				CCX168	CCX168-M1
	Hepatic Uptake Transporters OATP1B1	HEK293-OATP1B1-LV/HEK293-MOCK-LV	The uptake of CCX168 and CCX168-M1 was determined using cells overexpressing the respective transporter and control cells at one incubation time point (10 min) and at four concentrations of test article. CCX168 concentrations: 0.6-20 µmol/L; CCX168-M1 concentrations: 0.2-2 µmol/L.	<2 Not a substrate	<2 Not a substrate
	Hepatic Uptake Transporters OATP1B3	HEK293-OATP1B3-LV/HEK293-MOCK-LV	The uptake of CCX168 and CCX168-M1 was determined using cells overexpressing the respective transporter and control cells at one incubation time point (10 min) and at four concentrations of test article. CCX168 concentrations: 0.6-20 µmol/L; CCX168-M1 concentrations: 0.2-2 µmol/L.	<2 Not a substrate	<2 Not a substrate
	P-gp	MDCKII-MDR1/MDCKII-wildtype	The apparent apical to basolateral permeability, $P_{app\ (A-B)}$, and the apparent basolateral to apical permeability, $P_{app\ (B-A)}$, were determined for CCX168 or CCX168-M1 in MDCKII-MDR1 and MDCKII wild type cell lines in the absence and presence of P-gp inhibitor valspodar (10 µmol/L). CCX168 concentrations: 0.6-25 µmol/L; CCX168-M1 concentrations: 0.2-2 µmol/L.	<2 Not a substrate	52.77 Substrate
	BCRP	MDCKII-BCRP/MDCKII-wildtype	The apparent apical to basolateral permeability, $P_{app\ (A-B)}$, and the apparent basolateral to apical permeability, $P_{app\ (B-A)}$, were determined for CCX168 or CCX168-M1 in MDCKII-BCRP and MDCKII wild type cell lines in the absence and presence of BCRP inhibitor Ko143 (1 µmol/L). CCX168 concentrations: 0.6-25 µmol/L; CCX168-M1 concentrations: 0.2-2 µmol/L.	<2 Not a substrate	<2 Not a substrate
Additional Information: ER = Efflux ratio.					

2.6.5.15.7 ステロイド代謝酵素（11β-HSD1 及び 11β-HSD2）の阻害

	Test Article: CCX168 and CCX168-M1	
	Location in CTD: 4.2.1.2.5	
	Study No.: PC0469_168	
Type of Study: Inhibition of Steroid-Metabolizing Enzymes 11β-HSD1 and 11β-HSD2		
Method: Test article was incubated at concentrations up to 10 µmol/L (CCX168 or CCX168-M1) or 30 µmol/L (positive control) in duplicates with pooled human liver or kidney microsomes in the presence of cortisone or cortisol as the respective substrates for the 11β-HSD1 reductase activity or the 11β-HSD2 dehydrogenase activity.		
Tabulated Results:	IC_{50} (µmol/L)	
Compound Tested	11β-HSD1 Reductase	11β-HSD2 Dehydrogenase
CCX168	NI	NI
T0504	0.03	—
11α-OH-P	—	0.18
CCX168-M1	>10	NI
T0504	0.02	—
11α-OH-P	—	0.18
Additional Information: NI = No Inhibition at 10 µmol/L. 3-Adamantan-1-yl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4.3-a]azepine (T0504) and 11-α-Hydroxyprogesterone (11-α-OH-P) are the positive inhibitors for 11β-HSD1 and 11β-HSD2, respectively.		

2.6.5.15.8 プレドニゾン又はプレドニゾロンの血漿蛋白結合へ及ぼす影響

	Test Article: CCX168	
	Location in CTD: 4.2.2.6.9	
	Study No.: PC0466_168	
Type of Study: Effect of CCX168 on Protein Binding of Prednisone or Prednisolone in Human Plasma		
Method: An equilibrium dialysis method was used to determine the bound and free concentrations of prednisone and prednisolone in human plasma in the presence or absence of 1 µmol/L CCX168.		
Tabulated Results:	Unbound Fraction (f_u) in Human Plasma	
Compound Tested	Without CCX168	With CCX168
Prednisone 1 µmol/L	0.264 ± 0.059	0.236 ± 0.054
Prednisone 10 µmol/L	0.376 ± 0.060	0.400 ± 0.051
Prednisolone 1 µmol/L	0.160 ± 0.011	0.175 ± 0.010
Prednisolone 10 µmol/L	0.361 ± 0.053	0.327 ± 0.071
Additional Information: None		

2.6.5.16 薬物動態試験：その他

該当資料なし