2.6.4 薬物動態試験の概要文

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略語一覧

略号	省略していない表現（英）	省略していない表現（日）
ADME	absorption, distribution, metabolism and excretion	吸収・分布・代謝・排泄
AMS	accelerator mass spectrometry	加速質量分析法
AUC0-24h	area under the drug plasma concentration-time curve (time 0 to 24h)	血漿中薬物濃度-時間曲線下面積（時間 0～24 時間）
AUC0-t	area under the drug plasma concentration-time curve (time 0 to infinity)	血漿中薬物濃度-時間曲線下面積（時間 0～t）
AUCinf	area under the drug plasma concentration-time curve (time 0 to infinity)	血漿中薬物濃度-時間曲線下面積（0～無限大）
BCRP	breast cancer resistance protein	乳癌耐性蛋白質
BSEP	bile salt export pump	-
CL/F	apparent clearance	見かけのクリアランス
Cmax	maximal drug plasma concentration	最高血漿中薬物濃度
Cmax,ss	maximal drug plasma concentration at steady state	定常状態における最高血漿中薬物濃度
CYP	cytochrome P450	チトクローム P450
ELISA	enzyme-linked immunosorbent assay	酵素結合免疫測定（吸着）法
HPLC	high performance liquid chromatography	高速液体クロマトグラフィー
IC_{50}	half maximal (50%) inhibitory concentration	50%阻害濃度
i.m.	intramuscular	筋肉内
i.v.	intravenous	静脈内
Km	Michaelis constant	ミカエリス定数
LAR	Long acting release	-
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
LOQ	limit of quantification	定量限界
MRP	multidrug resistance associated protein	多剤耐性関連蛋白質
NADPH	nicotinamide adenine dinucleotide phosphate	ニコチンアミドアデニンジヌクレオチドリン酸
OAT	organic anion transporter	有機アニオントランスポーター
OATP	organic anion transporting polypeptide	有機アニオントランスポーターポリペプチド
OCT	organic cation transporter	有機カチオントランスポーター
P-gp	P-glycoprotein	P-糖蛋白
p.o.	per os	経口
QWBA	quantitative whole body autoradiography	定量的全身オートラジオグラフィー
RIA	radioimmunoassay	ラジオイムノアッセイ
s.c.	subcutaneous(ly)	皮下
Tmax	time to reach the maximum drug plasma concentration following drug administration	最高血漿中薬物濃度到達時間
UGT	UDP-glucuronosyl transferase	UDP-グルクロン酸転移酵素
V/F	apparent distribution volume	見かけの分布容積

1 まとめ

マウス，ラット（HanWistar / Long Evans Hooded），ウサギ（New Zealand White），及びイヌ（Beagle）における吸収，分布，代謝及び排泄（ADME）について，放射能（^{14}C）標識又は非標識 SOM230（パシレオチド，SOM）を用いて *in vitro* 及び *in vivo* で検討した。Table 1-1 使用した薬物動態試験，TK 試験及び臨床試験に薬物動態試験，トキシコキネティクス（TK）試験及び臨床試験の一覧を示す。なお，薬物動態試験には毒性試験と同一の動物種及び系統を用いた。

なお，本邦では SOM の筋注用徐放性製剤（SOM LAR）の開発が行われたが，外国では皮下投与製剤（SOM SC）の開発が先行していたため，薬物動態試験の多くは皮下投与にて行った。吸収過程を除き，全身循環血に移行した後の体内動態は SOM LAR を筋肉内投与後と SOM SC を皮下投与後で同じと考えられることから，本申請においても皮下投与試験の成績を用いた。

Table 1-1 使用した薬物動態試験，TK 試験及び臨床試験

動物	放射性標識	投与量 (mg/kg)	投与剤形	投与経路	投与期間	報告書番号
マウス	-[a]	1	溶液	皮下	反復	0470037
	-	2.5	溶液	皮下	反復	0470037
	-	5	溶液	皮下	反復	0470037
	-	10	溶液	皮下	反復	0470037
ラット	^{14}C	1	溶液	皮下	単回	R01-0388
	^{14}C	2[b]	溶液	静脈内	単回	R99-2095
	^{14}C	1[b]	溶液	皮下	単回	R0500319
	^{14}C	10[c]	溶液	皮下	単回	R0201643
	^{14}C	1[d]	溶液	皮下	単回	R0900555
	-	0.05	溶液	静脈内	単回	R00-2234
	-	0.1	溶液	皮下	単回	R00-2234
	-	0.008/day	溶液	皮下	反復	0210056
	-	0.024/day	溶液	皮下	反復	0210056
	-	0.08/day	溶液	皮下	反復	0210056
	-	0.24/day	溶液	皮下	反復	0210056
	-	6 mg/animal	筋注用徐放性製剤	筋肉内	単回	R0600360
ウサギ	-	0.05/day	溶液	皮下	反復	0470018
	-	1/day	溶液	皮下	反復	0470018
	-	5/day	溶液	皮下	反復	0470018
サル	^{14}C	0.6	溶液	皮下	単回	R0900554
	-	0.4/day	溶液	皮下	反復	0270130
	-	1.6/day	溶液	皮下	反復	0270130
	-	3.2/day	溶液	皮下	反復	0270130
ヒト	^{14}C	0.6 mg/subject	溶液	皮下	単回	CSOM230B2112

Source [Table 2.6.5.4A-Study 0470037], [Table 2.6.5.5A-Study R01-0388], [Table 2.6.5.5B-Study R99-2095], [Table 2.6.5.5C-Study R0500319], [Table 2.6.5.8-Study R0201643], [Table 2.6.5.9C-Study R0900555], [Table 2.6.5.3B- R00-2234], [Table 2.6.5.3C- R00-2234], [Table 2.6.5.3D- R0600360], [Table 2.6.5.4A-Study 0210056], [Table 2.6.5.7B-Study 0470018], [Table 2.6.5.9D-Study R0900554], [Table 2.6.5.4H-Study 0270130], [5.3.3.1-3-CSOM230B2112]

a 非放射標識

b 有色ラットにおける組織分布，全身オートラジオグラフィー

c 妊娠ラットにおける組織分布，全身オートラジオグラフィー

d 乳汁中移行試験

1.1 吸収及び薬物動態

1.1.1 皮下投与

SOM は皮下投与後，検討したすべての動物種において良好な吸収率を示し，投与量の 84%～100%が吸収された。吸収は比較的速やかであり，Tmax は 0.25～2 時間の範囲であった。皮下投与後の終末相の見かけの半減期は 1.3～56 時間であり，皮下与後の絶対バイオアベイラビリティは約 100%であった。AUC はトキシコキネティクス試験におけるすべての動物種において投与量にほぼ比例していた。マウスでは 2.5～10 mg/kg の用量で雌よりも雄の方が約 1.2～1.8 倍曝露量が高く，ラットでも 1.3～2.2 倍雄の方が高かったが，サルで性差はみられなかった。ラットにおいて反復投与による累積はみられなかったが，サルにおいて約 2 倍の累積がみられた。

ヒトに皮下投与後，Tmax は 0.25～0.5 時間と早く，血漿中で代謝物は検出されなかったことから，投与部位から全身循環血へ移行するまでの過程で代謝による消失は生じないと考えられる。このため，ヒトでの皮下投与のバイオアベイラビリティは動物と同様にほぼ 100%であると推察される。

1.1.2 筋肉内投与

製造工程の異なる 2 種類の SOM LAR をラットに単回投与したとき，SOM 血漿中濃度推移は投与後 63 日まで持続的な放出を示した。SOM LAR の絶対バイオアベイラビリティは 85%～108%であり，SOM を皮下投与したときと同程度であった。ラットに SOM LAR を 1 ヶ月 1 回の頻度で 3 回又は 6 回反復筋肉内投与後の曝露量は，投与量に比例して増加した。

1.2 分布

SOM の血球移行性は低く，血漿中濃度は血液中よりも高かった。ラット，イヌ及びヒトにおける血漿蛋白結合率は 88%～94%と中程度であった。

有色ラットに単回静脈内投与後，大部分の組織中放射能濃度は血液よりも低かった。ラットにおける組織分布は速やかであり，大部分の組織で投与後 5 分に，その他の組織でも投与後 1 時間に放射能濃度が最大となった。高い放射能濃度が観察された組織は腎臓，血管壁，耳，食道，リンパ節，脾臓及び肝臓であった。放射標識物質の消失は遅く，投与後 1，3 及び 14 週の屍体中総

放射能はそれぞれ投与量の 29%，14%及び 2%であった。有色又はアルビノラットに単回皮下投与後，投与部位を除く分布は静脈内投与後と同様であった。投与後 1 時間から 3 時間の間で血液及び大部分の組織中放射能濃度がプラトーに達した。組織中放射能の消失は血液での終末相半減期である 11 時間よりもはるかに遅く，大部分が 100 時間より長かった。組織中最高濃度と血液中最高濃度の比（組織/血液中最高濃度比）を算出したところ，大部分の組織で 1 未満であった。高い組織/血液中最高濃度比が観察された組織は投与部位（500），褐色脂肪（52），腎皮質（15），血管壁（5.7），肝臓（4.6）及び小腸壁（4.5）であった。皮膚やブドウ膜のメラニンと薬剤関連放射能との特異的な結合はみられなかった。いくつかの生殖組織及び中枢神経組織に薬剤関連放射能の分布が認められたが，組織/血液中最高濃度比はそれぞれ 0.11 及び 0.03 以下であった。妊娠ラットでは母動物血液から胎仔への薬剤関連放射能の移行は 13 日目で約 6%と低く，18 日目ではわずかであった。妊娠ウサギにおいて胎仔/母動物血漿中濃度比は約 0.46～1.0 であった。

1.3 代謝

SOM はラット及びヒト肝ミクロソーム，並びにヒト腎ミクロソームにおいて代謝的に安定であった。サルの肝ミクロソームでは，NADPH 依存的に代謝物 P2 がわずかに生成した。代謝物を検出するために高濃度の SOM（4.6 及び 49 µmol/L）とヒト肝ミクロソーム蛋白濃度 1 mg/mL を用いて代謝試験を行った。ヒト肝ミクロソームにおける SOM の代謝経路は P24（トリプトファン部位の一酸化体）と M27（リジン部位の脱アミノ化）の生成であった。SOM の代謝速度は遅く，SOM 濃度 4.6 及び 49 µmol/L で検討した結果，それぞれ 0.20 及び 2.5 nmol/mg microsomal protein/h であった。この代謝反応のミカエリス定数（Km）は高く，約 49 µmol/L 以上であると推察された。*In vitro* 代謝におけるこれら SOM の代謝経路は CYP3A4 及び CYP3A5 によって触媒された。

皮下投与後のラット，サル及びヒトにおける SOM の代謝物は，Table 5-1 皮下投与後の SOM230 代謝物及び試料の種類及びFigure 5-2に示したように，数種の代謝物のみであった。主要な代謝物は M27 であり，他の代謝物は生成量が少なく，構造は同定されていない。ラット，サル及びヒトの血漿中では主に SOM 未変化体として存在しており， 未変化体の AUC は総放射濃濃度の AUC に対してそれぞれ 93%～96%，93%，及び 100%であった。

1.4 排泄

すべての動物種において総放射能の排泄経路は主に糞中排泄で，投与量の 48%～95%が糞中に排泄された。尿中排泄は投与量の 6%～9%であった。動物の糞中に排泄された SOM 未変化体の量は，投与量の 48%（ラット）から 78%（サル）の範囲であった。ヒトにおいては，投与量の 4.16%～8.06%が尿中で未変化体として検出され，尿中排泄のうち，約 84%が未変化体であった。同様に糞中では投与量の 30.0%～46.2%が未変化体で検出され，糞中排泄のうち未変化体が約 82%を占めていた。

1.5 薬物相互作用

1.5.1 酵素阻害

SOM は *in vitro* で，ヒト肝ミクロソーム中の CYP1A2，CYP2B6，CYP2C8，CYP2C19，CYP2E1 及び CYP3A4/5 に対して弱い阻害作用を示し，IC_{50} 値は約 10～100 μmol/L であった。CYP2C9 及び CYP2D6 に対してはより強い阻害作用を示しており IC_{50} 値は約 5 μmol/L であった。しかしながら先端巨大症患者における SOM の臨床用量では Cmax,ss は 0.025 μmol/L 以下であり，SOM と CYP の基質となる併用薬との薬物相互作用は起こらないと予測される。

SOM は UGT1A1 に対して非常に弱い阻害作用を示し，IC_{50} 値はヒト肝ミクロソームでは 100 μmol/L 以上であり，組み換え UGT1A1 では約 59 μmol/L であった。先端巨大症患者における Cmax,ss よりも IC_{50} 値は高く，*in vivo* において SOM が UGT1A1 によって代謝される併用薬の代謝クリアランス又はビリルビンの抱合を阻害する可能性は低い。

SOM の CYP3A4 及び CYP3A5 による代謝は遅く，ヒト肝ミクロソームによる SOM の代謝反応から得られる Km は約 49 μmol/L 以上と高かった。ヒト ADME 試験では，血中には主に SOM 未変化体が検出され，代謝物は検出されなかった。投与された SOM の大部分が未変化体として糞及び尿中に排泄された。よって，併用薬により CYP3A4/5 が阻害されたとしても SOM の PK に与える影響は小さいと予測された。

1.5.2 酵素誘導

3 名のドナーから調製したヒト肝細胞で CYP1A2，CYP2B6，CYP2C8，CYP2C19 又は CYP3A の mRNA 量及び酵素活性を検討したところ，SOM はこれらを誘導しなかった。SOM は CYP1A1，CYP1B1，CYP2J2，P-gp 又は MRP2 の mRNA も誘導しなかった。1 名のドナーの肝臓では CYP2C9 の mRNA 量は 2.81～4.97 倍に誘導されたが，他の 2 名のドナーではみられなかった。CYP2C9 の酵素活性はすべてのドナーの肝臓で誘導されなかった。1 名のドナーの肝臓では UGT1A1 の酵素活性は 2.15 倍に誘導されたが，他の 2 名のドナーではみられなかった。UGT1A1 の mRNA 量は SOM によって誘導されなかった。よって，SOM が酵素誘導によって併用薬のクリアランスを増加させる可能性は低いと予測される。

1.5.3 トランスポーター

SOM は Caco-2 細胞試験において膜透過性が低い化合物であることが示され，受動膜透過係数は約 0.1×10^{-5} cm/min であった。SOM は P-gp の基質となる可能性があるが，本剤は筋肉内に投与されるため，投与部位からの吸収に薬物間相互作用は想定されない。

In vitro 反転膜小胞試験系で SOM は P-gp を阻害する可能性が示唆されたが（IC_{50} 0.85 μmol/L），MDA435 T0.3 細胞（P-gp 過剰発現細胞）で P-gp の基質であるローダミン 123 の排出に対する阻害は弱かった。先端巨大症患者での Cmax,ss は 0.025 μmol/L 以下であり，*in vivo* で SOM と P-gp の基質との間での薬物間相互作用は予測されない。

SOM は BCRP，OCT1，OATP1B1， OATP1B3 及び OATP2B1 の基質ではなかった。また，SOM は OATP1B1，OATP1B3，OCT1 又は OCT2 を阻害しなかった。

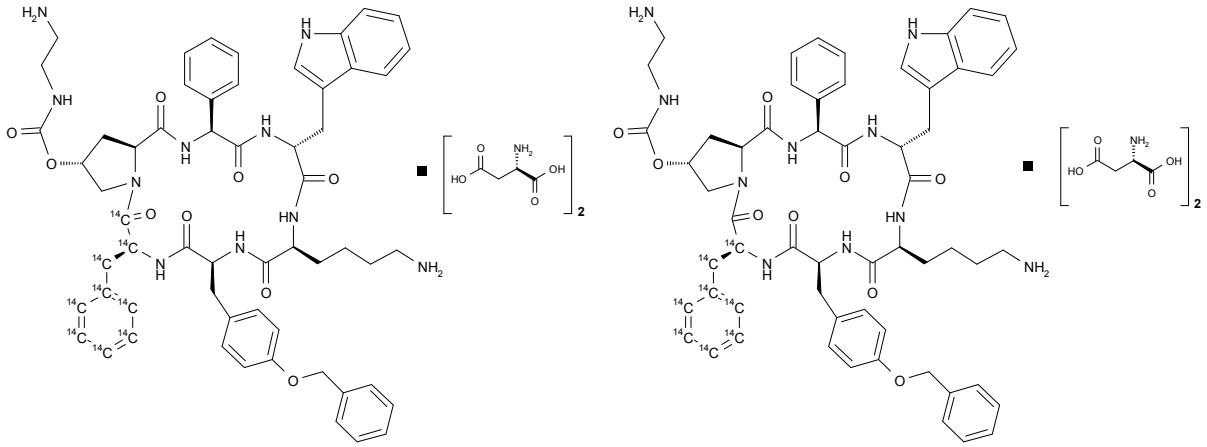
SOM は BCRP，MRP2，BSEP，OAT1 及び OAT3 を濃度依存的に阻害したが，先端巨大症患者における Cmax,ss（0.025 µmol/L）は IC_{50} 値より低いため，*in vivo* において SOM が BCRP，MRP2，BSEP，OAT1 及び OAT3 を阻害する可能性は低い。

2 分析法

2.1 放射性標識体

放射性標識 SOM はノバルティス ファーマ社で合成されたものを使用した。^{14}C-標識体の化学構造式と標識位置をFigure 2-1に示す。開発初期では $^{14}C_9$，開発後期は $^{14}C_8$ で標識されたものを使用した。使用した標識体の放射化学的純度は 放射能検出器を接続した HPLC によって定量し，いずれも 97%以上であった（Table 2-1）。

Figure 2-1 ^{14}C-SOM230 の構造式及び標識部位



[$^{14}C_9$] SOM230 [$^{14}C_8$] SOM230

Table 2-1 放射性標識 SOM230 の比放射能及び放射化学的純度

バッチ	比放射能	放射化学的純度（%）	報告書番号
RSE055-2	1.0878 MBq/mg	約 98	DMPK R99-2095
RSE055-4	11.78 MBq/mg	≥98	DMPK R01-0388，DMPK R01-749-01
RSE219-2	7.86 MBq/mg	98.3	DMPK R0201643
RSE219-3	3.326 MBq/mg	97.3	DMPK R0500108-01
RSE219-8	4.655 MBq/mg	97.9	DMPK R0900555
RSE219-9	2.259 MBq/mg	98.8	DMPK R0900554
E-15133-025-12	3.326 MBq/mg	97.3	DMPK R0500319

2.2 放射能の分析

放射能は液体シンチレーションカウンターにより測定した。試料は直接又はホモジネートし可溶化した後，一定量を採取し適切なシンチレーターを添加し分析した。

代謝物検索では，放射能はマイクロプレート液体シンチレーションカウンターにより測定した。ヒト ADME 試験では，^{14}C は AMS（加速器質量分析法）により測定した。組織分布は QWBA により測定した。

2.3 未変化体の分析

未変化体の血漿及び組織中濃度は，動物試験では酵素結合免疫測定法（ELISA 法）又は放射免疫測定法（RIA 法）（Table 2-2）を，ヒト試料では RIA 法を用いて測定した[Table 2.6.5.2A-Study R01-0742-01]。

放射標識化された SOM を投与後の動物の各組織中 SOM 濃度は，放射能検出器を備えた高速液体クロマトグラフィー（HPLC）を用いて定量した[Table 2.6.5.5A-Study R01-0388], [Table 2.6.5.9D-Study R0900554], [Table 2.6.5.9C-Study R0900555]。

ラットに LAR 製剤を投与後の抗パシレオチド抗体は，ビオチン化 SOM230 及びヤギ抗ラット IgG 抗体を用いた直接的 ELISA 法により測定した[Table 2.6.5.4E-Study 0770082, 0470138]。

Table 2-2 血漿中 SOM230 濃度の定量法

動物種	測定法	定量下限	試料	Source
ラット	ELISA	0.6 ng/mL	血漿	Table 2.6.5.2A-Study R01-0742-02 Table 2.6.5.2A-Study R01-0742-03
	RIA	30 pg/mL	血漿	Table 2.6.5.2A-Study nbx-rs602618
サル	ELISA	0.6 ng/mL	血漿	Table 2.6.5.2A-Study R01-0742
	RIA	40 pg/mL	血漿	Table 2.6.5.2A-Study nbx-rs653234

2.4 代謝物の同定及び構造解析

代謝物は放射能検出器を接続した HPLC を用いて定量した。可能な場合には，高速液体クロマトグラフィ-タンデム質量分析（LC-MS/MS）を用いて代謝物を同定した[Table 2.6.5.5A-Study R01-0388], [Table 2.6.5.9D-Study R0900554], [Table 2.6.5.9C-Study R0900555], [5.3.3.1-3-CSOM230B2112]。

3 吸収

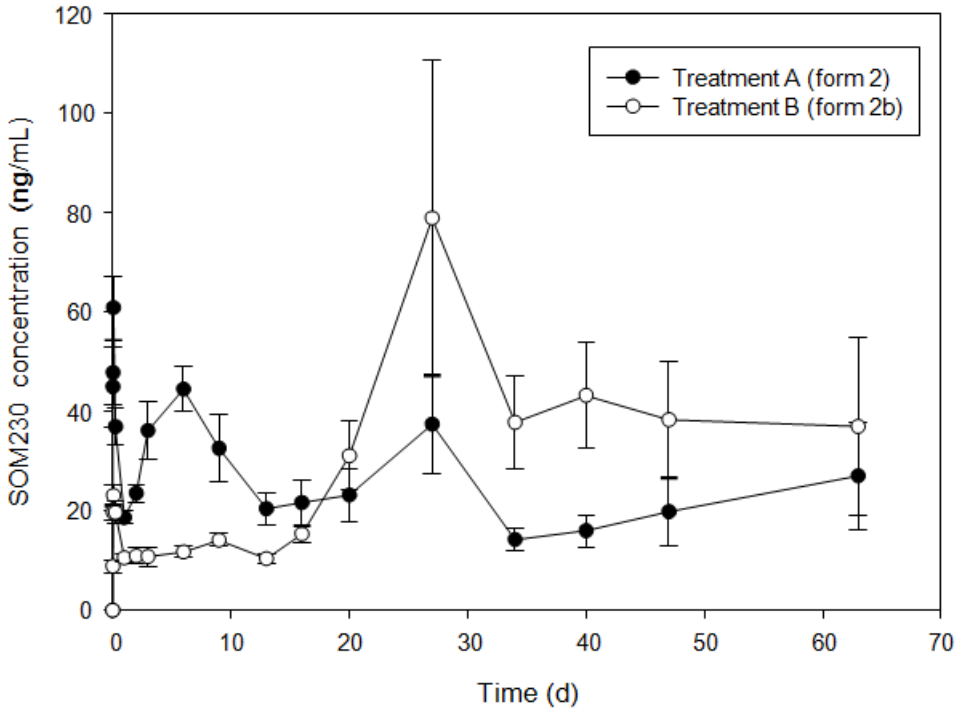
3.1 筋肉内投与（SOM LAR）時の吸収

製造工程の異なる 2 種類の SOM LAR 製剤（製剤 2 及び製剤 2b）の薬物動態について，ラットを用いて評価した [Table 2.6.5.3D-Study R0600360]。なお，臨床試験において，製剤 2 は数種類の

SOM LAR 製剤を投与して PK プロファイルを比較検討した C2101 試験でのみ使用され，C2101 試験を含む SOM LAR を用いたすべての臨床試験では製剤 2b が使用された[2.7.1-1.1 項-Table 1-2]。両製剤 6 mg をそれぞれラットに単回投与したとき，いずれも SOM 血漿中濃度推移は投与後 63 日まで持続的な放出を示した。製剤 2 では投与直後のピーク以降に二峰性のピークを Day 6 及び Day27 で示した。また，製剤 2b では投与直後のピーク以降に Day 27 に Tmax を示した。製剤 2 及び製剤 2b の絶対バイオアベイラビリティはそれぞれ 85%及び 108%であり，SOM を皮下投与したときと同程度であった。

ラットに SOM LAR を 1 ヶ月 1 回の頻度で 3 回又は 6 回反復投与後の曝露量は，投与量に比例して増加した [Table 2.6.5.4E-Study R0770082][Table 2.6.5.4E-Study R0470138] 。

Figure 3-1　　製剤 2 及び製剤 2b をラットに単回筋肉内投与後の平均血漿中濃度時間推移図



Source: 4.2.2.2-3-Figure 8-1

平均値±標準誤差

製剤 2 は計 20 例及び製剤 2b は計 18 例のラットの各時点 4～14 例の平均値を示す。

3.2　　皮下投与時の吸収

検討した動物種及びヒトに ^{14}C-SOM 及び SOM を皮下投与後の吸収に関するパラメータをTable 3-1に示す。すべての動物種及びヒトにおいて，未変化体の Tmax は 0.25～2.0 時間であり吸収は速やかであった。ラット及びサルにおいて，皮下投与後の吸収率は 84%～100%と高かった。ヒ

トに皮下投与後 10 日までに回収された放射能より算出した吸収率は 56%と動物に比べ低かったが，これは終末相半減期が約 211 時間と長く，10 日までの回収では短かったためと考えられた。Tmax が 0.25～0.5 時間と短いこと，及び血漿中では未変化体のみが検出されていることから，投与部位から全身循環血への吸収過程では代謝による分解を受けないと考えられ，ヒトでの吸収率はほぼ 100%であると考えられる。

Table 3-1 単回投与 ADME 試験，反復皮下投与 TK 試験及び SOM230 及び ^{14}C-SOM230 及び SOM230 を用いた臨床試験による吸収パラメータ

動物	投与量 (mg/kg/day)	Tmax[a]（h）		吸収率[b]（%）	報告書番号
		放射能	SOM230		
マウス[c]	1	-	1.0，0.5	-	0470037
	2.5	-	0.5，0.5	-	0470037
	5	-	0.5，0.5	-	0470037
	10	-	0.5，0.5	-	0470037
ラット	1 mg/kg[d]	4.0	-	84-100[f]	R01-0388
	1 mg/kg[d]	1.0	1.0	-	R0900555
	0.1 mg/kg[d]	-	1.0-2.0	107	R00-2234
	0.008[e]	-	0.5，-	-	0210056
	0.024	-	0.5，	-	0210056
	0.08[e]	-	-，1.0	-	0210056
	0.24[e]		1.0，2.0		0210056
ウサギ[g]	0.05	-	1.0	-	0470018
	1	-	1.0	-	0470018
	5	-	1.0	-	0470018
サル[h]	0.6 mg/kg	0.83	0.92	100	R0900554
	0.4	-	0.5-2.0, 0.5-1.0	-	0270130
	1.6	-	0.5-1.0,1.0	-	0270130
	3.2	-	1, 1-2.0	-	0270130
ヒト	0.6 mg/subject	0.25-0.5	0.25-0.5	56-100[i]	CSOM230B2112

Source [Table 2.6.5.4A-Study 0470037], [Table 2.6.5.5A-Study DMPK(CH) R01-0388], [Table 2.6.5.9C-Study R0900555], [Table 2.6.5.3B- R00-2234], [Table 2.6.5.4B-Study 0210056], [Table 2.6.5.7B-Study 0470018], [Table 2.6.5.9D-Study R0900554], [Table 2.6.5.4H-Study 0270130], [5.3.3.1-3- CSOM230B2112]

a 2 つの値が示されている場合それぞれ雄及び雌の値を示す。

b BA 又は投与量に対する排泄された割合を示した。

c 2 週間非標識 SOM を反復投与し，2 週目の結果を示した。

d 単回投与

e 26 週間非標識 SOM を反復投与したときの，22 週目の結果を示した。

f 糞尿のデータは 72 時間までしか集められていないため，実際の吸収は糞便中の回収率より高いと考えた。

g 妊娠から 20 日目の結果を示した。

h 39 週間 SOM を反復投与したときの 35 週目の結果を示し，2 つの値が示されているものはそれぞれ雄及び雌の値を表した。

i 終末相半減期（211 時間）が長く，投与 10 日後までの回収では十分でなかったため，吸収率は排泄された 56%よりも高いと判断した。

-：未算出

3.3 単回及び反復投与における薬物動態

動物に単回及び反復皮下投与したときの最高血液又は血漿中濃度（Cmax）及び血液又は血漿中薬物濃度-時間曲線下面積（AUC）の結果についてTable 3-2及びTable 3-3に示す。また，各動物種及び投与量間での比較を行うため，投与量で標準化した値も合わせて示す。

SOM230 未変化体濃度に関して，反復投与後のマウスでの AUC 及び Cmax は 1～10 mg/kg の用量範囲では概ね用量に比例して増加した。ラット，ウサギ及びサルでの AUC もマウスと同様に用量に比例したが，Cmax は用量比例性をやや下まわった（Table 3-3）。

マウスでは 2.5～10 mg/kg の用量で雄の AUC は雌よりも 1.2～1.8 倍高かった。性差は他のマウスの試験においても観察された（1.2～1.5 倍）[Table 2.6.5.4A-Study 0570087]。ラットにおいても雌よりも雄の AUC は 1.3～2.2 倍高く，性差が見られた。サルにおいては顕著な性差は見られなかった（Table 3-3）。

ラットにおいて 26 週間連日反復投与後に累積は示唆されなかったが[Table 2.6.5.4B-Study 0210056]，サルでは 39 週間反復投与後の AUC で約 2 倍の累積が示唆された[Table 2.6.5.4H-Study 0270130]。

SOM 及び ^{14}C-SOM を投与したときの Cmax 及び AUC をヒトとラット又はサルと比較したときの結果をTable 3-4に示す。投与量あたりの総放射能測定の Cmax は，ヒトはラットよりも約 3 倍高いが，サルとは同等であった。同様に AUC に関してもヒトはサルと同等であった。一方，投与量で標準化された SOM の Cmax 及び AUC を比較したところ，いずれもサルよりもわずかにヒトで高かった。検討された動物種で Cmax 及び AUC が最も高いサルより人は高いことから，SOM はヒトでより代謝的に安定であることが示唆された。実際，ヒト血漿中では代謝物は検出されていない（5.2 項）。

Table 3-5に示したように，単回皮下投与後のラット及びサルにおける SOM の絶対バイオアベイラビリティは 100%であり，単回筋肉内投与後のラットでも同様の結果が得られた（85%～108%）。上記 3.2 項で述べたように，ヒトにおける SOM の吸収は動物（100%）と同様に高いと考えられる。また，Tmax は 0.25～0.5 時間と早く，血漿中に代謝物が検出されないことから，SOM を皮下投与後投与部位から循環血中への吸収の過程での初回通過効果の影響は受けないと予測される。

Table 3-2 ^{14}C-SOM230 単回皮下投与後（ADME 試験）の血液又は血漿中総放射能濃度（Cmax 及び AUC）

動物	投与量 (mg/kg)	Cmax (ngEq/mL) [a]	AUClast (ngEq·h/mL) [a]	投与量で標準化した Cmax	投与量で標準化した AUClast	報告書番号
ラット	1	638 [343]	5120 [3000]	638 [343]	5120 [3000]	R01-0388

動物	投与量 (mg/kg)	Cmax (ngEq/mL) [a]	AUClast (ngEq·h/mL) [a]	投与量で標準化した Cmax	投与量で標準化した AUClast	報告書番号
ラット	1	638	5120	638	5120	R01-0388
サル	0.6	1340 [780]	5840 [3080]	2230 [1300]	9730 [5130]	R0900554
ヒト	0.00795 [b]	16.6 [9.89]	85.1 [57.7]	2090 [1240]	10700 [7260]	CSOM230B2112

Source [Table 2.6.5.3A-Study R01-0388], [Table 2.6.5.3A-Study R0900554], [5.3.3.1-3- CSOM230B2112]

a 血液中の結果は[ ]内に示した。

b 平均体重 75.5 kg，投与量 0.6 mg に基づいて算出した。

Table 3-3 単回投与 ADME 試験，反復皮下投与 TK 試験及び ^{14}C-SOM230 又は SOM230 を用いた臨床試験における血漿中 SOM230 の Cmax 及び AUC

動物	投与量 (mg/kg/day)	Cmax [a,c] (ng/mL)	AUC0-24h [a,c] (ng·h/mL)	投与量で標準化した [c] Cmax	投与量で標準化した [c] AUClast	報告書番号
マウス [b]	1	1440, 667	4560, 948	1440, 667	4560, 948	0470037
	2.5	4620, 2770	3770, 3030	1850, 1110	1510, 1210	0470037
	5	9620, 4100	19300, 10500	1930, 820	3870, 2100	0470037
	10	17800, 14100	55700, 42200	1780, 1410	5570, 4220	0470037
ラット [d]	0.1 mg/kg [e]	107	420	1070	4200	R00-2234
	0.008	9.03, -	19.4, -	1130, -	2420, -	0210056
	0.024	26.8, 16.0	95.9, 44.3	1120, 669	4000, 1840	0210056
	0.08	-, 42.9	-, 143	-, 536	-, 1790	0210056
	0.24	143, 144	748, 560	594, 602	3120, 2330	0210056
ウサギ [f]	0.05	45.0	114	901	2280	0470018
	1	753	1910	753	1910	0470018
	5	2710	11800	542	2350	0470018
サル [g]	0.6 mg/kg [e]	1020	4150 (inf)	1700	6920	R0900554
	0.4	855, 1150	3540, 3870	2140, 2870	8860, 9680	0270130
	1.6	2250, 2970	11400, 15900	1400, 1860	7110, 9950	0270130
	3.2	4850, 5440	28000, 29900	1520, 1700	8750, 9340	0270130
ヒト [h]	0.00795 [e]	18.1	73.8 (inf)	2280	9280	CSOM230B2112

Source [Table 2.6.5.4A-Study 0470037], [Table 2.6.5.3B- R00-2234], [Table 2.6.5.4B-Study 0210056], [Table 2.6.5.7B-Study 0470018], [Table 2.6.5.3B-Study R0900554], [Table 2.6.5.4H-Study 0270130], [5.3.3.1-3- CSOM230B2112]

a すべての値は有効数字 3 桁で示した。

b 4 週間反復投与試験の 4 週目の結果を示した。

c 2 つの値が示されている場合それぞれ雄及び雌の値を示す。

d 26 週間反復投与試験は 22 週目の結果を示した。

e 単回投与の結果を示した。

f 反復投与胎仔試験の妊娠 20 日目の結果を示した。

g 39 週間 SOM 反復投与試験の 35 週目の結果を示した。

h 投与量 0.6 mg，平均体重 75.5 kg より算出した。

Table 3-4 SOM230 単回皮下投与後投与量で標準化した Cmax 及び AUC の動物/ヒト比（ADME 試験）[a]

	動物	投与量 (mg/kg)	Cmax 比（動物/ヒト）	AUC 比（動物/ヒト）
^{14}C-SOM230	ラット	1	0.31	0.59
	サル	0.6	1.1	1.1
SOM230	ラット	1	-	-
	サル	0.6	0.75	0.75

Source [Table 2.6.5.3B- R00-2234], [Table 2.6.5.3D- R0600360], [Table 2.6.5.13C-Study R0900554], [5.3.3.1-3-CSOM230B2112]

a 放射能データは Table 3-2 から，SOM データは Table 3-3 から引用し，比較のためにヒトは単回皮下投与の ADME 試験（CSOM230B2112）を使用した。

Table 3-5 単回皮下又は筋肉内投与後の SOM230 のバイオアベイラビリティ

動物	投与経路/投与剤形	投与量 (mg/kg)	絶対バイオアベイラビリティ(%)	報告書番号
ラット	s.c./solution	0.1	complete（107）	R00-2234
	i.m./筋注用徐放性製剤	11.3-12.6(6 mg/animal)	complete（85-108）	R0600360
				R00-2234
サル	s.c./solution	0.6	100	R0900554
ヒト	s.c./solution	0.00795 [a]	56-100 [b]	CSOM230B2112

Source [Table 2.6.5.3B- R00-2234], [Table 2.6.5.3D- R0600360], [Table 2.6.5.13C-Study R0900554], [5.3.3.1-3-CSOM230B2112]

a 投与量 0.6 mg，平均体重 75.5 kg より算出した。

b 終末相半減期（211 時間）が長く，投与 10 日後までの回収では不十分であったため，実際の吸収率は 56%よりも高いと判断した。投与部位からの吸収過程での初回通過効果は受けないと予測されるため，動物の結果と同様ヒトにおける絶対バイオアベイラビリティも 100%と推察される。

単回皮下投与後の動物における血漿中総放射能濃度の半減期は，39 時間から 187 時間であった（Table 3-6）。サルと同様に，ヒトでの放射能の終末相半減期は 211 時間と長かった。それに対しラットの終末相の放射能半減期は 39 時間であり，血漿中放射能濃度はヒト及びサルよりも速やかに減少した。SOM の見かけの終末相半減期はラットにおいては比較的短く（1.3 時間），サルでは長かった（56 時間）。

Table 3-7に示したように，血漿クリアランスはラット (0.25 L/h/kg)，サル(0.05～0.28 L/h/kg)及びヒト (0.12 L/h/kg)で同程度であった。定常状態における分布容積はサル(1.1 L/kg)及びヒト(0.87 L/kg)よりもラット(0.29 L/kg)の方が小さかった。

Table 3-6 ^{14}C-SOM230 皮下投与後の放射能及び SOM230 の血漿中半減期

動物	投与量 (mg/kg)	見かけの終末相半減期（時間） SOM230	放射能	報告書番号
ラット	1	-	39	R01-0388
ラット[a]	0.1	1.3	-	R00-2234

動物	投与量 (mg/kg)	見かけの終末相半減期（時間） SOM230	放射能	報告書番号
サル	0.6	56	187	R0900554
ヒト	0.00795 [b]	7.8	211	CSOM230B2112

Source [Table 2.6.5.3A-Study R01-0388], [Table 2.6.5.3B- R00-2234], [Table 2.6.5.3A-Study R0900554], [Table 2.6.5.3B-Study R0900554], [5.3.3.1-3- CSOM230B2112]

a 非放射標識 SOM を投与したラットから得られたデータを示した。

b 平均体重 75.5 kg の被験者に対し 0.6 mg を投与

Table 3-7 ^{14}C-SOM230 の血漿クリアランス及び定常状態での分布容積

動物	静脈内投与量 (mg/kg)	クリアランス [a] (L/h/kg)	Vss [a] (L/kg)	報告書番号
ラット	0.05	0.25 ± 0.025	0.29 ± 0.029	R00-2234
サル	0.015-0.15	0.05 - 0.118 [b]	Not calculated	0580076
	0.6（s.c.）	0.28 ± 0.14 [c]	1.1 ± 0.14（Vss/F） [c]	R0900554
ヒト	0.6/subject（s.c.）	0.12 ± 0.030 [c]	1.29 ± 0.34（Vz/F） [c]	CSOM230B2112
			0.87 ± 0.28（Vss/F） [c]	

Source [Table 2.6.5.3C- R00-2234], [Table 2.6.5.4F-Study 0580076], [Table 2.6.5.9D-Study R0900554], [5.3.3.1-3-CSOM230B2112]

a 値は有効数字 2 ケタで表示した。

b 14 日目のデータを用いて Dose/AUC24h として算出した。

c 値（平均 ± 標準偏差）は 皮下投与のクリアランス (CL/F)及び分布容積 (V/F)を表示した。ヒト ADME 試験において平均体重は 75.5 kg とした。

4 分布

4.1 蛋白結合及び血球移行性

ラット，イヌ及びヒトで SOM の血球と血漿での分布を *in vitro* 試験で検討した結果，血球より血漿での濃度が高く，種差はなかった。SOM はほぼ血漿中に分布しており，ラット，イヌ及びヒトの血漿中に血液中 ^{14}C-SOM のそれぞれ最高で 99%，87%及び 91%が存在していた[Table 2.6.5.6-Study R99-2082]。血液/血漿中 SOM 濃度比は 0.5 から 0.6 の範囲であり，0.1～10 µg/mL の範囲では濃度に依存しなかった。これらの結果は，単回皮下投与後のラット，サル及びヒトでの血液/血漿中放射能濃度比を *in vivo* 試験で検討した結果と同様であり[Table 2.6.5.5A-Study R01-0388], [Table 2.6.5.9D-Study R0900554], [Table 2.6.5.9C-Study R0900555], [5.3.3.1-3-CSOM230B2112], 主な循環成分は SOM 未変化体であることが示唆された。

ラット，イヌ及びヒト血漿における *in vitro* 蛋白結合について，SOM を用いて 0.025～10 µg/mL の濃度で，限外濾過法により検討した [Table 2.6.5.6-Study R99-2082] 。37°C における SOM の血漿蛋白結合率はラット，イヌ及びヒトでそれぞれ 94%, 93% 及び 88%であり，すべての動物種で濃

度依存性は見られなかった。しかしながら，ろ過器具に 30%の化合物が残存していることが確認されているため，すべての種の血漿蛋白結合率は過大評価されている可能性がある。

4.2 組織及び臓器への分布

QWBA を用いて有色（Long Evans Hooded），アルビノ（HanWistar）ラット[Table 2.6.5.5B-Study R99-2095], [Table 2.6.5.5C-Study R0500319]及び妊娠ラット [Table 2.6.5.8-Study R0201643]における組織分布の検討を行った。

^{14}C-SOM 2 mg/kg をラットに単回静脈内投与後，放射能は大部分の組織に広範にかつ速やかに分布した。ほとんどの組織の放射能濃度は血液中放射能濃度よりも低かった。[Table 2.6.5.5B-Study R99-2095]。いくつかの組織は投与後 1 時間で最も高い放射能濃度を示したが，大部分の組織は投与後 0.083 時間で最も高い放射能濃度を示した。腎臓，血管壁，耳，食道，リンパ節，脾臓及び肝臓で最も高い放射能濃度が示された。放射能由来の物質は投与後 1，3 及び 14 週後の屍体中にそれぞれ 29%，14%及び 2%存在しており消失は遅かった。

^{14}C-SOM を単回皮下投与後の分布は，投与部位以外は静脈内投与後と同様であった[Table 2.6.5.5C-Study R0500319]。投与後 1 時間から 3 時間で血液及び大部分の組織で放射能濃度はプラトーに達していた。血液中の放射能は投与後 24 時間で既に定量下限値未満であったが，大部分の組織では投与後 336 時間でも定量下限値よりも高かった。組織中の放射能の消失は血液（半減期 11 時間）中よりもはるかに遅く，大部分の組織での半減期は 100 時間より長かった。半減期の長い組織は骨髄（2900 時間）と副腎皮質（2750 時間）であり，次いで精巣，脳下垂体，胸腺及び副腎髄質（521～606 時間）であった。しかしながらこれら組織中の放射能濃度は低かった。

組織中最高濃度と血液中最高濃度の比（組織/血液中最高濃度比）は，大部分の組織で 1 以下であった。ほとんどの組織における組織/血液中 AUC 比は組織からの放射能の消失が緩やかであるために高値を示した。組織/血液中最高濃度比は，投与部位（500），褐色脂肪（52），腎皮質（15），血管壁（5.7），肝臓（4.6）及び小腸壁（4.5）で高かった。組織/血液中 AUC 比は，投与部位（4440），副腎皮質（588），腎皮質（224），骨髄（174）及び血管壁（149）で高かった。肝臓及び腎臓中濃度もこれまでに実施したラットを用いた ADME 試験の結果と一致していた[Table 2.6.5.5C-Study R0500319]。

皮膚又はブドウ膜中のメラニンと放射能との特異的な親和性は示されなかった。生殖器系（精巣）においては組織/血液中最高濃度比が 0.11 であった。中枢神経系（脳及び脊髄）における組織/血液中最高濃度比は 0.03 以下であることから，分布はごくわずかであることが確認された。

4.3 胎盤通過性

妊娠 13 日目のラットに SOM を 12.5 mg/kg 単回皮下投与したとき，母動物の腎臓，肝臓，脾臓，副腎，腸管壁，肺，リンパ節及び卵巣において，投与後 24 時間に最高濃度に達した[Table 2.6.5.8-Study R0201643]。妊娠 18 日目のラットでも同様に，母動物の投与部位，肝臓，脊髄神経，軟骨，血管壁，赤脾髄，副腎皮質及びリンパ節において，投与後 24 時間に最高濃度に達した。

胎盤での放射能濃度は血液及び羊膜よりわずかに高かった。母動物の血液から胎仔への放射能の移行の程度は妊娠 13 日目のラットにおいては低く（約 6%），妊娠 18 日目のラットではわずかであった。胎仔への全体的な曝露量は低く，その程度は妊娠の段階に依存していることが示唆された。

SOM を 0.05，1 又は 5 mg/kg 反復皮下投与後の妊娠ウサギでは，0.05 mg/kg 投与群ではすべての胎仔組織中 SOM 濃度は定量下限値(0.6 ng/g)未満であった。1 mg/kg 投与群及び 5 mg/kg 投与群において，投与後 24 時間（おおよそ胎仔組織回収時）の平均血漿中濃度はそれぞれ 4.75 及び 42.1 ng/mL であり，平均胎仔中濃度はそれぞれ 2.18 ng/g 組織及び 41.9 ng/g 組織であった。胎仔/母動物血漿中濃度比は約 0.46～1.0 であり，SOM の胎仔への分布は中程度であることが示唆された[Table 2.6.5.7B-Study R0470018]。

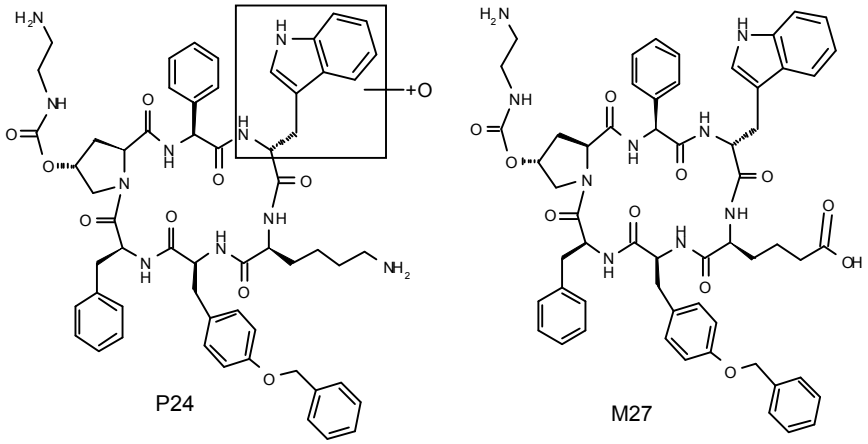
5 代謝（動物種間の比較）

5.1 *In vitro* 代謝

ラット，サル及びヒト肝ミクロソーム，ヒト腎ミクロソーム（ミクロソーム蛋白濃度 0.2 又は 0.5 mg protein/mL）及びラット肝細胞を用いて，SOM（1.0 µmol/L）の *in vitro* 代謝を検討した[Table 2.6.5.10A-Study R01-389]。SOM はラット及びヒト肝ミクロソーム，及びヒト腎ミクロソーム中で安定であった。ラット肝細胞中においても 4 時間まで安定であった。サル肝ミクロソーム中では SOM はわずかに代謝され，NADPH 依存的な代謝物 P2 が生成した（2%～4%）。^{14}C-SOM 合成時に生じた 3%～6%の放射性副生成物（P1）がコントロール群を含めすべての動物種で検出された。したがって，P1 は SOM の代謝物ではないと推察された。P1 は SOM の脱ベンジル化誘導体であることが示唆されたが，P2 の構造は不明である。

さらに SOM（4.6 及び 49 µmol/L）及びミクロソーム蛋白（1 mg protein/mL）を高濃度にし，代謝物が検出されるか検討した[Table 2.6.5.10B-Study R0400850]。ヒト肝ミクロソームにおける SOM の代謝経路は微量な P24（トリプトファン部位の一酸化体）と M27（リジン部位の脱アミノ化）の生成であった。SOM の代謝速度は遅く，SOM 濃度 4.6 及び 49 µmol/L で検討した結果，それぞれ 0.20 及び 2.5 nmol/mg microsomal protein/h であった。これら 2 濃度より得られた代謝速度は比例関係にあり，Km は 49 µmol/L より高いことが示唆された。ヒト組み換えチトクローム P450 発現系による検討から，P24 の生成には CYP3A4，M27 の生成には CYP3A5 が寄与することがわかった。これら代謝物の構造をFigure 5-1に示す。

Figure 5-1 *in vitro* 試験において検出された代謝物の構造



5.2 *In vivo* 代謝

ラット[Table 2.6.5.9A-Study R01-0388] [Table 2.6.5.9B-Study R01-0388] [Table 2.6.5.9C-Study R0900555]，サル[Table 2.6.5.9D-Study R0900554]及びヒト[Table 2.6.5.9E-Study CSOM230B2112] [Table 2.6.5.9F-Study CSOM230B2112]において SOM の *in vivo* 代謝について検討した。各動物種で血漿及び糞尿中に検出された代謝物をTable 5-1 皮下投与後の SOM230 代謝物及び試料の種類に，同定された物質の化学構造をFigure 5-2に，推定された代謝経路をFigure 5-3に示す。血漿及び糞尿中 SOM 及び ^{14}C-SOM ピークのレベルをTable 5-2，Table 5-3及びTable 5-4に示した。

雄性ラットに ^{14}C-SOM 1 mg/kg を単回皮下投与後[Table 2.6.5.9A-Study R01-0388] [Table 2.6.5.9B-Study R01-0388]，投与後 72 時間までに SOM 由来放射能の 77%が回収され，回収率で補正すると AUC0-24h の約 93%が SOM の未変化体であった（Table 5-2）。血漿，尿及び糞中には未変化体以外に少なくとも 2 つのピークが検出された。前述の通り P1（SOM の O-脱ベンジル化誘導体，Figure 5-2）は投与薬液中に含まれる不純物であると推察され，P3 の構造は生成量が低いため同定されていない。投与後 24，48 及び 72 時間における肝臓及び腎臓中放射能は未変化体に由来するものであった。SOM 未変化体は尿中では投与量の 4.2%（総尿中排泄率の約 49%）であり，糞中では投与量の 48%（総糞中排泄率の約 77%）であった（Table 5-3，Table 5-4）。

皮下投与で行われたラット乳汁移行性試験では [Table 2.6.5.9C-Study R0900555]，未変化体，及び 3 種のグルコース抱合体，A22.7，A23.5 及び A23.9 が認められた。しかしながら，3 種のグルコース抱合体のピークは代謝過程ではなく主にサンプル処理の過程で生成したと推察される。未変化体及びこれら 3 種のグルコース抱合体で放射能の AUC0-24h の 95.7%を占めた。その他に未同定のピークである A22.3，A27.2 及び A28 が検出され，その合計は AUC0-24h の 4.27%であった。これらは生成量が低いため構造同定はされておらず，これらもまたサンプル処理の過程で一部生成したと考えられた。ラット乳汁中においても AUC0-24h のうち 93.8%が未変化体であり，クロマトグラムから得られたその他すべての微量のピークも血漿中で検出されており，プロファイルは血漿中と同様であった[Table 2.6.5.9C-Study R0900555]。

皮下投与で実施されたサル ADME 試験では，血漿中でみられた顕著なピークはラット同様に SOM 未変化体及び 3 種のグルコース抱合体 A22.7，A23.5 及び A23.9 であり，これらで AUC0-24h の 93.1%を占めた。ラットの結果と同様に，これらのグルコース抱合体は代謝過程ではなくサンプル処理の過程で一部生成したと推察された。さらに人的要因で生成されたと考えられる 2 種類の物質（A25.5 及び A28）と一種の代謝物（M27）が AUC0-24h のそれぞれ 4.45%及び 2.68%を占めた。A25.5 及び A28 は生成量が低いため構造同定はされておらず，サンプル処理の過程で一部生成したと考えられた。M27 は *in vitro* 試験で検出された末端のアミノ基がカルボン酸に変換した代謝物と同様であった（Table 5-2）。SOM と 2 種のグルコース抱合体 A22.7 及び A23.5 は糞中にも検出された（投与量の 77.6%）。糞中において代謝物 M27 は投与量の 8.47%を占めた。

糞中のその他の未同定のピーク（A25.5，A26.7 及び A28）もまた投与量の 8.47%を占めた（Table 5-4）。

Table 5-1　皮下投与後の SOM230 代謝物及び試料の種類

代謝物	ラット（ADME 試験）	ラット（乳汁移行試験）	サル	ヒト
P1（不純物）	P，U，F	-	-	-
P3	F	-	-	-
P10	-	-	-	U
P19	-	-	-	U
M27	-	-	P，F	-
P28	-	-	-	F
その他のピーク [a]	P，U，F	P，M	P，F	-
SOM230 [b]	P，U，F	P，U，F，M	P，U，F	P，U，F

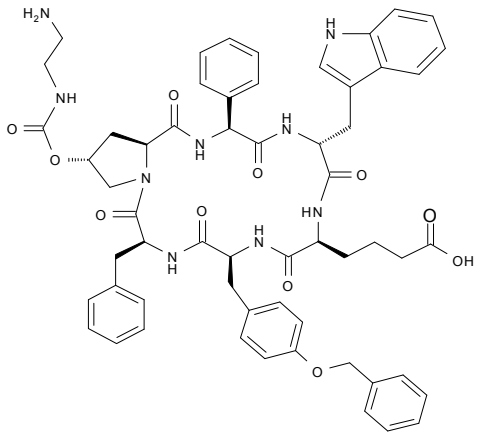
-：未検出又は未確認

P：血漿，U：尿，F：糞，M：乳汁

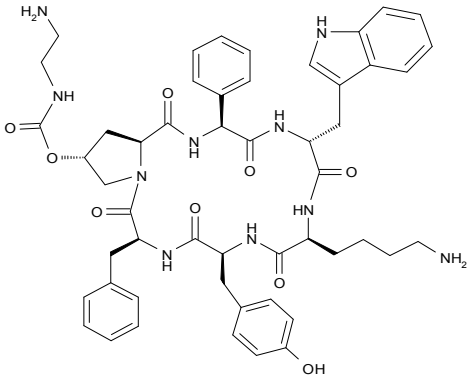
a ラット乳汁移行性試験ではサンプル処理過程で生成したと考えられる A22.3，A27.2 及び A28 が含まれ，サルの試験においては A25.5 及び A28 が含まれる。

b ラット乳汁移行性試験及びサルの試験ではサンプル処理過程で生成されたグルコース抱合体 A22.7，A23.5 及び A23.9 が含まれる。

Figure 5-2　SOM230 代謝物 M27 及び不純物 P1



M27



P1 (不純物)

Figure 5-3 サルにおける SOM230 の代謝経路

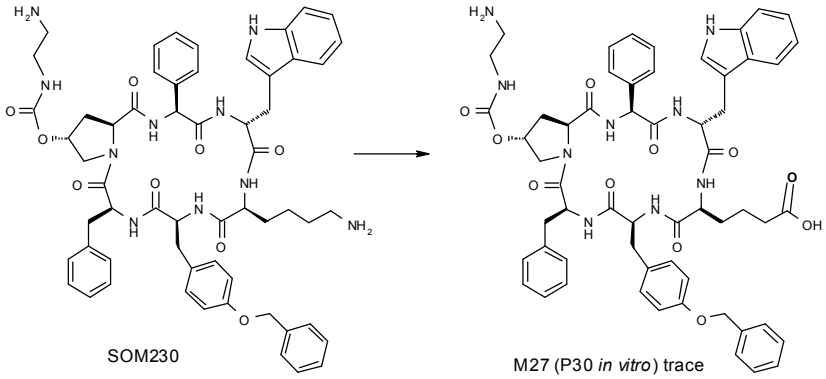


Table 5-2 ^{14}C-SOM230 皮下投与後の SOM230 及び代謝物の血漿 AUC 中の割合（%）

代謝物	ラット (1 mg/kg) (0-72 h)	ラット (1 mg/kg) (0-24 h)	サル (0.6 mg/kg) (0-24 h)	ヒト (0.00795 mg/kg) (0-12 h)
P1（不純物）	2	-	-	-
M27	-	-	2.68	-
その他のピーク	4	4.27 [a]	4.45 [a]	-
SOM230	77	95.7 [b]	93.1 [b]	100
Source	[Table 2.6.5.9A-Study R01-0388]	[Table 2.6.5.9C- Study R0900555]	[Table 2.6.5.9D-Study R0900554]	[Table 2.6.5.9E-CSOM230B2112]

-：未検出又は未確認

a ラットの試験では A22.3，A27.2 及び A28 が含まれ，サルの試験では A25.5 及び A28 が含まれる。

b A22.7，A23.5 及び A23.9 を含む。

Table 5-3 ^{14}C-SOM230 単回皮下投与後の尿中 SOM230 代謝物の投与量に対する割合（%）

代謝物	ラット (1 mg/kg) (0-48 h)	サル (0.6 mg/kg) (0-24 h)	ヒト (0.00795 mg/kg) (0-144 h)
P1	1.5	-	-
P3	-	-	-
P10	-	-	0.41
P19	-	-	0.737
その他のピーク	2.8	-	-
SOM230	4.2	3.52	5.90
Source	[Table 2.6.5.9B- Study R01-0388]	[Table 2.6.5.9D- Study R0900554]	[Table 2.6.5.9F-CSOM230B2112]

-：未検出又は未確認

ヒトに ^{14}C-SOM を 0.6 mg 皮下投与したときの血漿，尿及び糞中の代表的な代謝プロファイルをFigure 5-4 及びFigure 5-5に示した。プールした血漿中では代謝物は検出されず SOM のみが検出された（Figure 5-4）。尿中には SOM 未変化体が投与量の 5.9%（4.16%～8.06%の範囲）検出され，総尿中排泄率の約 84%を占めた。2 種の微量な構造未同定のピーク（保持時間約 10 及び約 19 分）が 4 名の被験者共に検出されており，そのうち 3 名では投与量の約 0.3%～0.5%とほぼ同量であり，1 名では約 1.9%であった。糞中では SOM 未変化体が投与量の 37.2%（30.0～46.2%の範囲）検出され，総糞中排泄率の約 82%を占めていた。1 種の構造未同定の代謝物（保持時間約 28 分）が検出され，その代謝物の投与量に対する割合は一人の被験者では 23%であったが他の被験者では約 3%であった。この被験者においては便排泄の頻度が他の被験者よりも少なかったため，消化管で SOM が分解を受けたと推察される。これらの結果から，ヒトにおける SOM の代謝の寄与は小さいと推察される。

以上より，すべての動物種において血漿中では主に SOM 未変化体として存在しており，ヒト血漿中では代謝物は検出されなかった。サル血漿中で検出された M27 を除いて，ラット及びサル血漿中のピークの多くはサンプル処理等で生じた人為産物であった。SOM の消失は未変化体の排泄が主要経路である。いくつかの微量放射能ピークの構造は生成量が低かったため同定されなかった。

Figure 5-4　ヒトに ^{14}C-SOM230 600 µg を単回皮下投与後の代表的な血漿中代謝プロファイル（0 時間から 12 時間までプールした試料）

(Subject USA/0501/00002)

血漿

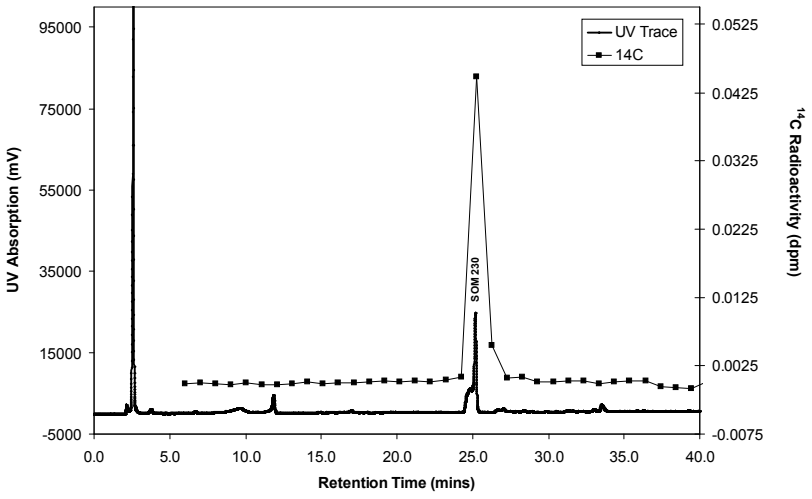
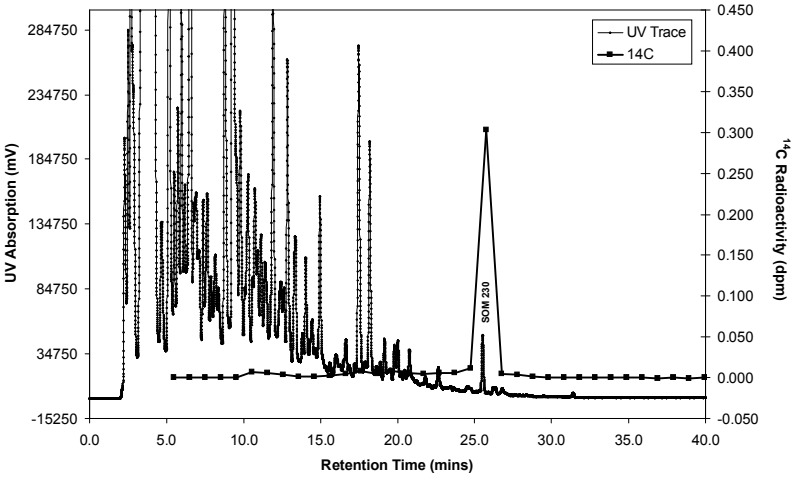


Figure 5-5 ヒトに ^{14}C-SOM230 600 µg を単回皮下投与後の代表的な尿及び糞中代謝プロファイル

尿



糞

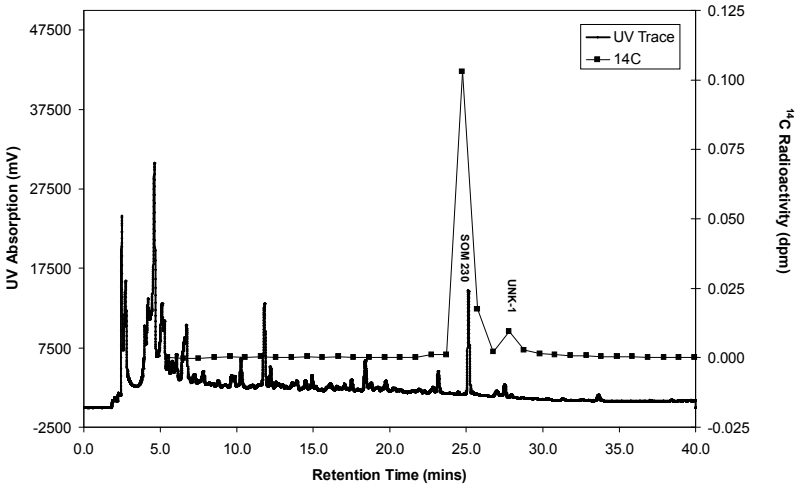


Table 5-4 ^{14}C-SOM230 単回皮下投与後糞中 SOM230 代謝物の投与量に対する割合（%）

代謝物	ラット (1 mg/kg) (0-48 h)	サル (0.6 mg/kg) (0-72 h)	ヒト (0.00795 mg/kg) (0-168 h)
P1(不純物)	1.3	-	-
P3	3.4	-	-
M27	-	8.47	-
P28	-	-	8.10
その他のピーク	9.5	8.47 [a]	-
SOM230	48	77.6 [b]	37.2
Source	[Table 2.6.5.9B- Study R01-0388]	[Table 2.6.5.9D- Study R0900554]	[Table 2.6.5.9F- CSOM230B2112]

-：未検出又は未確認

a A25.5，A26.7 及び A28 が含まれる。

b A22.7 及び A23.5 が含まれる。

6 排泄

^{14}C-SOM を単回皮下投与後の尿及び糞中排泄をTable 6-1に示した。ラット，サル及びヒトにおいて，放射能は主に糞中に排泄され，投与量の 48.3%～94.5%であり，尿中に排泄されたのは投与量の 6.27%～8.9%であった。SOM は主に未変化体として体内より排泄され，代謝物として消失するのはごくわずかであった（5.2 項）。ヒト血漿中濃度推移から腸肝循環は示唆されなかった。

Table 6-1 ^{14}C-SOM230 単回皮下投与後の SOM230 及び総放射能の排泄

		投与量に対する排泄量の割合(%)					
		尿			糞		
		放射能		SOM230	放射能		SOM230
動物	投与量 (mg/kg)	0-24 h	0-168 h	0-24 h	0-24 h	0-168 h	0-72 h
ラット [a]	1	8.3	8.9(0-72 h)	4.2(0-48 h)	66.6	74.8(0-72 h)	48(0-48 h)
サル [b]	0.6	4.48	6.27	3.52	6.69	94.5	77.6
ヒト [c]	0.00795	5.15	7.63(0-240 h)	5.9(0-144 h)	0.881	48.3(0-240 h)	37.2(0-168 h)

a [Table 2.6.5.13A-Study R01-0388]

b [Table 2.6.5.13C-Study R0900554]

c [Table 2.6.5.13D- Study CSOM230B2112]; 平均体重 75.5 kg の被験者に 0.6 mg を投与

SOM 1 mg/kg を授乳中のラットに単回皮下投与後，放射能の乳汁への移行を検討した [Table 2.6.5.13B-Study R0900555]。AUCinf を用いて算出した総放射能の乳汁/血漿中曝露量比は 0.28 であった。ラットの結果をヒトに外挿すると，毎日 1 L の母乳を摂取することによって曝露されうる SOM の量は，成人に筋肉内投与したときの投与量の 0.4%以下と推察される。血漿及び乳汁中の

代謝プロファイルは同様であり，SOM 未変化体が AUC の 93%以上を占め主な構成成分であった。SOM 未変化体に関して乳汁中と血漿中の Cmax 及び AUC0-24h を比較すると乳汁中の方が低い値であった。ラット血漿及び乳汁中にいくつかのピークが検出されたがそれらの構造は生成量が少なく同定できなかった。

7 薬物動態学的薬物相互作用

7.1 CYP に対する阻害

In vitro ヒト肝ミクロソーム系において，CYP 分子種に選択的なプローブ基質を用いて SOM の CYP 阻害作用を検討した[Table 2.6.5.12B-Study R0300356] [Table 2.6.5.12C-Study R1100187]。CYP1A2，CYP2B6，CYP2C8，CYP2C19，CYP2E1 及び CYP3A4/5 に対する IC_{50} 値は 10～100 µmol/L であり，これらの CYP 分子種に対する阻害効果は弱かった。一方，CYP2C9 及び CYP2D6 に対しては，他の分子種より強い阻害効果がみられ，IC_{50} 値は約 5 µmol/L であった。しかしながら，SOM LAR 60 mg を先端巨大症患者に 28 日に 1 回筋肉内投与したときの SOM の Cmax,ss は 0.025 µmol/L 以下であり[2.7.2-3.7 項]，SOM とこれら CYP の基質となる併用薬との間での薬物間相互作用は起こらないと予測された。

7.2 UGT1A1 に対する阻害

SOM のヒト UGT1A1 酵素活性に対する阻害効果を，プールしたヒト肝ミクロソーム及びヒト組み換え UGT1A1 を用いて検討した[Table 2.6.5.12D-Study R1100760]。UGT1A1 の *in vitro* 代謝プローブ反応であるエストラジオール 3β グルクロン酸抱合体の生成に関して，SOM は非常に弱い阻害作用を示し，IC_{50} 値はヒト肝ミクロソームでは 100 µmol/L 以上，組み換え UGT1A1 では約 59 µmol/L であった。先端巨大症患者における Cmax,ss よりも IC_{50} 値は高く，*in vivo* において SOM が UGT1A1 によって代謝される併用薬の代謝クリアランス又はビリルビンの抱合を阻害する可能性は低い。

7.3 CYP 分子種の同定

組み換えヒト CYP1A1，CYP1A2，CYP1B1，CYP2A6，CYP2B6，CYP2C8，CYP2C9(Arg_{144}，Ile_{359})，CYP2C18，CYP2C19，CYP2D6，CYP2E1，CYP2J2，CYP3A4，CYP3A5，CYP4A11 を用いて，ヒトにおける SOM の代謝に寄与する CYP 分子種について検討した[Table 2.6.5.10B-Study R0400850]。その結果，P24 及び P30 の代謝には，主にそれぞれ CYP3A4 及び CYP3A5 が関与することが示された。

ヒト肝ミクロソームによる SOM の代謝は遅く（5.1 項），ヒト ADME 試験ではヒト血漿及び尿糞中では主に未変化体が認められ，代謝物はほとんど検出されなかったことから（5.2 項），SOM の肝代謝クリアランスに寄与する CYP3A4/5 が阻害された時の影響は低いと予測される。

7.4 酵素誘導

In vitro 試験において，SOM が CYP 酵素と UGT1A1 の mRNA 及び酵素活性，P-gp 及び MRP2 の mRNA を誘導するか，3 名のドナーの肝臓から調製したヒト肝細胞を用いて検討を行った [Table 2.6.5.12A-Study R0800722] 。mRNA は RT-PCR によって定量し，酵素活性変化の評価は誘導期間後に酵素選択的プローブ基質の代謝物を LC-MS/MS を用いて評価した。CYP 酵素誘導の陽性対照としてリファンピシン及びフェノバルビタールを用いた。CYP1A1 及び UGT1A1 誘導の陽性対照として α-ナフトフラボンを用いた。なお，酵素活性又は mRNA の上昇がコントロール群と比較して 2 倍以下であった時及び/又は陽性対照の最大反応の 40%未満であった時，誘導効果がないと判断した。SOM は先端巨大症患者の臨床最高用量時の平均 Cmax の 40 倍にあたる 1 µmol/L まで CYP1A2，CYP2B6，CYP2C8，CYP2C19 又は CYP3A の mRNA 及び活性を誘導しなかった。CYP1A1，CYP1B1，CYP2J2，P-gp 又は MRP2 の mRNA も誘導しなかった。CYP2C9 の mRNA は 1 名のドナーの肝細胞において 0.005～0.1 µmol/L の濃度で 2.81 から 4.97 倍まで誘導されたが，酵素活性についてはどの肝細胞においても誘導されなかった。UGT1A1 酵素活性は一つの肝細胞で 0.1 µmol/L で 2.15 倍まで誘導されたが，他の肝細胞では誘導されなかった。また，UGT1A1 mRNA は誘導されなかった。これらより，SOM による酵素誘導及びそれに伴う併用薬のクリアランス上昇の可能性は低いことが示唆された。

7.5 *In vitro* 膜透過性評価及びトランスポーターに対する相互作用

Caco-2 細胞単層膜を用いて SOM の *in vitro* 膜透過性及びトランスポーターを介した相互作用の可能性を評価した [Table 2.6.5.16A-Study R99-2281] 。SOM の膜透過性は濃度依存的であり，SOM 濃度 10 µmol/L 以下では Apical 側から Basal 側への取り込み（A to B）は Basal 側から Apical 側への取り込み(B to A)より低かったが，SOM 濃度 50 µmol/L での B to A/ A to B 比は約 1.2 であった。このときの膜透過係数（Papp）は約 0.12×10^{-5} cm/min であり，膜透過性の低いマンニトール（1.9×10^{-5} cm/min）より小さい値であることから，SOM は膜透過性が低いことが示唆された。

SOM 濃度 0.2 µmol/L かつ P-gp 阻害剤であるシクロスポリン A（10 µmol/L）又は P-gp 及び MRP 阻害剤であるベラパミル（100 µmol/L）存在下では SOM の Papp は 0.09～0.13×10^{-5} cm/min であり，SOM 濃度 50 µmol/L で阻害剤非存在下での Papp（0.12×10^{-5} cm/min）と同程度であった。この結果より SOM は P-gp の基質になることが示唆されたが，投与経路が筋肉内投与であるため，投与部位からの吸収に影響を与える薬物相互作用は予測されない。

BCRP が SOM の輸送に寄与する可能性を Caco-2 細胞単層膜及びマウス BCRP を安定発現した Mandin-Darby canine kidney 細胞（MDCK/mBCRP）を用いて検討した [Table 2.6.5.16C-Study R1000737] 。BCRP 阻害剤である Ko143（1.0 µmol）存在下と非存在下で，Caco-2 細胞において SOM（2.1 及び 12 µmol）の見かけの透過係数に変化は見られなかったことから，BCRP は寄与しないことが示唆された。MDCK/mBCRP においても BCRP 阻害剤による変化は見られず，SOM が BCRP の基質になる可能性が低いことが示唆された。

肝臓への SOM の取り込みを *in vitro* で凍結ヒト肝細胞懸濁液を用いて評価した [Table 2.6.5.16D-Study R1000572] 。主な肝取り込みトランスポーター（OCT1，OATP1B1，OATP1B3 及び OATP2B1）阻害剤の存在下と非存在下での SOM の肝への取り込みは，それぞれ 112±11 pmol mg protein^{-1} 及び 118±19 pmol mg protein^{-1} であり大きな差はなかった。SOM のヒト肝細胞への取り込みには肝取り込みトランスポーターは関与しないことが示唆された。

7.6 *In vitro* におけるトランスポーターに対する阻害

P-gp 又は BCRP の活性を SOM が阻害する可能性を，P-gp 又は BCRP 高発現反転膜小胞又は P-gp 高発現細胞である MDA435 T0.3 細胞を用いて評価した。反転膜小胞において SOM は P-gp に阻害効果を示し（基質：[^{3}H]N-メチルベラパミル，IC_{50}：0.851 ± 0.41 µmol），BCRP には弱い阻害効果を示した（基質：[^{3}H]エストロン-3-硫酸，IC_{50}：約 10 µmol）[Table 2.6.5.16F-Study 1200248-01] 。MDA435 T0.3 細胞で P-gp の基質であるローダミン 123 の排出に対する阻害を評価した結果，阻害はみられたが，臨床で想定される血漿中濃度（0.025 µmol/L 以下）を大きく上回る SOM 10 µmol/L でもその程度は陽性対照であるシクロスポリン A よりも弱かった [Table 2.6.5.16B-Study R0600583] 。以上より SOM は *in vitro* で P-gp 及び BCRP を阻害することが示唆されたが，推定される治療濃度が低いため（0.025 µmol/L 以下），P-gp 及び BCRP に与える影響は小さく，これらトランスポーターの基質となる薬物の PK に SOM が影響する可能性は低いと考えられる。

SOM が肝又は腎取り込みトランスポーターを阻害する可能性を OATP1B1，OATP1B3 [Table 2.6.5.16D-Study R1000572]，OCT1，OCT2 [Table 2.6.5.16G-Study R1200761]，OAT1 又は OAT3 [Table 2.6.5.16H-Study R1200835] を安定発現させた human embryonic kidney（HEK）細胞を用いて評価した。OATP1B1 の基質である[^{3}H]エストラジオール-17β-D-グルクロナイド ([^{3}H]$E_2$17βG) の取り込みは，1.0 µmol/L の SOM 存在及び非存在では，それぞれ 7.64±0.25 pmol・mg protein^{-1} 及び 7.42±0.21 pmol・mg protein^{-1} であり差はなかった。OATP1B3 の基質である[^{3}H]コレシストキニン 8 の取り込みは，1.0 µmol/L の SOM 存在及び非存在では，それぞれ 0.52±0.052 pmol・mg protein^{-1} 及び 0.64±0.056 pmol・mg protein^{-1} で差はなかった。OCT1 の基質である[^{3}H]メチル-4-フェニルピリジニウム及び OCT2 の基質である[^{14}C]メトフォルミンの取り込みは，0.1～10 µmol/L の濃度範囲で SOM によって阻害されなかった。OAT1 の基質である[^{3}H]シドフォビル及び OAT3 の基質である[^{3}H]エストロン-3-硫酸の取り込みは，SOM 濃度が最も高い 10 µmol/L でそれぞれ 50.6%及び 84.0%に低下した。OAT1 及び OAT3 の IC_{50} はそれぞれ約 10 µmol/L 及び 1.7±0.37 µmol/L であった。先端巨大症での治療濃度は約 0.025 µmol/L と推定されることを考慮すると，SOM が OATP1B1，OATP1B3，OCT1，OCT2，OAT1 又は OAT3 の基質と薬物相互作用を起こす可能性は低いと考えられる。

MRP2 及び BSEP を SOM が阻害する可能性を，ヒト排出型トランスポーターを過剰発現させた昆虫細胞より単離した反転膜小胞を用いて評価した [Table 2.6.5.16E-Study R1100482] 。SOM は

0.1～10 μmol/L の範囲で弱いが濃度依存的に MRP2（基質：[^{3}H]$E_2$17βG）及び BSEP（基質： [^{3}H]タウロコール酸）を阻害したが，IC_{50} 値は約 10 μmol/L であり，先端巨大症患者に筋注用徐放性製剤製剤を 28 日毎 60 mg 筋肉内投与したときに推定される Cmax,ss（約 0.025 μmol/L）の 400 倍以上であった。SOM の膜透過性は低く（7.5 項）ヒト肝細胞では OATP による取り込みは認められていないため，ヒト肝臓中濃度が高くなる可能性は低い。ラットの組織分布[Table 2.6.5.5B-R99-2095]及びラット血液/血漿中濃度比[Table 2.6.5.6-R99-2082]から算出したラット肝臓/血漿中濃度比は 2.3 であった。これをヒトに外挿した場合，先端巨大症患者のヒト肝臓中濃度は 0.063 μmol/L 以下と予測される。これらの結果より，*in vivo* において SOM が MRP2 及び BSEP を阻害する可能性は低いと考えられた。

7.7 免疫抑制剤との相互作用の可能性

ソマトスタチンアナログは臓器移植による急性又は慢性拒絶反応の治療に用いられることがあるため，SOM とシクロスポリン A との相互作用の可能性についてイヌを用いて検討した[Table 2.6.5.15-Study RD-2001-01165]。SOM 3 μg/kg/hr を持続皮下投与したとき，シクロスポリン A の消化管吸収が低下して AUC0-24h は単剤投与時の約 54%に減少した。

8 考察及び結論

SOM はマウス，ラット，ウサギ，サル及びヒトにおいて皮下投与後のバイオアベイラビリティはほぼ 100%であり良好な吸収性を示した。また，2 種類の SOM LAR をラットに単回投与したときの絶対バイオアベイラビリティは 85%～108%であり，SOM を皮下投与したときと同程度であった。

マウス及びラットでは雌よりも雄の方がわずかに曝露量が高かったが，サルでは明確な性差はみられなかった。サルでは反復皮下投与により約 2 倍の累積が示唆されたが，ラットではみられなかった。

血漿蛋白結合率はヒトにおいて最も低く 88%であり，ラット及びイヌではそれぞれ 94%及び 93%であった。蛋白結合率はそれほど高くないことから，蛋白結合率の変化が本薬の動態に重要な影響を与えること可能性は低いと予測される。組織からの SOM 及びその代謝物の消失は遅かった。SOM 及びその代謝物は主に副腎皮質，腎皮質，骨髄，血管壁，リンパ節，脾臓及び肝臓に分布していたが，脳への移行性は低く，また皮膚やブドウ膜などのメラニンとの特異的な結合はみられなかった。ラット及びウサギの胎仔への SOM 及び/又はその代謝物の移行性が示された。ラットにおいて SOM に関連した放射能の乳汁への移行が観察された。ラットの結果をヒトへ外挿すると，乳幼児が 1 日 1 L の乳汁を摂取すると本薬を成人に筋肉内投与したときの曝露量の約 0.4%以下の曝露量に相当すると推察された。

SOM は UGT1A1 の非常に弱い阻害剤であり，IC_{50} 値は 59 μmol/L 以上であった。しかしながら，推定臨床用量における Cmax,ss（0.025 μmol/L 以下）が低いため，*in vivo* において SOM が

UGT1A1 によって代謝される併用薬の代謝クリアランス又はビリルビンの抱合を阻害する可能性は低い。SOM は *in vitro* において CYP2C9 及び CYP2D6 の活性を阻害するが（IC_{50} 値は約 5 μmol/L），推定臨床用量における Cmax,ss を考慮すると，*in vivo* でこれら CYP 分子種の基質となる併用薬と SOM で薬物相互作用が起こる可能性は低い。循環血中で代謝物が検出されないこと，及び糞及び尿中排泄のうち 82%以上が未変化体として回収されたことから，SOM の肝代謝クリアランスに関与する CYP3A4/5 が阻害されたときの影響は非常に小さいと予測される。SOM はラット，サル及びヒトにおいて腎排泄及び糞中排泄により消失する。そのうち約 88%が糞中排泄であるため，肝機能の変化が SOM の消失に影響を与える可能性がある。

SOM は P-gp の基質であるが，投与経路が筋肉内投与であるため，消化管吸収における P-pg 阻害薬との薬物相互作用は生じないと考えられる。SOM は P-gp の阻害剤又は誘導剤ではないため，SOM と P-gp の基質との薬物相互作用は予測されない。

さらに SOM は BCRP，OCT1，OATP1B1，OATP1B3 及び OATP2B1 の基質ではない。また OATP1B1，OATP1B3，OTC1 及び OCT2 の阻害剤でもなく，MRP2 の誘導剤でもない。SOM は BCRP，MRP2， BSEP 及び OAT1 に対し IC_{50} 値は約 10 μmol/L，OAT3 に対し 1.7 μmol/L の弱い阻害作用を示したが，先端巨大症患者の Cmax, ss は 0.025 μmol/L 以下であり，これらより低い濃度である。したがって，*in vivo* において SOM と併用薬の間でトランスポーターを介した薬物間相互作用が生じる可能性は低い。

2.6.5 薬物動態試験概要表

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略号一覧

略号	省略していない表現（英）	省略していない表現（日）
^{1}H-NMR	proton nuclear magnetic resonance spectroscopy	プロトン核磁気共鳴
ADME	Absorption, Distribution, Metabolism and Excretion	吸収・分布・代謝・排泄
AMS	accelerator mass spectrometry	加速器質量分析法
AUC	area under the concentration-time curve (unit: µg·h/mL)	血漿中薬物濃度-時間曲線下面積（単位：µg·h/mL）
BCRP	breast cancer resistance protein	乳癌耐性蛋白質
BSA	Bovine serum albumin	ウシ血清アルブミン
BSEP	bile salt export pump	—
C	Calibration	校正
CL	clearance (unit: L/h/kg)	クリアランス（単位：L/h/kg）
Cmax	maximum drug plasma concentration (unit: µg/mL)	最高血漿中薬物濃度（単位：µg/mL）
CS	C sample	校正試料
D	day	日
DDI	Drug drug interaction	薬物間相互作用
DT	Diphteria toxoid	ジフテリアトキソイド
DMAP	4-Dimethylaminopyridine	4-ジメチルアミノピリジン
DMSO	Dimethyl sulfoxide	ジメチルスルホキシド
ELISA	enzyme-linked immunosorbent assay	酵素結合免疫測定（吸着）法
F	female	雌
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
HPLC	high performance liquid chromatography	高速液体クロマトグラフィー
LC-MS/MS	HPLC coupled to tandem mass spectrometry (MS^2)	高速液体クロマトグラフィータンデム質量分析
HPLC-RA	high performance liquid chromatography coupled with radioactivity detection	高速液体クロマトグラフィー放射能検出法
HPLC-UV	high performance liquid chromatography coupled with ultraviolet detection	高速液体クロマトグラフィー紫外吸光度検出法
i.m.	Intramuscular administration	筋肉内投与
i.v., iv	intravenous administration	静脈内投与
LAR	Long-Acting Release	-
LLOQ	lower limit of quantification	定量下限
LOQ	limit of quantification	定量限界
LSC	liquid scintillation counting	液体シンチレーションカウンター
M	male	雄
MALDI-TOF-MASS	Matrix assisted laser desorption ionization time of flight mass spectrometry	マトリックス支援レーザー脱離イオン化飛行時間型質量分析計
MRP2	multidrug resistance associated protein 2	多剤耐性関連蛋白質 2
NA	not assessed	評価されず
ND	not determined	定量されず

略号	省略していない表現（英）	省略していない表現（日）
NI	not investigated	検討されず
NMR	nuclear magnetic resonance	核磁気共鳴
OAT	organic anion transporter	有機アニオントランスポーター
OCT	organic cation transporter	有機カチオントランスポーター
OD	optical density	光学濃度
OVA	Ovalbumin	オボアルブミン
P-gp	P-glycoprotein	P-糖蛋白
p.o.	oral administration	経口投与
PK	pharmacokinetics	薬物動態
QC	quality control	品質管理
radio-HPLC	high performance liquid chromatography coupled to radioactivity detection	放射能検出器付高速液体クロマトグラフィー
RIA	radioimmunoassay	ラジオイムノアッセイ
RT	room temperature	室温
s.c.	subcutaneous	皮下投与
SM	stock solution	保存溶液
TFA	Trifluoroacetic acid	トリフルオロ酢酸
TK	toxicokinetic study	トキシコキネティクス
Tmax, tmax	time to reach C_{max} (unit: h)	最高血漿中薬物濃度到達時間
UGT	uridine glucuronic acid transferase	UDP-グルクロン酸転移酵素
Vss	distribution volume at steady state (unit: L/kg)	定常状態における分布容積（単位：L/kg）
Wk	week	週

2.6.5.1 薬物動態試験：一覧

Type of Study	Test System or Species / Strain	Admini-stration	Duration Dosing	Doses (mg/kg) or Concentrations	GLP Compliance	Testing Facility	Report Number	Location in CTD
Absorption, Distribution, Metabolism and Excretion	Rat, Han:Wist	s.c.	single	1.0 [^{14}C]SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R01-0388]	4.2.2.4-1
Absorption, Metabolism and Excretion	Monkey, Cyno	s.c.	single	0.6 [^{14}C] SOM230	not required	Novartis US	[DMPK R0900554]	4.2.2.4-2
Absorption, Distribution, Metabolism and Excretion	Human	s.c.	single	600 µg [^{14}C] SOM230	not required	[redacted] US	[CSOM230B 2112]	5.3.3.1-3
Absorption	Rat, Han:Wist	i.v. s.c.	single	0.05 i.v. SOM230 0.1 s.c. SOM230	not required	Novartis Pharma AG Switzerland	[DMPK R00-2234]	4.2.2.2-1
Absorption	Monkey, Cyno	s.c.	single	1.0 SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R0101556]	4.2.2.2-2
Absorption	Rat, Han:Wist	i.m.	single	6 mg/animal SOM230	not required	Novartis Pharma AG Switzerland	[DMPK R0600360]	4.2.2.2-3
Blood/plasma distribution / Plasma protein binding	Rat, Han:Wist Dog, Beagle Human	in vitro	-	25-10000 ng/mL [^{14}C] SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R99-2082]	4.2.2.3-1
Distribution	Rat, LE Pigmented	i.v.	single	2.0 [^{14}C] SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R99-2095]	4.2.2.3-2
Distribution	Rat, Han:Wist Pregnant	s.c.	single	10.0 [^{14}C] SOM230	not required	Novartis US	[DMPK R0201643]	4.2.2.3-3
Distribution	Rat, LE Pigmented	s.c.	single	1.0 [^{14}C] SOM230	not required	Novartis US	[DMPK R0500319]	4.2.2.3-4

Type of Study	Test System or Species / Strain	Admini-stration	Duration Dosing	Doses (mg/kg) or Concentrations	GLP Compliance	Testing Facility	Report Number	Location in CTD
Metabolism	Rat, monkey and human liver microsomes and hepatocytes	in vitro	-	1.0 µmol/L [^{14}C] SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R01-389]	4.2.2.4-3
Metabolism	Human liver microsomes	in vitro	-	4.6 µmol/L or 49 µmol/L [^{14}C] SOM230	not required	Novartis US	[DMPK R0400850]	5.3.2.2-4
Excretion into milk	Rat, Han:Wist Lactating	s.c.	single	1.0 [^{14}C] SOM230	not required	Novartis US	[DMPK R0900555]	4.2.2.5-1
DDI	Primary human hepatocytes	In vitro	-	0.005 – 1 µmol/L SOM230	not required	Novartis US	[DMPK R0800722]	5.3.2.2-5
DDI	Human liver microsomes	in vitro	-	0 – 100 µmol/L SOM230	not required	Novartis US	[DMPK R0300356]	5.3.2.2-1
DDI	Human liver microsomes	in vitro	-	0 – 100 µmol/L SOM230	not required	Novartis US	[DMPK R1100187]	5.3.2.2-2
DDI	Human liver microsomes and recombinant UGT1A1	in vitro	-	0 – 100 µmol/L SOM230	not required	Novartis US	[DMPK R1100760]	5.3.2.2-3
DDI	Caco-2 monolayer	In vitro	-	0.2 – 50 µmol/L [^{14}C] SOM230	not required	Novartis Pharma AG Switzerland	[DMPK(CH) R99-2281]	5.3.2.3-1
DDI	P-glycoprotein inhibition by flow cytometry	In vitro	-	0 – 10 µmol/L SOM230	not required	Novartis US	[DMPK R0600583]	5.3.2.3-2
DDI	Caco-2 and MDCK/mBCRP cell monolayers	In vitro	-	2.1 – 13 µmol/L [^{14}C]SOM230	not required	Novartis US	[DMPK R1000737]	4.2.2.6-1
DDI	Primary human hepatocytes	In vitro	-	1 µmol/L [^{14}C]SOM230	not required	Novartis US	[DMPK R1000572]	5.3.2.3-3
DDI	MRP2 and BSEP (expressed in inside-out membrane vesicles)	In vitro	-	0 – 10 µmol/L SOM230	not required	Novartis US	[DMPK R1100482]	5.3.2.3-4

Type of Study	Test System or Species / Strain	Admini-stration	Duration Dosing	Doses (mg/kg) or Concentrations	GLP Compliance	Testing Facility	Report Number	Location in CTD
DDI	P-gp and BCRP (expressed in inside-out membrane vesicles)	In vitro	-	0 – 10 µmol/L SOM230	not required	Novartis US	[DMPK R1200248-01]	5.3.2.3-5
DDI	OCT1 and OCT2 (stably expressed in HEK cells)	In vitro	-	0 – 10 µmol/L SOM230	not required	Novartis US	[DMPK R1200761]	5.3.2.3-6
DDI	OAT1 and OAT3 (stably expressed in HEK293 cells)	In vitro	-	0 – 10 µmol/L SOM230	not required	Novartis US	[DMPK R1200835]	5.3.2.3-7
DDI	Dog, Beagle	s.c. and p.o.	Infusion and oral gavage	3 µg/kg/h SOM230 1, 3 or 10 µg/kg/h SMS201-995 10 mg/kg oral CsA	not required	Novartis US	[RD-2001-01165]	4.2.2.6-2
Toxicokinetic	Rat, Han:Wist	s.c.	12 days	0, 1, 5 and 10 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0470017]	4.2.3.5.2-2
Toxicokinetic	Rabbit, New Zealand White	s.c.	2 weeks	0, 0.05, 1 and 5 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0470018]	4.2.3.5.2-4
Toxicokinetic	CD-1 mice	s.c.	2 weeks	0, 0.2, 1, 5 and 10 mg/kg/day SOM230	No	Novartis Pharma AG Switzerland	[0220072]	4.2.3.2-1
Toxicokinetic	CB6F1/*Jic-TgrasH2@Tac* mice	s.c.	4 weeks	0, 1, 2.5, 5 and 10 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0470037]	4.2.3.4.2-1
Toxicokinetic	Mouse, CB6F1/TgrasH2	s.c.	26 weeks	0, 0.5, 1 and 2.5 mg/kg/day SOM230	Yes	Novartis US	[0470111]	4.2.3.4.2-3
Toxicokinetic	Mouse, CB6F1/TgrasH2	s.c.	4 weeks	0, 10, 20 and 30 mg/kg/day SOM230	Yes	Novartis US	[0570087]	4.2.3.4.2-2
Toxicokinetic	Rat, Han:Wist	s.c.	4 weeks	0, 0.08, 0.24 and 0.8 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0680209]	4.2.3.7.2-1

Type of Study	Test System or Species / Strain	Admini-stration	Duration Dosing	Doses (mg/kg) or Concentrations	GLP Compliance	Testing Facility	Report Number	Location in CTD
Toxicokinetic	Rat, Han:Wist	s.c.	4 weeks	0, 0.008, 0.08, 0.8 (bid) and 0.8 (q.d.) mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0170115]	4.2.3.2-5
Toxicokinetic	Rat, Han:Wist	s.c.	26 weeks	0, 0.008, 0.024, 0.08, and 0.24 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0210056]	4.2.3.2-6
Toxicokinetic	Rat, Han:Wist	s.c.	2 years	0, 0.01, 0.05 and 0.3 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0670694]	4.2.3.4.1-1
Toxicokinetic	Rat, Han:Wist	p.o	1 week	30, 100 and 300 mg/kg/day SOM230	No	Novartis Pharma AG Switzerland	[0410111]	4.2.3.2-2
Toxicokinetic	Rat, Han:Wist	p.o	4 weeks	10, 30 and 80 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0520005]	4.2.3.2-3
Toxicokinetic	Rat, Han:Wist	i.v.	2 weeks	0, 0.015, 0.05, and 0.15 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0410037]	4.2.3.2-9
Toxicokinetic	Rat, Han:Wist	s.c.	2 weeks	0, 0.04, 0.4 and 4 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[017039]	4.2.3.2-4
Toxicokinetic	Rat, Han:Wist	s.c.	1-26 days	0, 0.008 and 0.8 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0520067]	4.2.3.7.6-7
Toxicokinetic	Rat, Han:Wist	s.c.	4 weeks	0, 0.01 and 1 mg/kg/day SOM230	Yes	[redacted] France	[0970162]	4.2.3.7.6-8
Toxicokinetic	Rat, Han:Wist	i.m.	3 months 3 cycles (1 per month)	0, 3 and 6 mg/animal/month SOM230	Yes	[redacted] USA	[0770082]	4.2.3.2-8

Type of Study	Test System or Species / Strain	Admini-stration	Duration Dosing	Doses (mg/kg) or Concentrations	GLP Compliance	Testing Facility	Report Number	Location in CTD
Toxicokinetic	Rat, Han:Wist	i.m.	6 months 6 cycles (1 per month)	3.125 and 6.25 mg/animal/month SOM230	Yes	Novartis Pharma AG Switzerland	[0470138]	4.2.3.2-7
Toxicokinetic	Dog, Beagle	s.c.	2 weeks	0.07, 0.1, 1 and 5 mg/kg/day SOM230	No	Novartis Pharma AG Switzerland	[0110034]	4.2.3.2-10
Toxicokinetic	Monkey, Cyno	s.c.	2 weeks	0, 0.04, 0.8 and 1.6 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0170060]	4.2.3.2-12
Toxicokinetic	Monkey, Cyno	s.c.	4 weeks	0, 0.4, 0.8 and 1.6 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0170114]	4.2.3.2-13
Toxicokinetic	Monkey, Cyno	s.c.	4 weeks	0, 1.6, 3.2 and 6.4 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0270087]	4.2.3.2-14
Toxicokinetic	Monkey, Cyno	s.c.	39 weeks	0, 0.4, 1.6 and 3.2 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0270130]	4.2.3.2-15
Toxicokinetic	Monkey, Cyno	p.o.	14 days	0, 10, 30 and 100 mg/kg/day SOM230	No	Novartis Pharma AG Switzerland	[0580075]	4.2.3.2-11
Toxicokinetic	Monkey, Cyno	i.v.	7 days	0, 0.019, 0.038, 0.135 and 0.376 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0580074]	4.2.3.2-16
Toxicokinetic	Monkey, Cyno	i.v.	14 days	0, 0.015, 0.075 and 0.150 mg/kg/day SOM230	Yes	Novartis Pharma AG Switzerland	[0580076]	4.2.3.2-17

2.6.5.2A 薬物動態試験：分析方法（非標識体）

Test article: SOM230

	Monkey	Human	Rat	Rat
Study number:	[ICPP(EU) R01-0742]	[ICPP(EU) R01-0742-01]	[ICPP(EU) R01-0742-02]	[ICPP(EU) R01-0742-03]
Study title:	Quantitative determination of SOM230 in Cynomolgus monkey plasma by an enzyme-linked immunosorbent assay (ELISA): Method description and validation	Quantitative determination of SOM230 in human plasma by Radio Immunoassay (RIA): Method description and validation	Quantitative determination of SOM230 in rat plasma by an enzyme-linked immunosorbent assay (ELISA)	Amendment: Quantitative determination of SOM230 in rat plasma by an enzyme-linked immunosorbent assay (ELISA)
GLP compliance: Yes				
Location in CTD:	4.2.2.1-1	5.3.1.4-1	4.2.2.1-2	4.2.2.1-3
Test facility:	Novartis Pharma AG Integrative Compound and Product Profiling, MAD, Basel, Switzerland	Novartis Pharma AG Integrative Compound and Product Profiling, MAD, Basel, Switzerland	Novartis Pharma AG Integrative Compound and Product Profiling, MAD, Basel, Switzerland	Novartis Pharma AG Integrative Compound and Product Profiling, MAD, Basel, Switzerland
Analyte	Pasireotide, SOM230 di-aspartate; batch 0121001	[^{125}I]	Pasireotide, SOM230 di-aspartate; batch 0121001	Pasireotide, SOM230 di-aspartate; batch 0121001
Reference compound	Pasireotide, SOM230[redacted] batch LJE-4658/11; purity 89.7%	[^{125}I]Pasireotide	Pasireotide, SOM230[redacted] batch LJE-4658/11; purity 89.7%	Pasireotide, SOM230[redacted] batch LJE-4658/11; purity 89.7%
Assay	Competitive enzyme linked immunosorbent assay (ELISA)	Competitive radioimmunoassay (RIA)	Competitive enzyme linked immunosorbent assay (ELISA)	Competitive enzyme linked immunosorbent assay (ELISA)

	Monkey	Human	Rat	Rat
Method description	Plasma samples and biotinylated SOM230 were added to rabbit antisera previously coated on an anti-rabbit antibody pre-coated microtiter plate. Peroxidase-conjugated Streptavidin solution was added followed by the addition of OPD-substrate. Color development is stopped by the addition of 2N H_2SO_4. The signal is measured at 490/650 nm (OD). The OD measured is directly proportional to the amount of biotinylated SOM230 present, which decreases as the amount of bound analyte is increasing. Bound analyte (SOM230 in samples) is determined by the use of standards of known concentration	Plasma samples, tracer (iodinated SOM230) and rabbit anti SOM230 were mixed. After incubation, the immunological complex was captured by the addition of anti-rabbit coated magnetic beads. After elimination of unbound reagents by washing, the bound radioactivity was measured using a gamma counter. The radioactive signal (corresponding to the immune complex bound to the magnetic beads) decreases when the SOM230 concentration increases in the sample. Plotting the signal versus the SOM230 concentration produces the standard curve	Plasma samples and biotinylated SOM230 were added to rabbit antisera previously coated on an anti-rabbit antibody pre-coated microtiter plate. Peroxidase-conjugated Streptavidin solution was added followed by the addition of OPD-substrate. Color development is stopped by the addition of 2N H_2SO_4. The signal is measured at 490/650 nm (OD). The OD measured is directly proportional to the amount of biotinylated SOM230 present, which decreases as the amount of bound analyte is increasing. Bound analyte (SOM230 in samples) is determined by the use of standards of known concentration	Coating buffer used for the method validation for the measurement of SOM230 in rat was PBS, pH 7.4 as mentioned in the raw data. Carbonate-buffer pH 9.6 mentioned in the validation report is a mistake.
Sample preparation	A volume of 100 µL of each sample (unknowns, standards and QC samples) was mixed with 900 µL of acetonitrile containing 0.1% TFA. Samples were centrifuged 10 min (3000 rpm) at 4°C. Then, the organic phase is decanted and evaporated using a vacuum centrifuge (1h, 37°C). After complete evaporation, the residue is reconstituted with 120 µL of assay buffer and 120 µL of tracer solution (biotin-SOM230). The tubes are shaken for 10 minutes at room temperature on a vortex prior to distribution to the microtiter plate.	Two different stock solutions were used for preparation of C and QC samples. C and QC samples were prepared from the same human plasma pool on all analysis days. For C and QC, a first set of dilutions from the respective stock solution is prepared in ethanol at the beginning of the week. It could be utilized at least for one week stored at 4°C. A second set of dilutions is freshly prepared on each analysis day by dilution of the first set solutions in human plasma.	A volume of 100 µL of each sample (unknowns, standards and QC samples) was mixed with 900 µL of acetonitrile containing 0.1% TFA. Samples were centrifuged 10 min (3000 rpm) at 4°C. Then, the organic phase is decanted and evaporated using a vacuum centrifuge (1h, 37°C). After complete evaporation, the residue is reconstituted with 120 µL of assay buffer and 120 µL of tracer solution (biotin-SOM230). The tubes are shaken for 10 minutes at room temperature on a vortex prior to distribution to the microtiter plate.	

	Monkey	Human	Rat	Rat
Results:				
LLOQ	0.6 ng/mL	0.03 ng/mL	0.6 ng/mL	
Stability	Not assessed due to solubility issues of the di-aspartate salt	SOM230[redacted] is stable in spiked human plasma at least 24 h at room temperature and at 4°C. SOM230[redacted] is stable in spiked human plasma after 3 freeze-thaw cycles and after 12 weeks at –20°C. Stability in true samples cannot be assessed due to severe solubility issues of the di-aspartate salt. Stability of the I-125 tracer is a major point for the efficiency of the method. The tracer (reconstituted) is stable 1 week at 4°C.	The stability of SOM230 in unknown plasma samples (i.e. containing di-aspartate salt) cannot be assessed due to solubility issues.	

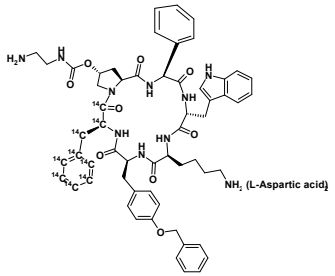
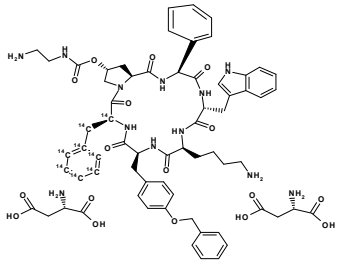
	Rat	Monkey	Rabbit
Study number:	[NBxRS602618]	[NBxRS653234]	[0470018]
Study title:	Validation of radioimmunoassay for the determination of SOM230 in rat plasma sample	Validation of a radioimmunoassay for the determination of SOM230 in monkey plasma sample; Method description and validation	A subcutaneous embryo-fetal development study in rabbits
GLP compliance: Yes			
Location in CTD:	4.2.2.1-4	4.2.2.1-5	4.2.3.5.2-4
Test facility:	[redacted]	[redacted]	Novartis Pharma AG DMPK/Bioanalytics section Basel, Switzerland
Analyte	(^{125}I)	(^{125}I)	SOM230
Reference compound	4007043.001 (SOM230 pamoate); Batch 0824015	4007043.001 (SOM230 pamoate); Batch 0824015	SOM230 (Batch No.: L.-J.E-4658/11)
Assay	Competitive radioimmunoassay (RIA)	Competitive radioimmunoassay (RIA)	ELISA

	Rat	Monkey	Rabbit
Method description	SOM230 method consists of a radioimmunoassay based on the competition between ^{125}I-SOM230 and SOM230 for a fixed number of antibody binding sites. Samples or standards were incubated with ^{125}I-SOM230 tracer and anti-serum. After incubation, the immunological complexes were captured by the addition of anti-rabbit coated magnetic beads. After elimination of unbound fraction by washing, the bound radioactivity was determined in a gamma counter.	SOM230 method consists of a radioimmunoassay based on the competition between ^{125}I-SOM230 and SOM230 for a fixed number of antibody binding sites. Samples or standards were incubated with ^{125}I-SOM230 tracer and anti-serum. After incubation, the immunological complexes were captured by the addition of anti-rabbit coated magnetic beads. After elimination of unbound fraction by washing, the bound radioactivity was determined in a gamma counter.	The microtiter plates were coated overnight with a solution of goat anti-rabbit IgG (Fc). The next day the plates were blocked with blocking buffer and a solution of rabbit antiserum (anti-SOM230) was added. Then the pre-treated samples (plasma or homogenized fetus tissue) were pipetted into the wells. The color reaction was initiated with peroxidase-conjugated Streptavidin and the substrate *o*-Phenylenediamine dihydrochloride and H_2O_2. The reaction was stopped by adding 2N H_2SO_4. Optical densities (OD) of the wells were determined at 490/650 nm.
Sample preparation	Calibrators and QC High, Medium, Low and LLOQ samples were freshly prepared on each analysis assay by successive dilutions of SM in DMSO and each solution was diluted 1:25 in matrix (rat plasma). A calibration curve was established on each validation day using the C samples. The quality of the individual calibration curves was assessed by the accuracies of the back-calculated concentrations of the CS.	Calibrators and QC High, Medium, Low and LLOQ samples were freshly prepared on each analysis assay by successive dilutions of SM in DMSO and each solution was diluted 1:25 in matrix (monkey plasma diluted 1:5 in human plasma). A calibration curve was established on each validation day using the C samples. The quality of the individual calibration curves was assessed by the accuracies of the back-calculated concentrations of the CS.	A volume of 100 µL of each sample was mixed with 900 µL of acetonitrile containing 0.1% TFA. The tubes were shaken, centrifuged and the supernatant was decanted and evaporated. The residue was reconstituted with 120 µL of assay buffer and 120 µL of tracer solution (biotin-SOM230) were added. The tubes were shaken and the pre-treated samples were applied to the microtiter plate.
Results:			
LLOQ	30 pg/mL in rat EDTA plasma	40 pg/mL in monkey EDTA plasma	0.6 ng/mL

	Rat	Monkey	Rabbit
Stability	Stable in rat plasma at RT for at least 4 hours and 3 months at -20°C.	Not assessed	Stability of the aspartate salt of SOM230 in sample matrix was not tested.

2.6.5.2B 薬物動態試験：分析方法（標識体）

Study number:	[DMPK(CH) R01-749-01(RSE055-4)]	[DMPK R0500108-01(RSE219-3)]
Study title:	[^{14}C]SOM230 Synthesis and Release Analysis	[$^{14}C_8$]SOM230 Synthesis and release analysis
GLP compliance:	Yes	Yes
Location in CTD:	4.2.2.1-6	4.2.2.1-7
Test facility:	Novartis Pharma AG Isotope laboratory Basel, Switzerland	Novartis Pharma AG Isotope laboratory Basel, Switzerland
Labeled compound:	[^{14}C] SOM230	[$^{14}C_8$]SOM230
Substance number:	PKF 227-230	SOM230
Synthesis number:	RSE 055-4	RSE 219
Chemical name:	Cyclo[-Pro(4-OCO-NH-CH2-CH2-NH2)-Phg-DTrp-Lys-Tyr(Bzl)-[U-^{14}C]Phe-], bis aspartate (2-Amino-ethyl)-carbamic acid 11-(4-amino-butyl)-5-[U-^{14}C]benzyl-8-(4-benzyloxy-benzyl)-14-(1.H.-indol-3-yl-methyl)-4,7,10,13,16,19-hexaoxo-17-phenyl-eicosahydro-3a,6,9,12,15,18-hexaaza-cyclopenta[4,5-^{14}C]cyclooctadecen-2-yl ester bisaspartate	Cyclo[-Pro(4-OCO-NH-CH_2-CH_2-NH_2)-Phg-DTrp-Lys-Tyr(Bzl)-[$^{14}C_8$]Phe-],bis aspartate (2-Amino-ethyl)-carbamic acid 11-(4-amino-butyl)-5-[U-^{14}C]benzyl-8-(4-benzyloxy-benzyl)-14-(1.H.-indol-3-yl-methyl)-4,7,10,13,16,19-hexaoxo-17-phenyl-eico-sahydro-3a,6,9,12,15,18-hexaaza-cyclopenta[5-^{14}C]cyclo-octadecen-2-yl ester bis aspartate

Structural formula:		
Description:	Fmoc-L-[U-^{14}C]phenylalanine **A0** with specific activity of 495 mCi/mmol was coupled to the pre-prepared backbone of SOM230 on AMRES-resin **Z0**. After Fmoc-deprotection and cleaving from the resin support, the resulting open-chain peptide **A2** was cyclised with diphenylphosphoryl azide in the presence of Hünig-base and DMAP catalytic. The resulting cyclic peptide **A4** was treated with aqueous trifluoroacetic and purified by preparative reverse phase HPLC to give the triflic salt of [^{14}C]SOM230. The desired aspartate salt was prepared after liberation of the base and treatment with 2 equivalent of aspartic acid.	Successive coupling of labeled Fmoc-L-[$^{14}C_8$]phenylalanine **A0** (specific activity of 13.9 GBq/mmol, purchased from *ARC*) followed by non labeled amino acid **Z1** to the pre-prepared backbone of SOM230 resin **Z0**, gave peptide **A2**. After Fmoc-deprotection and cleaving from the resin support, the resulting open-chain peptide **A3** was cyclised with diphenylphosphoryl azide in the presence of Hünig-base and catalytic amounts of DMAP. The resulting cyclic peptide **A4** was deprotected with aqueous trifluoroacetic and purified by preparative reverse phase HPLC to give [$^{14}C_8$]SOM230 as its trifluoroacetate salt. The desired aspartate salt was prepared after liberation of the base and treatment with 2 equivalent of aspartic acid.

Confirmation of identity:	The identity of the labeled compound was confirmed by MALDI-TOF-MS, NMR and chromatographic methods. SOM230 di-aspartate batch 0121001 (expiry date: August 2001) was used as cold reference compound for all analytical tests.	The identity and purity of the labeled compound was confirmed by NMR and HPLC. SOM230 was used as an unlabeled comparison compound for all analytical tests.
Determination of specific activity:	The specific activity was determined by liquid scintillation counting using a Packard Tri-Carb 2500 TR.	The specific activity was determined by liquid scintillation counting using a Wallac WinSpectral α/β 1414 Liquid Scintillation Counter.
Radiochemical purity:	≥ 98% by HPLC-RA	97.3% by HPLC-RA
Chemical purity:	≥ 98% by HPLC-UV	98.4% by HPLC-UV

2.6.5.3A 薬物動態試験：単回皮下投与後の吸収（標識体）

Single subcutaneous (SC) dose - Radioactivity

	Rat		Monkey	
Study number:	[DMPK (CH) R01-0388]		[DMPK R0900554]	
GLP compliance:	not required		not required	
Location in CTD:	4.2.2.4-1		4.2.2.4-2	
Gender(M/F) / Number of animals:	M/9 (Han Wistar)		M/3 cynomolgus	
Feeding condition:	Fed		Fed	
Vehicle / Formulation:	Solution in saline		Solution in saline	
Method of Administration:	Subcutaneous injection		Subcutaneous injection	
Dose (mg/kg):	1.0		0.6 (0.57 µmol/kg)	
Sample:	Blood	Plasma	Blood	Plasma
Analyte:	Radioactivity – ^{14}C	Radioactivity – ^{14}C	Radioactivity – ^{14}C	Radioactivity – ^{14}C
Assay:	Liquid scintillation counting	Liquid scintillation counting	Liquid scintillation counting	Liquid scintillation counting
PK parameters:	mean	mean	mean ± SD	mean ± SD
Tmax (h)	4.0	4.0	0.75 ± 0.43	0.83 ± 0.29
Cmax (ngEq/mL)	343	638	780 ± 242	1340 ± 397
AUClast (ngEq•h/mL)	3000	5120	3080 ± 1070	5840 ± 2160
Tlast (h)	72.0	72.0	168	168
AUC0-inf (ngEq•h/mL)	[a]	[a]	3830	6760 ± 2950
Terminal t1/2 (h):	35.0	39	15	187 ± 108
% Bioavailability	[a]	[a]	[a]	[a]

[a] Not applicable or not determined

Single subcutaneous (SC) dose - Radioactivity

	Human	
Study number:	[CSOM230B2112]	
GLP compliance:	not required	
Location in CTD:	5.3.3.1-3	
Gender(M/F) / Age range / Number of subjects:	M / 18-25 yrs / 4	
Formulation:	Sterile aqueous drug solution	
Method of Administration:	Subcutaneous injection	
Dose (µg/kg):	600 (0.232 µCi)	
Sample:	Blood	Plasma
Analyte:	Radioactivity – ^{14}C	
Assay:	AMS	AMS
PK parameters:	Mean ± SD	Mean ± SD
Cmax (ngEq/mL)	9.89 ± 3.05	16.6 ± 5.28
Tmax (h)[b,c]	0.5 (0.5-1.0)	0.5 (0.25-0.5)
t1/2 (h):	289 ± 334	211 ± 87.3
AUC0-240h (ngEq•h/mL)[a]	57.7 ± 13.8	85.1 ± 22.5
AUC0-inf (ngEq•h/mL)	74.2 ± 38.8	93.3 ± 20.6

[a] The last time point included in the calculation of AUC was 216 hours for Subject USA/0501/00003, since the 240-hour sample was not collected due to withdrawal.

[b] Values are median for Tmax instead of mean

[c] Values are range for Tmax instead of SD

2.6.5.3B 薬物動態試験：単回皮下投与後の吸収（非標識体）

Single subcutaneous dose – Parent drug

	Rat			Monkey
Study number:	[DMPK R00-2234]			[DMPK(CH) R0101556]
GLP compliance:	not required			Not required
Location in CTD:	4.2.2.2-1			4.2.2.2-2
Gender(M/F) / Number of animals:	Male/4	Male/4	Male/4	M/3
Feeding condition:	Fasted	Fasted	Fasted	Fed
Vehicle / Formulation:	Solution / 25 mM acetate buffer, pH 4.0	Solution / 25 mM acetate buffer, pH 4.0	Solution / 25 mM acetate buffer, pH 4.0	Solution in water + acetic acid, pH 6
Method of Administration:	s.c. injection	s.c. injection	s.c. injection	s.c.
Dose (mg/kg):	0.1	0.1	0.1	1.0
Sample	Plasma	Plasma	Plasma	Plasma
Analyte:	SOM230	SOM230	SOM230	SOM230
Assay:	ELISA	ELISA	ELISA	ELISA
PK parameters:	[redacted] salt (mean ± SD)	Aspartate salt (mean ± SD)	Pamoate salt (mean ± SD)	mean ± SD
Tmax (h)[b]	0.75 [0.50 – 1.0]	2.0 [1.0 – 2.0]	2.0 [2.0 – 2.0]	0.5 – 2[c]
Cmax (ng/mL)	110 ± 25.4	107 ± 24.4	91.6 ± 13.2	1220 ± 342
AUClast (ng•h/mL)	358 ± 60.8	420 ± 76.4	413 ± 27.8	9030 ± 4240
Tlast (h)	8	8	8	96
T1/2 (h)	1.22 ± 0.13	1.30 ± 0.098	1.66 ± 0.42	[a]
Absorption (%)	91.3 ± 15.4	107 ± 19.6	105 ± 7.1	[a]

[a] not applicable or not calculated.

[b] Tmax given as median [range].

[c] Tmax given as range.

Single subcutaneous dose – Parent drug

	Human	Monkey
Study number:	[CSOM230B2112]	[DMPK R0900554]
GLP compliance:	not required	not required
Location in CTD:	5.3.3.1-3	4.2.2.4-2
Gender(M/F) / Age range / Number of subjects:	M / 18-40 yrs / 4	M/3 cynomolgus
Formulation:	Sterile aqueous drug solution	Solution in saline
Method of Administration:	Subcutaneous injection	Subcutaneous injection
Dose (µg):	600 (0.232 µCi)	0.6 mg/kg
Sample:	Plasma	Plasma
Analyte:	SOM230	SOM230
Assay:	RIA	RIA
PK parameters:	Mean ± SD	Mean ± SD
Cmax (ng/mL)	18.1 ± 6.66	1020 ± 372
Tmax (h)	0.25 [0.25-5.0][a]	0.92 ± 0.95
AUClast (ng•h/mL)	68.0 ± 19.8[b]	4110 ± 1680
AUCinf (ng•h/mL)	73.8 ± 21.4	4150 ± 1700
t1/2 (h):	7.8 ± 0.78	56 ± 39
CL/F (L/h)	8.7 ± 2.3	0.28 ± 0.14
Vz/F (L)	97.5 ± 25.5	1.1 ± 0.20

[a] Tmax given as median [range].

[b] The last time point included in the calculation of AUC was 24 hours for all subjects

2.6.5.3C 薬物動態試験：単回静脈内投与

Single intravenous dose – Parent drug

	Rat
Study number:	[DMPK R00-2234]
GLP compliance:	not required
Location in CTD:	4.2.2.2-1
Gender(M/F) / Number of animals:	Male/4
Feeding condition:	Fasted
Vehicle / Formulation:	Solution / 25 mM acetate buffer, pH 4.0
Method of Administration:	i.v.
Dose (mg/kg):	0.05
Sample	Plasma
Analyte:	SOM230
Assay:	ELISA
PK parameters:	Mean ± SD
Tmax (h)[a,b]	0.08 [0.08 – 0.08]
Cmax (ng/mL)	238 ± 12.9
AUClast (ng•h/mL)	196 ± 18.2
Tlast (h)	8
T1/2 (h)	1.51 ± 0.294
CL (mL/min/kg)	4.23 ± 0.416
Vss (L/kg)	0.285 ± 0.029

[a] Concentration at the first sampling time (0.083 h).
[b] Median [range].

2.6.5.3D 薬物動態試験：単回筋肉内投与後の吸収

Single intramuscular dose – Parent drug

	Rat	
Study number:	[DMPK R0600360]	
GLP compliance:	not required	
Location in CTD:	4.2.2.2-3	
Gender(M/F) / Number of animals:	Male/5 per group, 4 groups	Male/5 per group, 4 groups
Feeding condition:	Non-fasted	Non-fasted
Formulation:	Formulation 2	Formulation 2b
Method of Administration:	i.m.	i.m.
Dose (mg/animal):	5.07	5.66
Sample	Plasma	Plasma
Analyte:	SOM230	SOM230
Assay:	ELISA	ELISA
PK parameters:	Mean	Mean
Tmax (d)	6	27
Cmax (ng/mL)	44.5	140 (79.0)*
AUC0-63d (ng•d/mL)	1570	3840 (2220)*
AUC0-63d /Dose (ng•d/mL)/(mg/animal)	261	640 (392)*
AUC0-63d /Dose (ng•d/mL)/(mg/kg)	139	305 (176)*
Bioavailability (%)**	85	187 (108)*

*Two rats among 20 (#5 and #14) in this group had unexpected high plasma concentration values. This, in part, could be associated with microparticles/inflammation at the close proximity of the saphenous vein. After exclusion of those two rats data, the mean values are 79.0 ng/mL for Cmax and 2220 (ng/mL)*d for AUC0-65d and the concentration-time profile was more similar to that of the form 2.

** The bioavailability was estimated based on the i.v. data (AUC/Dose = 196/24/0.05 = 163 (ng•d/mL)/(mg/kg)) [Table 2.6.5.3C-R002234].

2.6.5.4A 薬物動態試験：反復皮下投与後の吸収（マウス）

Toxicokinetic data	Mouse
Study number:	[0570087]
GLP compliance:	Yes
Location in CTD:	4.2.3.4.2-2
Gender(M/F) / Number of animals:	F / 10 CB6F1/TgrasH2 wildtype M / 10 CB6F1/TgrasH2 wildtype
Vehicle / Formulation:	Solution in saline
Method of Administration:	Once daily by s.c. injection for 4 weeks
Dose (mg/kg/day):	0, 10, 20 and 30 mg/kg
Sample	Plasma
Analyte:	SOM230
Assay:	ELISA

PK parameters:	mean		mean		mean	
Dose (mg/kg/day)	10.0		20.0		30.0	
Gender	M	F	M	F	M	F
Tmax (h)	1	1	1	1	0.5	1
Cmax (ng/mL)	8720	7100	12000	10300	13300	10700
Cmax /Dose (ng/mL)/(mg/kg/day)	872	710	599	516	442	356
AUC0-24 h (ng•h/mL)	29800	22400	57700	36400	66300	42300
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	2980	2240	2890	1820	2210	1410

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Mouse							
Study number:	[0470111]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.4.2-3							
Gender(M/F) / Number of animals:	F / 8 CB6F1/TgrasH2 M / 8 CB6F1/TgrasH2 wild type 4 animals / sex/ zero dose level groups							
Vehicle / Formulation:	Solution in saline							
Method of Administration:	Once daily by s.c. injection for 26 weeks							
Dose (mg/kg/day):	0, 0.5, 1 and 2.5 mg/kg/day							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	CB6F1-TgrasH2 Cmax (ng/mL) mean (n=2)		Cmax (ng/mL) mean (n=2)		Cmax (ng/mL) mean (n=2)		CB6F1 wild-type Cmax (ng/mL) mean (n=2)	
Dose (mg/kg/day)	0.5		1.0		2.5		2.5	
Gender	M	F	M	F	M	F	M	F
Week 4								
1 h	91.1	59.7	214	67.9	1030	340	1240	359
2 h	23.3	9.4	113	21.0	182	27.5	142	93.7
Week 23								
1 h	404	70.4	815	144	1340	793	1900	793
2 h	107	393	173	555	314	663	320	484

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Mouse							
Study number:	[0220072]							
GLP compliance:	No							
Location in CTD:	4.2.3.2-1							
Gender(M/F) / Number of animals:	F / 6 / CD-1 mice/dose level M / 6 / CD-1 mice/dose level							
Vehicle / Formulation:	Solution in sodium acetate trihydrate, mannitol, glacial acetic acid, water for injection							
Method of Administration:	Once daily by s.c. injection for 14 days							
Dose (mg/kg/day):	0, 0.2, 1, 5, 10 mg/kg/day							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.2		1.0		5.0		10	
Gender	M	F	M	F	M	F	M	F
AUC0-8 h (ng•h/mL)	30.3	12.4	75.3	48.4	20600	278	8290	12600
Tmax (h)	0.25	0.25	0.25	0.25	1.0	0.25	0.25	1.0
Cmax (ng/mL)	50.7	16.3	68.1	41.4	5030	134	28500	6380

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Mouse							
Study number:	[0470037]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.4.2-1							
Gender(M/F) / Number of animals:	F / 10 / CB6F1/TgrasH2 M / 10 / CB6F1/TgrasH2							
Vehicle / Formulation:	Solution							
Method of Administration:	Once daily by s.c. injection for 4 weeks							
Dose (mg/kg/day):	0, 1.0, 2.5, 5,10 mg/kg/day							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	1.0		2.5		5.0		10	
Day	1/2		1/2		1/2		1/2	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	1	1	0.5	0.5	0.5	1	0.5	1
Cmax (ng/mL)	519	265	4230	2140	2970	5610	4290	6060
Cmax /dose (ng/mL)/(mg/kg/day)	519	265	1690	856	594	1120	429	606
AUC0-24 h (ng•h/mL)	1500	778	8290	1410	5660	17200	14800	17700
AUC0-24 h /dose (ng•h/mL)/(mg/kg/day)	1500	778	3320	565	1130	3450	1480	1770

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Mouse							
Study number:	[0470037] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.4.2-1							
Gender(M/F) / Number of animals:	F / 10 / CB6F1/TgrasH2 M / 10 / CB6F1/TgrasH2							
Vehicle / Formulation:	Solution							
Method of Administration:	Once daily by s.c. injection for 4 weeks							
Dose (mg/kg/day):	0, 1.0, 2.5, 5,10 mg/kg/day							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	1.0		2.5		5.0		10	
Week	4		4		4		4	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cmax (ng/mL)	1440	667	4620	2770	9620	4100	17800	14100
Cmax /dose (ng/mL)/(mg/kg/day)	1440	667	1850	1110	1930	820	1780	1410
AUC0-24 h (ng•h/mL)	4560	948	3770	3030	19300	10500	55700	42200
AUC0-24 h /dose (ng•h/mL)/(mg/kg/day)	4560	948	1510	1210	3870	2100	5570	4220

All PK values were rounded up to 3 significant figures

2.6.5.4B 薬物動態試験：反復皮下投与後の吸収（ラット）

Toxicokinetic data	Rat							
Study number:	[017039]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-4							
Gender(M/F) / Number of animals:	F / 10 / group; 2 / timepoint M / 10 / group; 2 / timepoint							
Vehicle / Formulation:	Solution / 25 mM acetate buffer, pH 4.0							
Method of Administration:	Twice daily by s.c. injection for 2 weeks							
Dose (mg/kg/day):	0, 0.04, 0.4 and 4							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.04		0.4		4		0.04	
Day	1/2		1/2		1/2		14/15	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	2	1	6	0.5	0.5	0.5
Cmax (ng/mL)	22.8	15.8	181	114	471	324	30.4	20.4
Cmax /Dose (ng/mL)/(mg/kg/day)	456	315	362	228	94.3	64.8	608	409
AUC0.5-2 h (ng•h/mL)	26.4	13.9	226	146	570	466	30.3	17.6
AUC0.5-2 h/Dose (ng•h/mL)/(mg/kg/day)	527	278	453	292	114	93.2	605	352

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Rat				Rat			
Study number:	[017039]continued				[0170115]			
GLP compliance:	Yes				Yes			
Location in CTD:	4.2.3.2-4				4.2.3.2-5			
Gender(M/F) / Number of animals:	F / 10 / group; 2/timepoint M / 10 / group; 2/timepoint				F / 10 / group M / 10 / group			
Vehicle / Formulation:	Solution / 25 mM acetate buffer, pH 4.0				Solution in acetate buffer, pH ~ 4.5			
Method of Administration:	Twice daily by s.c. injection for 2 weeks				Twice daily by s.c. injection for 4 weeks. Rats from group 5 were dosed q.d.			
Dose (mg/kg/day):	0, 0.04, 0.4 and 4				0, 0.008, 0.08, 0.8 (bid) and 0.8 (q.d.)			
Sample	Plasma				Plasma			
Analyte:	SOM230				SOM230			
Assay:	ELISA				ELISA			
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.4		4		0.008		0.08	
Day	14/15		14/15		1		1	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	2	0.5	2	2	0.5	1	0.5	1
Cmax (ng/mL)	225	169	1800	1230	5.3	2.2	83.9	20.7
Cmax /Dose (ng/mL)/(mg/kg/day)	450	338	361	245	1060	440	1680	414
AUC (ng•h/mL)	326*	221*	2130*	1620*	12.7**	5.60**	157**	36.4**
AUC /Dose (ng•h/mL)/(mg/kg/day)	651*	443*	425*	324*	2540**	1120**	3130**	729**

All PK values were rounded up to 3 significant figures

* AUC0.5-2 h, ** AUC0-6 h

Toxicokinetic data	Rat							
Study number:	[0170115] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-5							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5							
Method of Administration:	Twice daily by s.c. injection for 4 weeks. Rats from group 5 were dosed q.d.							
Dose (mg/kg/day):	0, 0.008, 0.08, 0.8 (bid) and 0.8 (q.d.)							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:								
Dose (mg/kg/day)	0.8		0.008		0.08		0.8	
Day	1		Week 3		Week 3		Week 3	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	1	0.5	0.5	0.5	2	0.5
Cmax (ng/mL)	213	128	6.9	5.3	61.7	38.9	345	339
Cmax /Dose (ng/mL)/(mg/kg/day)	427	257	1380	1060	1230	778	690	678
AUC0-6 h (ng•h/mL)	838	359	16.1	8.38	153	71.3	1290	558
AUC0-6 h /Dose (ng•h/mL)/(mg/kg/day)	1680	718	3220	1680	3060	1430	2580	1120

Rats were injected at 0 and 6 hours, blood was drawn until 6 hours, thus toxicokinetic parameters were calculated from 0 to 6 hours. As a consequence, dose normalized parameters were calculated using half of the daily dose.

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Rat				Rat			
Study number:	[0170115] continued				[0210056]			
GLP compliance:	Yes				Yes			
Location in CTD:	4.2.3.2-5				4.2.3.2-6			
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group				F / 10 / group M / 10 / group			
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5				Solution in acetate buffer, pH ~ 4.5			
Method of Administration:	Twice daily by s.c. injection for 4 weeks. Rats from group 5 were dosed q.d.				Once daily by s.c. injection for 26 weeks.			
Dose (mg/kg/day):	0, 0.008, 0.08, 0.8 (bid) and 0.8 (q.d.)				0, 0.008, 0.024, 0.08, and 0.24			
Sample	Plasma				Plasma			
Analyte:	SOM230				SOM230			
Assay:	ELISA				ELISA			
PK parameters:								
Dose (mg/kg/day)	0.8 (q.d.)		0.8 (q.d)		0.008		0.024	
Day	1		Week 3		1		1	
Gender	M	F	M	F	M	F	M*	F
Tmax (h)	2	0.5	1	1	1	n/a	(1)	0.5
Cmax (ng/mL)	365	167	597	319	5.81	n/a	(16.7)	22.6
Cmax /Dose (ng/mL)/(mg/kg/day)	365	167	597	319	726	n/a	(697)	939
AUC0-6 h (ng•h/mL)	1450[a]	679[a]	2330[a]	876[a]	15.8[b]	n/a	(48.9)[b]	38.5[b]
AUC0-6 h /Dose (ng•h/mL)/(mg/kg/day)	1450[a]	679[a]	2330[a]	876[a]	1980[b]	n/a	(2040)[b]	1600[b]

All PK values were rounded up to 3 significant figures; n/a = not applicable or not sampled.

[a] = AUC0-6 h, [b] = AUC0-24 h

* Values at 0.5 h not used for calculations (animals 91 and 92 received low dose formulation in error); results may be underestimated.

Toxicokinetic data	Rat							
Study number:	[0210056] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-6							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5							
Method of Administration:	Once daily by s.c. injection for 26 weeks.							
Dose (mg/kg/day):	0, 0.008, 0.024, 0.08, and 0.24							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:								
Dose (mg/kg/day)	0.08		0.24		0.008		0.024	
Day	1		1		Week 4		Week 4	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	n/a	1	0.5	n/a	0.5	0.5
Cmax (ng/mL)	95.9	80.4	n/a	192	8.94	n/a	37.7	22.5
Cmax /Dose (ng/mL)/(mg/kg/day)	1200	1010	n/a	801	1120	n/a	1570	938
AUC0-24 h (ng•h/mL)	359	249	n/a	708	20.5	n/a	86.9	46.1
AUC0-24 h /Dose (ng•h/mL)/(mg/kg/day)	4490	3110	n/a	2950	2570	n/a	3620	1920

All PK values were rounded up to 3 significant figures; n/a = not applicable or not sampled.

Toxicokinetic data	Rat							
Study number:	[0210056] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-6							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5							
Method of Administration:	Once daily by s.c. injection for 26 weeks.							
Dose (mg/kg/day):	0, 0.008, 0.024, 0.08, and 0.24							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:								
Dose (mg/kg/day)	0.08		0.24		0.008		0.024	
Day	Week 4		Week 4		Week 22		Week 22	
Gender	M*	F	M	F	M	F	M	F
Tmax (h)	0.5	1	n/a	1	0.5	n/a	0.5	0.5
Cmax (ng/mL)	83.8	71.0	n/a	219	9.03	n/a	26.8	16.0
Cmax /Dose (ng/mL)/(mg/kg/day)	1050	888	n/a	910	1130	n/a	1120	669
AUC0-24 h (ng•h/mL)	321	190	n/a	715	19.4	n/a	95.9	44.3
AUC0-24 h /Dose (ng•h/mL)/(mg/kg/day)	4010	2370	n/a	2980	2420	n/a	4000	1840

All PK values were rounded up to 3 significant figures; n/a = not applicable or not sampled.

* Animals were administered 0.08 mg/kg/day from week 1 to 5 and 0.24 mg/kg/day from week 6 onward

Toxicokinetic data	Rat			
Study number:	[0210056] continued			
GLP compliance:	Yes			
Location in CTD:	4.2.3.2-6			
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group			
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5			
Method of Administration:	Once daily by s.c. injection for 26 weeks.			
Dose (mg/kg/day):	0, 0.008, 0.024, 0.08, and 0.24			
Sample	Plasma			
Analyte:	SOM230			
Assay:	ELISA			
PK parameters:				
Dose (mg/kg/day)	0.08		0.24	
Day	Week 22		Week 22	
Gender	M	F	M*	F
Tmax (h)	n/a	1	1	2
Cmax (ng/mL)	n/a	42.9	143	144
Cmax /Dose (ng/mL)/(mg/kg/day)	n/a	536	594	602
AUC0-24 h (ng•h/mL)	n/a	143	748	560
AUC0-24 h /Dose (ng•h/mL)/(mg/kg/day)	n/a	1790	3120	2330

All PK values were rounded up to 3 significant figures; n/a = not applicable or not sampled.

* Animals were administered 0.08 mg/kg/day from week 1 to 5 and 0.24 mg/kg/day from week 6 onward

Toxicokinetic data	Rat							
Study number:	[0520067]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.7.6-7							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5							
Method of Administration:	Once daily by s.c. injection for 28 days.							
Dose (mg/kg/day):	0, 0.008 and 0.8							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.008 (pamoate salt)		0.8 (pamoate salt)		0.008 (+ impurities)		0.8 (+ impurities)	
Day	1/2		1/2		1/2		1/2	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	1	0.5	1	7	0.5	0.5	1	1
Cmax (ng/mL)	5.15	4.24	346	181	9.50	7.32	225	163
Cmax /Dose (ng/mL)/(mg/kg/day)	644	530	433	226	1190	915	281	204
AUC0-24 h (ng•h/mL)	12.4*	9.27*	3340	2620	19.3*	14.7*	2210	1240
AUC0-24 h /Dose (ng•h/mL)/(mg/kg/day)	1540*	1160*	4170	3280	2410*	1840*	2760	1550

All PK values were rounded up to 3 significant figures

*AUC values based on only 3 concentration values above LLOQ in the TK profile, therefore these values are given only as an indication

Toxicokinetic data	Rat							
Study number:	[0520067] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.7.6-7							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Vehicle / Formulation:	Solution in acetate buffer, pH ~ 4.5							
Method of Administration:	Once daily by s.c. injection for 28 days.							
Dose (mg/kg/day):	0, 0.008 and 0.8							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.008 (pamoate salt)		0.8 (pamoate salt)		0.008 (+ impurities)		0.8 (+ impurities)	
Day	25/26		25/26		25/26		25/26	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	3	1	1	0.5	1	1
Cmax (ng/mL)	8.84	7.29	376	390	6.01	7.34	382	250
Cmax /Dose (ng/mL)/(mg/kg/day)	1110	911	470	488	751	918	478	313
AUC0-24 h (ng•h/mL)	22.3*	13.3*	4650	4240	14.5*	10.6*	3140	2280
AUC0-24 h /Dose (ng•h/mL)/(mg/kg/day)	2780*	1660*	5810	5300	1810*	1320*	3930	2850

All PK values were rounded up to 3 significant figures

*AUC values based on only 3 concentration values above LLOQ in the TK profile, therefore these values are given only as an indication

Toxicokinetic data	Rat					
Study number:	[0970162]					
GLP compliance:	Yes					
Location in CTD:	4.2.3.7.6-8					
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group					
Vehicle / Formulation:	Solution					
Method of Administration:	Once daily by s.c. injection for 4 weeks.					
Dose (mg/kg/day):	0, 0.01 and 1					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean		mean		mean	
Dose (mg/kg/day)	0.01 (+ impurities)		1 (+ impurities)		1	
Day	4 weeks		4 weeks		4 weeks	
Gender	M	F	M	F	M	F
Tmax (h)	0.5	0.5	1.0	1.0	1.0	1.0
Cmax (ng/mL)	15.1	11.2	1200	1050	856	1130
Cmax /Dose (ng/mL)/(mg/kg/day)	1890	1400	1500	1310	1070	1410
AUClast (ng•h/mL)	38.4	19.9	7250	5530	5250	3630
AUClast /Dose (ng•h/mL)/(mg/kg/day)	4800	2490	9060	6910	6560	4540
AUC interval (h)	0.5 - 6	0.5 - 6	0.5 - 24	0.5 - 24	0.5 - 24	0.5 - 24

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Rat					
Study number:	[0680209]					
GLP compliance:	Yes					
Location in CTD:	4.2.3.7.2-1					
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group					
Vehicle / Formulation:	Solution					
Method of Administration:	Once daily by s.c. injection for 28 days.					
Dose (mg/kg/day):	0, 0.08, 0.24 and 0.8					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
Dose (mg/kg/day)	0.08		0.24		0.8	
Day	21		21		21	
SOM concentration (ng/mL):	mean / CV%		mean / CV%		mean / CV%	
Gender	M	F	M	F	M	F
Time						
0.5 h	68.1 / 34.4	58.4 / 34.4	199 / 30.4	129 / 24.9	499 / 33.7	483 / 32.7
24 h	0.390 / 146	0.131 / 211	2.14 / 49.1	0.785 / 72.5	7.86 / 32.7	3.80 / 32.6

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Rat							
Study number:	[0670694]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.4.1-1							
Gender(M/F) / Number of animals:	F / 50 / group M / 50 / group							
Vehicle / Formulation:	Solution							
Method of Administration:	Once daily by s.c. injection for 2 years.							
Dose (mg/kg/day):	0, 0.01, 0.05 and 0.3							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.01		0.05		0.3		0.01	
week	4		4		4		39	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	1	0.5	1	1	1	0.5
Cmax (ng/mL)	17.9	10.1	111	63.7	438	394	17.7	9.99
Cmax/dose (ng/mL)/(mg/kg)	1790	1010	2220	1270	1460	1310	1770	999
AUC0-24h (ng·h/mL)	35.8	17.4	309	100	2160	985	56.2	28.8
AUC0-24h/dose (ng·h/mL)/(mg/kg)	3580	1740	6180	2010	7200	3280	5620	2880

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Rat			
Study number:	[0670694] continued			
GLP compliance:	Yes			
Location in CTD:	4.2.3.4.1-1			
Gender(M/F) / Number of animals:	F / 50 / group M / 50 / group			
Vehicle / Formulation:	Solution			
Method of Administration:	Once daily by s.c. injection for 2 years.			
Dose (mg/kg/day):	0, 0.01, 0.05 and 0.3			
Sample	Plasma			
Analyte:	SOM230			
Assay:	ELISA			
PK parameters:	mean		mean	
Dose (mg/kg/day)	0.05		0.3	
week	39		39	
Gender	M	F	M	F
Tmax (h)	1	1	1	0.5
Cmax (ng/mL)	94.8	168	883	499
Cmax/dose (ng/mL)/(mg/kg)	1900	3360	2940	1660
AUC0-24h (ng·h/mL)	347	363	3980	1900
AUC0-24h/dose (ng·h/mL)/(mg/kg)	6950	7250	13300	6330

All PK values were rounded up to 3 significant figures

2.6.5.4C 薬物動態試験：反復経口投与後の吸収（ラット）

Toxicokinetic data	Rat						Rat	
Study number:	[0410111]						[0520005]	
GLP compliance:	No						Yes	
Location in CTD:	4.2.3.2-2						4.2.3.2-3	
Gender(M/F) / Number of animals:	F / 5 / group M / 5 / group						F / 10 / group + 6 recovery M / 10 / group + 6 recovery	
Vehicle / Formulation:	Solution / 25 mM acetate buffer, pH 4.0						Solution in sterile water	
Method of Administration:	Once daily by oral gavage for 1 week						Once daily by oral gavage for 4 weeks with a 4-week recovery period.	
Dose (mg/kg/day):	30, 100 and 300						10, 30 and 80	
Sample	Plasma						Plasma	
Analyte:	SOM230						SOM230	
Assay:	ELISA						ELISA	
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	30		100		300		10	
Day	Day 7		Day 7		Day 2		1/2	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	0.5	0.5	1	1	0.5	0.5
Cmax (ng/mL)	9.30	12.3	776	35.4	445	3940	1.50	1.63
Cmax /Dose (ng/mL)/(mg/kg/day)	0.310	0.409	7.76	0.354	1.48	13.1	0.150	0.163
AUC0-24 h (ng•h/mL)	44.0	27.5	1300	81.3	1240	9390	-*	-*
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	1.47	0.918	13.0	0.813	4.14	31.3	-*	-*

All PK values were rounded up to 3 significant figures

-* = no AUC values given due to only 2 concentration values above LLOQ (0.6 ng/mL) in the TK profile.

Toxicokinetic data	Rat							
Study number:	[0520005] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-3							
Gender(M/F) / Number of animals:	F / 10 / group + 6 recovery M / 10 / group + 6 recovery							
Vehicle / Formulation:	Solution in sterile water							
Method of Administration:	Once daily by oral gavage for 4 weeks with a 4-week recovery period.							
Dose (mg/kg/day):	10, 30 and 80							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	30		80		10		30	
Day	1/2		1/2		29/30		29/30	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	1	0.5	0.5	1	1	1
Cmax (ng/mL)	4.04	5.05	15.8	7.75	2.40	2.18	5.63	5.84
Cmax /Dose (ng/mL)/(mg/kg/day)	0.135	0.168	0.197	0.097	0.240	0.218	0.188	0.195
AUC0-24 h (ng•h/mL)	9.57**	9.40**	79.8	19.4	6.71**	4.56**	41.9	24.5
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	0.319**	0.313**	0.998	0.242	0.671**	0.456**	1.40	0.816
AUC0-7 h (ng•h/mL)	n/a	n/a	n/a	n/a	6.71	4.56	27.6	20.8
AUC0-7 h/Dose (ng•h/mL)/(mg/kg/day)	n/a	n/a	n/a	n/a	0.671	0.456	0.921	0.692

All PK values were rounded up to 3 significant figures. n/a = not applicable.

** = AUC values based on only 3 concentration values above LLOQ in the TK profile, therefore these values are given only as an indication.

Toxicokinetic data	Rat	
Study number:	[0520005] continued	
GLP compliance:	Yes	
Location in CTD:	4.2.3.2-3	
Gender(M/F) / Number of animals:	F / 10 / group + 6 recovery M / 10 / group + 6 recovery	
Vehicle / Formulation:	Solution in sterile water	
Method of Administration:	Once daily by oral gavage for 4 weeks with a 4-week recovery period.	
Dose (mg/kg/day):	10, 30 and 80	
Sample	Plasma	
Analyte:	SOM230	
Assay:	ELISA	
PK parameters:	mean	
Dose (mg/kg/day)	80	
Day	29/30	
Gender	M	F
Tmax (h)	1	1
Cmax (ng/mL)	10.2	8.08
Cmax /Dose (ng/mL)/(mg/kg/day)	0.128	0.101
AUC0-24 h (ng•h/mL)	73.0	72.2*
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	0.913	0.903*
AUC0-7 h (ng•h/mL)	50.6	29.9
AUC0-7 h/Dose (ng•h/mL)/(mg/kg/day)	0.632	0.373

All PK values were rounded up to 3 significant figures; n/a = not applicable.

* = For the 80 mg/kg/day dose group, the SOM230 concentration found for females on day 29/20 at 24 hours looked higher than expected, therefore AUC0-7 h

2.6.5.4D 薬物動態試験：反復静脈内投与（ラット）

Toxicokinetic data	Rat					
Study number:	[0410037]					
GLP compliance:	Yes					
Location in CTD:	4.2.3.2-9					
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group					
Vehicle / Formulation:	Solution					
Method of Administration:	Once daily by i.v. bolus for 2 weeks					
Dose (mg/kg/day):	0, 0.015, 0.05, and 0.15					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean		mean		mean	
Dose (mg/kg/day)	0.015		0.05		0.15	
Day	2 Weeks		2 Weeks		2 Weeks	
Gender	M	F	M	F	M	F
Tmax (h)	0.083	0.083	0.083	0.083	0.083	0.083
Cmax (ng/mL)	69.2	20.2	218	121	543	487
Cmax /Dose (ng/mL)/(mg/kg/day)	4610	1350	4360	2410	3620	3240
AUC0-24 h (ng•h/mL)	58.8	16.6	191	91.1	504	368
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	3920	1100	3810	1820	3360	2450

All PK values were rounded up to 3 significant figures

2.6.5.4E 薬物動態試験：反復筋肉内投与後の吸収（ラット）

Toxicokinetic data	Rat
Study number:	[0770082]
GLP compliance:	Yes
Location in CTD:	4.2.3.2-8
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group
Formulation:	LAR formulation A or B (suspension)
Method of Administration:	Once monthly by i.m. for 3 months
Dose (mg/animal/month) *:	0, 3 and 6
Sample	Plasma
Analyte:	SOM230
Assay:	ELISA

PK parameters:	mean		mean		mean		mean	
Dose (mg/rat/month)	3 (formulation B)		6 (Formulation B)		6 (Formulation A)		3 (Formulation B)	
Day	1st month		1st month		1st month		2nd month	
Gender	M	F	M	F	M	F	M	F
Tmax (day)	21	27	27	27	27	21	21	21
Cmax (ng/mL)	143	166	253	1170	46.5	227	1120	1920
Cmax /Dose (ng/mL)/mg	47.7	55.3	42.2	195	7.75	37.8	373	640
AUC0.083-27d (ng•d/mL)	1230	1100	2070	5300	408	1750	13700	18700
AUC0.083-27d/Dose (ng•d/mL)/mg	411	368	345	884	68.0	291	4580	6220

* Doses are given as the pamoate salt form, conversion to base = 0.7294

All PK values were rounded up to 3 significant figures

Note: At the end of treatment, ~70% of animals showed a positive immunogenicity response (ainti-SOM230 antibody). The immunogenicity could lead to an overestimation of SOM230 concentrations and the PK parameters after second dose would be less accurate. Therefore, the PK parameters after first injection, which would have less impact from anti-drug antibody, were considered to be the fair values.

Toxicokinetic data	Rat						Rat	
Study number:	[0770082] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-8							
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group							
Formulation:	LAR formulation A (suspension)							
Method of Administration:	Once monthly by i.m. for 3 months							
Dose (mg/animal/month) *:	0, 3 and 6							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		Mean	
Dose (mg/rat/month)	6 (Formulation B)		6 (Formulation A)		3 (Formulation B)		6 (Formulation B)	
Day	2nd month		2nd month		3rd month		3rd month	
Gender	M	F	M	F	M	F	M	F
Tmax (day)	21	27	27	27	21	27	27	21
Cmax (ng/mL)	1960	4730	2020	1350	3910	2550	4000	3680
Cmax /Dose (ng/mL)/mg	327	788	337	225	1300	850	667	613
AUC0.083-27d (ng•d/mL)	29700	45200	18900	17600	49400	36200	58200	59500
AUC0.083-27d/Dose (ng•d/mL)/mg	4940	7540	3150	2930	16500	12100	9710	9910

* Doses are given as the pamoate salt form, conversion to base = 0.7294

All PK values were rounded up to 3 significant figures

Note: At the end of treatment, ~70% of animals showed a positive immunogenicity response (ainti-SOM230 antibody). The immunogenicity could lead to an overestimation of SOM230 concentrations and the PK parameters after second dose would be less accurate. Therefore, the PK parameters after first injection, which would have less impact from anti-drug antibody, were considered to be the fair values.

Toxicokinetic data	Rat		Rat					
Study number:	[0770082] continued		[0470138]					
GLP compliance:	Yes		Yes					
Location in CTD:	4.2.3.2-8		4.2.3.2-7					
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group		F / 10 / group M / 10 / group					
Formulation:	LAR formulation A (suspension)		LAR formulation (suspension)					
Method of Administration:	Once monthly by i.m. for 3 months		Once monthly by i.m. for 6 months					
Dose (mg/animal/month) *:	0, 3 and 6		0, 3.125, and 6.25					
Sample	Plasma		Plasma					
Analyte:	SOM230		SOM230					
Assay:	ELISA		ELISA					
PK parameters:	mean		mean		mean		mean	
Dose (mg/rat/month)	6 (Formulation A)		3.125	6.25	3.125	6.25	3.125	6.25
Day	3rd month		1st month	1st month	2nd month	2nd month	3rd month	3rd month
Gender	M	F	M	M	M	M	M	M
Tmax (day)	14	27	27	27	0.083	7	0.083	7
Cmax (ng/mL)	2090	3980	68.8	133	87	354	521	1900
Cmax /Dose (ng/mL)/mg	348	663	22	21.3	27.8	56.6	167	304
AUC0.083-27d (ng•d/mL)	34000	46900	621	1063	1790	7170	6830	29600
AUC0.083-27d/Dose (ng•d/mL)/mg	5670	7810	199	170	571	1150	2190	4750

* Doses are given as the pamoate salt form; conversion to base = 0.7294 for [0770082]; the doses are expressed as base for [0470138]

All PK values were rounded up to 3 significant figures

Note [0470138]: 26 out of 59 animals (at week 25 and recovery) tested for anti-SOM230 antibody formation showed a positive immunogenicity response. The immunogenicity could lead to an overestimation of SOM230 concentrations and the PK parameters after second dose would be less accurate. Therefore, the PK parameters after first injection, which would have less impact from anti-drug antibody, were used for safety margin calculation.

Toxicokinetic data	Rat					
Study number:	[0470138] continued					
GLP compliance:	Yes					
Location in CTD:	4.2.3.2-7					
Gender(M/F) / Number of animals:	F / 10 / group M / 10 / group					
Formulation:	LAR formulation (suspension)					
Method of Administration:	Once monthly by i.m. for 6 months					
Dose (mg/animal/month) *:	0, 3.125, and 6.25					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean		mean		mean	
Dose (mg/rat/month)	3.125	6.25	3.125	6.25	3.125	6.25
Day	4th month	4th month	5th month	5th month	6th month	6th month
Gender	M	M	M	M	M	M
Tmax (day)	0.083	7	0.083	7	0.083	7
Cmax (ng/mL)	1410	2820	1800	2690	1740	2050
Cmax /Dose (ng/mL)/mg	451	451	576	430	557	328
AUC0.083-27d (ng•d/mL)	13300	38300	16800	34800	16200	28400
AUC0.083-27d/Dose (ng•d/mL)/mg	4250	6130	5380	5540	5170	4540

* Doses are given as the pamoate salt form; the doses are expressed as base for [0470138].

All PK values were rounded up to 3 significant figures.

Note [0470138]: 26 out of 59 animals (at week 25 and recovery) tested for anti-SOM230 antibody formation showed a positive immunogenicity response. The immunogenicity could lead to an overestimation of SOM230 concentrations and the PK parameters after second dose would be less accurate. Therefore, the PK parameters after first injection, which would have less impact from anti-drug antibody, were used for safety margin calculation.

2.6.5.4F 薬物動態試験：反復静脈内投与（サル）

Toxicokinetic data	Monkey		Monkey					
Study number:	[0580074]		[0580076]					
GLP compliance:	Yes		Yes					
Location in CTD:	4.2.3.2-16		4.2.3.2-17					
Gender(M/F) / Number of animals:	F / 1 / group M / 1 / group		F / 3 / group M / 3 / group					
Vehicle / Formulation:	Solution		Solution					
Method of Administration:	Once daily by i.v. bolus for 5 days		Once daily by i.v. bolus for 14 days					
Dose (mg/kg/day):	0 and 0.135		0, 0.015, 0.075 and 0.150					
Sample	Plasma		Plasma					
Analyte:	SOM230		SOM230					
Assay:	ELISA		ELISA					
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.135		0.015		0.075		0.150	
Day	5 days		1/2		1/2		1/2	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5	0.5	0.083	0.083	0.083	0.083	0.083	0.083
Cmax (ng/mL)	246	170	133	193	891	655	1760	1510
Cmax /Dose (ng/mL)/(mg/kg/day)	1820	1260	8860	12800	11900	8740	11700	10100
AUC0-24 h (ng•h/mL)	684	385	145	195	901	595	2140	2330
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	5070	2850	9660	13000	12000	7920	14200	15500

All PK values were rounded up to 3 significant figures

Toxicokinetic data	Monkey					
Study number:	[0580076] continued					
GLP compliance:	Yes					
Location in CTD:	4.2.3.2-17					
Gender(M/F) / Number of animals:	F / 3 / group M / 3 / group					
Vehicle / Formulation:	Solution					
Method of Administration:	Once daily by i.v. bolus for 14 days					
Dose (mg/kg/day):	0, 0.015, 0.075 and 0.150					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean		mean		mean	
Dose (mg/kg/day)	0.015		0.075		0.150	
Day	13/14		13/14		13/14	
Gender	M	F	M	F	M	F
Tmax (h)	0.083	0.083	0.083	0.083	0.083	0.083
Cmax (ng/mL)	128	228	919	752	1820	1830
Cmax /Dose (ng/mL)/(mg/kg/day)	850	15200	12300	10000	12100	12200
AUC0-24 h (ng•h/mL)	176	302	1040	633	1810	2110
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	11700	20200	13900	8440	12100	14100

All PK values were rounded up to 3 significant figures

2.6.5.4G 薬物動態試験：反復皮下投与後の吸収（イヌ）

Toxicokinetic data	Dog			
Study number:	[0110034]			
GLP compliance:	No			
Location in CTD:	4.2.3.2-10			
Gender(M/F) / Number of animals:	F / 1 / group M / 1 / group			
Vehicle / Formulation:	Solution in 2.5% glycerol or mannitol			
Method of Administration:	Twice daily by s.c. bolus for 2 weeks			
Dose (mg/kg/day):	5, 1, 0.1, and 0.07			
Sample	Plasma			
Analyte:	SOM230			
Assay:	ELISA			
PK parameters:	mean	mean	mean	mean
Dose (mg/kg/day)	5	1	0.1	0.07
Dosing duration (days)	3	1	1	1
Sampling day	7	3	3	3
Gender	M / F	M / F	M / F	M / F
Cmax (ng/mL)	44	4	16	3

All dose levels caused systemic clinical signs. They consisted of severe vomiting and diarrhea with the consequence of severe body weight loss. Therefore, treatment was stopped by day 3 of the study

2.6.5.4H 薬物動態試験：反復皮下投与後の吸収（サル）

Toxicokinetic data	Monkey
Study number:	[0170060]
GLP compliance:	Yes
Location in CTD:	4.2.3.2-12
Gender(M/F) / Number of animals:	M & F / 1 / rising dose phase M / 2 / group F / 2 / group 2 M + 2 F in recovery group
Vehicle / Formulation:	Solution, acetate buffer pH 4.5
Method of Administration:	Twice daily by s.c. bolus for 2 weeks + 4 week recovery
Dose (mg/kg/day):	0, 0.04, 0.8 and 1.6
Sample	Plasma
Analyte:	SOM230
Assay:	ELISA

PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	0.04		0.8		1.6		0.04	
Day	1		1		1		14	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	1 - 1	7 – 7	1 - 1	1 - 7	1 - 7	1 - 7	1 – 7	7 – 7
Cmax (ng/mL)	14.3	26.4	632	652	722	1070	20.7	24.9
Cmax /Dose (ng/mL)/(mg/kg/day)	286	528	632	652	361	534	413	497
AUClast (ng•h/mL)	68.9	134	3160	4050	3960	5750	112	144
AUClast /Dose (ng•h/mL)/(mg/kg/day)	1380	2680	3160	4050	1980	2880	2230	2870

All PK values were rounded up to 3 significant figures

T_{max} values given as range.

Toxicokinetic data	Monkey							
Study number:	[0170060] continued				[0170114]			
GLP compliance:	Yes				Yes			
Location in CTD:	4.2.3.2-12				4.2.3.2-13			
Gender(M/F) / Number of animals:	M & F / 1 / rising dose phase M / 2 / group F / 2 / group 2 M + 2 F in recovery group				M & F / 2 - 5			
Vehicle / Formulation:	Solution, acetate buffer pH 4.5				Solution, acetate buffer pH 4.5			
Method of Administration:	Twice daily by s.c. bolus for 2 weeks + 4 week recovery				Twice daily by s.c. bolus for 2 weeks + 4 week recovery			
Dose (mg/kg/day):	0, 0.04, 0.8 and 1.6				0, 0.4, 0.8 and 1.6			
Sample	Plasma				Plasma			
Analyte:	SOM230				SOM230			
Assay:	ELISA				ELISA			
PK parameters:	mean		mean		mean ± SD		mean ± SD	
Dose (mg/kg/day)	0.8		1.6		0.4		0.8	
Day	14		14		1/2		1/2	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	7 - 7	1 – 7	1 - 2	1 - 7	0.5 - 2	0.5	0.5	0.5
Cmax (ng/mL)	728	747	1410	1670	136 ± 39.8	157 ± 27.6	354 ± 100	483 ± 62.0
Cmax /Dose (ng/mL)/(mg/kg/day)	728	747	706	847	545 ± 159	629 ± 110	707 ± 200	966 ± 124
AUClast (ng•h/mL)	3290	3570	6580	9310	419 ± 129	385 ± 88.0	981 ± 297	1220 ± 250
AUClast /Dose (ng•h/mL)/(mg/kg/day)	3290	3570	3290	4650	1680 ± 517	1540 ± 353	1960 ± 593	2440 ± 500

All PK values were rounded up to 3 significant figures

T_{max} values given as range.

[0170114] SOM230 was administered at 0 and approximately 6 hours. TK parameters were calculated from 0 – 6 hours (before the second administration). Therefore, dose normalized parameters were calculated using half of the daily dose.

Toxicokinetic data	Monkey							
Study number:	[0170114] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-13							
Gender(M/F) / Number of animals:	M & F / 2 - 5							
Vehicle / Formulation:	Solution, acetate buffer pH 4.5							
Method of Administration:	Twice daily by s.c. bolus for 2 weeks + 4 week recovery							
Dose (mg/kg/day):	0, 0.4, 0.8 and 1.6							
Sample	Plasma							
Analyte:	Pasireotide, SOM230							
Assay:	ELISA							
PK parameters:	mean ± SD		mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)	1.6		0.4		0.8		1.6	
Day	1/2		22/23		22/23		22/23	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5 - 1	0.5 - 1	0.5	0.5	0.5 - 1	0.5	0.5	0.5 – 1
Cmax (ng/mL)	1240 ± 476	984 ± 301	330 ± 64.8	306 ± 18.8	870 ± 345	928 ± 341	1560 ± 176	1670 ± 348
Cmax /Dose (ng/mL)/(mg/kg/day)	1240 ± 476	984 ± 301	1320 ± 259	1220 ± 75.0	1740 ± 689	1860 ± 682	1560 ± 176	1670 ± 348
AUClast (ng•h/mL)	2700 ± 533	2380 ± 420	637 ± 102	584 ± 98.0	1800 ± 601	1720 ± 741	3870 ± 768	4200 ± 865
AUClast /Dose (ng•h/mL)/(mg/kg/day)	2700 ± 533	2380 ± 420	2550 ± 406	2340 ± 391	3600 ± 1200	3450 ± 1480	3870 ± 768	4200 ± 865

All PK values were rounded up to 3 significant figures

T_{max} values given as range.

[0170114] SOM230 was administered at 0 and approximately 6 hours. TK parameters were calculated from 0 – 6 hours (before the second administration). Therefore, dose normalized parameters were calculated using half of the daily dose.

Toxicokinetic data	Monkey					
Study number:	[0270087]					
GLP compliance:	Yes					
Location in CTD:	4.2.3.2-14					
Gender(M/F) / Number of animals:	3 M + 3 F / group 5 M + 5 F in recovery groups					
Vehicle / Formulation:	Solution, acetate buffer pH 4.5					
Method of Administration:	Once daily by s.c. bolus for 4 weeks + 4 week recovery					
Dose (mg/kg/day):	0, 1.6, 3.2 and 6.4					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)	1.6		3.2		6.4	
Day	1/2		1/2		1/2	
Gender	M	F	M	F	M	F
Tmax (h)	0.5	0.5	0.5 – 2	0.5 - 1	0.5 - 1	1
Cmax (ng/mL)	1630 ± 501	1840 ± 193	2130 ± 211	2680 ± 1220	3360 ± 573	4490 ± 371
Cmax /Dose (ng/mL)/(mg/kg/day)	815 ± 250	917 ± 97.0	533 ± 53.0	670 ± 305	420 ± 72.0	561 ± 46.0
AUClast (ng•h/mL)	6910 ± 2800	8470 ± 2410	14300 ± 2800	21100 ± 13400	29000 ± 9330	48200 ± 16300
AUClast /Dose (ng•h/mL)/(mg/kg/day)	3450 ± 1400	4230 ± 1210	3580 ± 699	5270 ± 3350	3620 ± 1170	6020 ± 2040

Doses are given as the di-aspartate salt form, conversion to base = 0.8

All PK values were rounded up to 3 significant figures

Tmax values given as range

Tlast = 24 h

Toxicokinetic data	Monkey					
Study number:	[0270087] continued					
GLP compliance:	Yes					
Location in CTD:	4.2.3.2-14					
Gender(M/F) / Number of animals:	3 M + 3 F / group 5 M + 5 F in recovery groups					
Vehicle / Formulation:	Solution, acetate buffer pH 4.5					
Method of Administration:	Once daily by s.c. bolus for 4 weeks + 4 week recovery					
Dose (mg/kg/day):	0, 1.6, 3.2 and 6.4					
Sample	Plasma					
Analyte:	SOM230					
Assay:	ELISA					
PK parameters:	mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)	1.6		3.2		6.4	
Week	4/5		4/5		4/5	
Gender	M	F	M	F	M	F
Tmax (h)	0.5	0.5 - 1	0.5 - 4	0.5 - 1	0.5 - 1	0.5 - 6
Cmax (ng/mL)	1770 ± 355	1990 ± 727	2170 ± 675	3450 ± 1030	4920 ± 2470	4410 ± 1110
Cmax /Dose (ng/mL)/(mg/kg/day)	886 ± 178	993 ± 364	543 ± 169	862 ± 256	615 ± 309	551 ± 139
AUClast (ng•h/mL)	7100 ± 2030	10200 ± 2580	18200 ± 5100	26700 ± 19500	42600 ± 19200	42300 ± 11500
AUClast /Dose (ng•h/mL)/(mg/kg/day)	3550 ± 1010	5100 ± 1300	4560 ± 1270	6690 ± 4870	5320 ± 2400	5280 ± 1430

Doses are given as the di-aspartate salt form, conversion to base = 0.8

All PK values were rounded up to 3 significant figures

Tmax values given as range

Tlast = 24 h

Toxicokinetic data	Monkey							
Study number:	[0270130]							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-15							
Gender(M/F) / Number of animals:	M / 4-6 / group F / 4-6 / group							
Vehicle / Formulation:	Solution, acetate buffer pH 4.5							
Method of Administration:	Once daily by s.c. injection for 39 weeks							
Dose (mg/kg/day):	0, 0.4, 1.6 and 3.2							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean ± SD		mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)*	0.4		1.6		3.2		0.4	
Day	1/2		1/2		1/2		Week 4	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5 - 1	0.5	0.5 - 2	0.5	0.5 - 1	0.5 - 1	0.5 - 2	0.5 - 1
Cmax (ng/mL)	473 ± 35.7	601 ± 193	1470 ± 156	1860 ± 239	2820 ± 958	3430 ± 488	545 ± 82.4	705 ± 201
Cmax /Dose (ng/mL)/(mg/kg/day)	946 ± 71.0	1200 ± 385	735 ± 78.0	929 ± 120	706 ± 240	857 ± 122	1090 ± 165	1410 ± 402
AUC0-24 h (ng•h/mL)	1580 ± 243	1750 ± 1020	6960 ± 1660	9270 ± 2200	13900 ± 1150	16100 ± 2340	2320 ± 556	2390 ± 936
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	3150 ± 487	3500 ± 2040	3480 ± 828	4630 ± 1100	3470 ± 287	4030 ± 584	4630 ± 1110	4780 ± 1870

* Doses are given as the di-aspartate salt, conversion factor to free-base is 0.8.

All PK values were rounded up to 3 significant figures

Tmax values given as range.

Toxicokinetic data	Monkey							
Study number:	[0270130] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-15							
Gender(M/F) / Number of animals:	M / 4-6 / group F / 4-6 / group							
Vehicle / Formulation:	Solution, acetate buffer pH 4.5							
Method of Administration:	Once daily by s.c. injection for 39 weeks							
Dose (mg/kg/day):	0, 0.4, 1.6 and 3.2							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean ± SD		mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)*	1.6		3.2		0.4		1.6	
Day	Week 4		Week 4		Week 22		Week 22	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5 - 2	0.5 - 2	1 - 2	0.5 - 2	0.5 - 1	0.5 - 1	1 - 2	1
Cmax (ng/mL)	1730 ± 477	2700 ± 246	3180 ± 1100	3060 ± 785	761 ± 161	1100 ± 358	2560 ± 493	4040 ± 325
Cmax /Dose (ng/mL)/(mg/kg/day)	867 ± 238	1350 ± 123	795 ± 274	765 ± 196	1520 ± 322	2210 ± 717	1280 ± 246	2020 ± 163
AUC0-24 h (ng•h/mL)	9220 ± 3430	14900 ± 5790	23900 ± 6630	21040 ± 7820	2900 ± 351	4780 ± 2520	13200 ± 2810	19000 ± 1660
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	4610 ± 1720	7450 ± 2900	5960 ± 1660	5260 ± 1960	5790 ± 703	9560 ± 5030	6610 ± 1400	9520 ± 831

* Doses are given as the di-aspartate salt, conversion factor to free-base is 0.8.

All PK values were rounded up to 3 significant figures

Tmax values given as range.

Toxicokinetic data	Monkey							
Study number:	[0270130] continued							
GLP compliance:	Yes							
Location in CTD:	4.2.3.2-15							
Gender(M/F) / Number of animals:	M / 4-6 / group F / 4-6 / group							
Vehicle / Formulation:	Solution, acetate buffer pH 4.5							
Method of Administration:	Once daily by s.c. injection for 39 weeks							
Dose (mg/kg/day):	0, 0.4, 1.6 and 3.2							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean ± SD		mean ± SD		mean ± SD		mean ± SD	
Dose (mg/kg/day)*	3.2		0.4		1.6		3.2	
Day	Week 22		Week 35		Week 35		Week 35	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	0.5 - 1	1 - 2	0.5 - 2	0.5 - 1	0.5 - 1	1	1	1 - 2
Cmax (ng/mL)	4950 ± 887	6780 ± 328	855 ± 44.7	1150 ± 316	2250 ± 858	2970 ± 470	4850 ± 1690	5440 ± 2630
Cmax /Dose (ng/mL)/(mg/kg/day)	1240 ± 222	1700 ± 82.0	1710 ± 89.0	2300 ± 632	1120 ± 429	1490 ± 235	1210 ± 422	1360 ± 657
AUC0-24 h (ng•h/mL)	27500 ± 5460	39300 ± 2300	3540 ± 506	3870 ± 1690	11400 ± 2320	15900 ± 3280	28000 ± 8220	29900 ± 6270
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	6870 ± 1370	9820 ± 574	7090 ± 1010	7740 ± 3390	5690 ± 1160	7960 ± 1640	7000 ± 2050	7470 ± 1570

All PK values were rounded up to 3 significant figures

* Doses are given as the di-aspartate salt, conversion factor to free-base is 0.8.

Tmax values given as range.

2.6.5.4l 薬物動態試験：反復経口投与後の吸収（サル）

Toxicokinetic data

	Monkey							
Study number:	[0580075]							
GLP compliance:	No							
Location in CTD:	4.2.3.2-11							
Gender(M/F) / Number of animals:	M / 1 / group F / 1 / group 2 M + 2 F in 100 mg/kg/day group							
Vehicle / Formulation:	Solution, acetate buffer pH 4.5							
Method of Administration:	Once daily by p.o. gavage for 14 days							
Dose (mg/kg/day):	0, 10, 30, and 100							
Sample	Plasma							
Analyte:	SOM230							
Assay:	ELISA							
PK parameters:	mean		mean		mean		mean	
Dose (mg/kg/day)	10		30		100		10	
Day	1/2		1/2		1/2		14/15	
Gender	M	F	M	F	M	F	M	F
Tmax (h)	1	1	1	1	3	2	0.5	0.5
Cmax (ng/mL)	4.66	6.57	170	97.4	1020	2360	186	198
Cmax /Dose (ng/mL)/(mg/kg/day)	0.466	0.657	5.65	3.25	10.2	23.6	18.6	19.8
AUClast (ng•h/mL)	30.5	34.6	603	499	6470	13100	922	1080
AUClast /Dose (ng•h/mL)/(mg/kg/day)	3.05	3.46	20.1	16.6	64.7	131	92.2	108

All PK values were rounded up to 3 significant figures

	Monkey			
Study number:	[0580075] continued			
GLP compliance:	No			
Location in CTD:	4.2.3.2-11			
Gender(M/F) / Number of animals:	M / 1 / group F / 1 / group 2 M + 2 F in 100 mg/kg/day group			
Vehicle / Formulation:	Solution, acetate buffer pH 4.5			
Method of Administration:	Once daily by p.o. gavage for 14 days			
Dose (mg/kg/day):	0, 10, 30, and 100			
Sample	Plasma			
Analyte:	SOM230			
Assay:	ELISA			
PK parameters:	mean		mean	
Dose (mg/kg/day)	30		100	
Day	14/15		14/15	
Gender	M	F	M	F
Tmax (h)	3	1	3	3
Cmax (ng/mL)	2300	369	5150	3130
Cmax /Dose (ng/mL)/(mg/kg/day)	76.5	12.3	51.5	31.3
AUClast (ng•h/mL)	8200	1380	35300	16200
AUClast /Dose (ng•h/mL)/(mg/kg/day)	273	46.0	353	162

All PK values were rounded up to 3 significant figures

2.6.5.5A 薬物動態試験：分布（標識体 1 mg/kg 皮下投与後の肝臓及び腎臓）

Study title:	Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1 mg/kg)		
GLP compliance:	not required		
Study Number:	[DMPK (CH) R01-0388]		
Location in CTD:	4.2.2.4-1		
Species:	Rat (Han Wistar)		
Gender(M/F) / number of animals:	M/9		
Feeding condition:	Water and food available ad libitum		
Vehicle / formulation:	Saline / solution		
Method of administration:	Subcutaneous injection		
Dose (mg/kg):	1 mg/kg		
Radionuclide:	[^{14}C]		
Specific activity:	318 µCi/mg		
Analyte / assay (unit):	Radioactivity, µgEq/g		
Sampling time:	24, 48, and 72 (h)		
Tissues / organs:	Concentration (µgEq/g) after 1 mg/kg subcutaneous dose		
	24h	48h	72h
Liver	1130 ± 216	903 ± 132	794 ± 136
Kidney	5460 ± 276	5340 ± 676	4450 ± 258

2.6.5.5B 薬物動態試験：分布（標識体 2 mg/kg 静脈内投与後の各組織）

Study title:	Quantitative Whole-Body Autoradioluminography in pigmented rats after a 2 mg/kg iv dose of [^{14}C]pasireotide
GLP compliance:	not required
Study Number:	[DMPK(CH) R99-2095]
Location in CTD:	4.2.2.3-2
Species:	Rat (Long Evans Hooded, pigmented)
Gender(M/F) / number of animals:	M/5
Feeding condition:	Water and food available ad libitum
Vehicle / formulation:	Solution in acetate buffer at pH 5.2
Method of administration:	Intravenous Bolus via the caudal vein
Dose (mg/kg):	2 mg/kg
Radionuclide:	[^{14}C]
Specific activity:	1.1 MBq/mg
Analyte / assay (unit):	Radioactivity, nmol/g
Sampling time:	0.083, 1, 4, 24, 72 and 168 h and 3 and 14 weeks postdose (p.d.)

	Concentration (nmol/g) after 2 mg/kg intravenous dose							
Tissues / organs:	0.083 h	1 h	4 h	24 h	72 h	168 h	3 wks	14 wks
Adrenal (cortex)	5.58	2.90	1.69	1.30	1.16	1.25	1.45	1.08
Adrenal (medulla)	nm	4.32	2.38	nm	nm	nm	0.53	0.19
Blood	6.73	2.42	0.35	0.06	T	T	nd	nd
Blood vessel wall	10.8	12.7	9.03	3.31	1.89	2.31	2.13	0.74
Bone marrow	2.85	1.20	0.64	0.62	0.36	0.58	0.47	T
Bone mineral	0.28	0.24	0.16	T	T	T	nd	nd
Brain	0.13	0.07	nd	nd	nd	nd	nd	nd
Brown fat	1.37	0.72	0.24	0.14	0.10	0.09	0.08	nd
Cartilage (femoral) bone	4.44	4.37	1.17	0.75	0.76	0.49	0.21	nd
Ear	6.86	11.5	10.6	3.34	1.88	1.95	1.66	0.40
Epidydimis	0.48	0.54	0.18	0.11	0.06	0.07	T	nd
Eye (lens)	nd	nd	nd	nd	nd	nd	nd	nd

Study title:	Quantitative Whole-Body Autoradioluminography in pigmented rats after a 2 mg/kg iv dose of [^{14}C]pasireotide							
Eye (ocular membranes)	2.46	2.25	0.43	0.24	0.16	0.23	0.13	nd
Eye (vitreous body)	nd	nd	nd	nd	nd	nd	nd	nd
Harderian gland	1.30	0.84	0.31	0.13	0.08	0.15	0.07	nd
Heart	3.03	1.06	0.31	0.15	0.12	0.15	0.06	nd
Intestine (colon)	7.50	1.24	0.51	0.20	ns	0.27	ns	nd
Intestine (duodenum)	9.09	1.29	4.57	1.04	0.32	0.46	0.57	0.08
Kidney (CM junction)	3.96	23.0	5.92	4.21	1.64	5.36	0.44	nd
Kidney (cortex)	10.5	15.1	11.5	9.31	4.78	4.62	1.18	0.18
Kidney (medulla)	5.92	8.62	0.92	0.59	0.31	0.60	0.18	nd
Kidney (pelvis)	13.7	26.0	0.72	0.43	0.31	0.55	0.20	nd
Lachrymal gland	1.35	0.88	0.35	0.18	0.10	0.11	0.10	nd
Liver	10.9	12.4	7.43	4.07	2.16	3.69	1.13	0.06
Lung	8.33	6.66	1.77	0.65	0.43	0.56	0.25	T
Lymph nodes (axillary)	1.71	1.44	0.40	0.40	0.21	0.27	0.12	0.10
Lymph nodes (mesenteric)	16.5	20.0	3.11	5.34	7.67	7.33	4.69	1.28
Muscle	0.61	0.30	0.07	T	T	T	nd	nd
Pancreas	1.79	0.97	0.35	0.27	0.17	0.31	0.13	nd
Pineal gland	2.00	1.10	0.45	0.23	0.18	0.16	0.15	nd
Pituitary gland	2.22	1.18	0.81	0.75	0.53	0.69	0.61	nd
Preputial gland	1.52	ns	ns	0.41	0.21	0.22	ns	nd
Salivary gland	2.57	1.39	0.34	0.31	0.15	0.34	0.12	nd
Seminal gland	0.73	0.03	ns	T	T	T	0.12	nd
Skin	0.83	1.87	0.35	0.28	0.14	0.24	T	nd
Spleen (red pulp)	4.76	3.87	2.54	2.25	1.61	2.59	2.11	0.98
Spleen (white pulp)	2.31	2.80	0.80	0.76	0.40	0.77	0.53	0.26
Stomach (glandular)	2.86	2.21	0.60	0.23	0.16	0.17	0.13	nd
Stomach (non glandular)	1.60	1.84	0.31	0.19	0.09	0.21	0.10	nd
Testis	0.13	0.19	0.13	0.06	T	T	nd	nd
Thymus	2.17	2.04	0.57	0.48	0.38	0.52	0.40	nd
Thyroid gland	3.49	1.98	0.71	0.59	0.39	0.41	0.33	nd

Study title:	Quantitative Whole-Body Autoradioluminography in pigmented rats after a 2 mg/kg iv dose of [^{14}C]pasireotide							
Tongue	2.95	2.07	0.56	0.39	0.19	0.14	0.14	nd
White fat	0.23	0.09	nd	nd	nd	nd	nd	nd

nm: not measured; ns: no sample; nd: below detection limit (0.03 nmol/g); T: traces, i.e. concentrations between detection limit and quantification limit (0.06 nmol/g)

2.6.5.5C 薬物動態試験：分布（標識体 1 mg/kg 皮下投与後の各組織）

Study title:	Tissue distribution following an subcutaneous dose of [^{14}C]SOM230 in the rat
GLP compliance:	not required
Study Number:	[DMPK R0500319]
Location in CTD:	4.2.2.3-4
Species:	rat
Gender(M/F) / number of animals:	10 LEH (pigmented) rats plus 1 HanWistar (non-pigmented) / male
Feeding condition:	Free access
Vehicle / formulation:	Saline / solution
Method of administration:	s.c. injection
Dose (mg/kg):	1.0
Radionuclide:	[^{14}C]
Specific activity:	89.9 µCi/mg
Analyte / assay (unit):	Radioactivity, ngEq/g

	Radioactivity concentration (ngEq/g)										
Time point	0.25 h	1 h	3 h	5 h	8 h	24 h	48 h	72 h	168 h	168 h	2 week
Sample	Rat #1 (LEH)	Rat #2 (LEH)	Rat #3 (LEH)	Rat #4 (LEH)	Rat #5 (LEH)	Rat #6 (LEH)	Rat #7 (LEH)	Rat #8 (LEH)	Rat #9 (LEH)	Rat #10 (HW)	Rat #11 (LEH)
Quality control[a]	2530	2510	2720	2110	2620	2210	2380	2520	2170	2540	2670
Adrenal cortex	159	250	378	279	347	386	137	415	238	203	386
Adrenal medulla	152	303	405	209	173	123	47.7	146	102	99.5	161
Bile	2850	7270	12500	8350	2270	917	707	653	38.9	62.9	30.9
Blood	249	349	380	246	41.5	BLD	3.59	BLQ	BLQ	BLD	BLD
Blood vessel wall	591	611	2150	1780	1220	554	1270	441	NM	701	414
Bone marrow	75.1	138	230	137	112	93.5	118	109	92.0	66.0	108
Bone mineral	21.8	19.1	49.8	23.3	12.6	11.3	18.9	8.78	9.03	BLD	N.S.
Brain	BLQ	BLQ	BLQ	BLQ	BLQ	BLD	BLQ	BLD	BLQ	BLD	BLD
Brown fat	19700	147	160	152	155	53.4	71.4	37.6	34.8	52.4	18.8

Study title:	Tissue distribution following an subcutaneous dose of [^{14}C]SOM230 in the rat										
Time point	0.25 h	1 h	3 h	5 h	8 h	24 h	48 h	72 h	168 h	168 h	2 week
	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6	Rat #7	Rat #8	Rat #9	Rat #10	Rat #11
Sample	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(HW)	(LEH)
Cartilage	152	603	531	2760	396	1060	1190	46.5	NM	NM	127
Colon wall	51.8	82.1	169	142	539	166	95.2	51.7	18.4	32.7	NM
Dosing site	54700	190000	84000	23600	24800	90700	493	14600	21800	35000	NM
Epididymis	32.4	85.5	87.5	59.1	43.2	27.8	52.3	31.8	15.7	25.3	14.5
Esophagus	98.6	139	231	134	80.9	36.3	52.9	54.6	N.S.	N.S.	22.2
Harderian gland	43.8	79.0	125	56.2	46.8	32.0	23.0	34.9	19.5	15.0	20.1
Heart	94.1	151	144	92.5	39.0	22.5	32.9	30.4	16.0	15.0	NM
Kidney cortex	1580	3220	5870	4020	5630	4370	3610	2900	1120	1360	254
Kidney medulla	510	336	815	236	534	111	144	119	60.6	88.6	35.3
Kidney pelvis	249	1240	1310	580	305	91.4	166	142	97.4	132	36.0
Lachrymal gland	47.0	65.0	88.0	152	46.6	21.0	13.9	37.8	8.29	BLQ	17.7
Liver	388	1220	1760	1050	1100	636	531	588	228	370	155
Lung	215	413	543	259	134	69.6	87.6	79.5	39.4	40.1	54.6
Lymph node	48.1	64.6	152	105	79.9	465	1150	758	NM	N.S.	303
Muscle	33.7	30.4	48.1	28.7	17.1	BLQ	16.3	15.4	BLQ	8.61	NM
Pancreas	75.8	174	188	118	72.6	59.7	67.0	65.1	NA	35.4	15.7
Pituitary gland	179	249	94.7	151	134	107	158	24.4	NM	91.4	89.2
Salivary gland	57.2	97.5	175	83.5	63.7	41.1	53.1	58.0	NA	26.3	33.0
Seminal vesicles	BLD	BLQ	BLQ	10.8	BLQ	N.S.	7.38	8.88	NM	NM	NM
Skin	81.4	178	279	174	100	71.7	76.9	60.2	NA	32.6	26.7
Small intestine wall	175	859	1700	926	651	67.7	85.1	369	NM	110	67.9
Spinal cord	BLQ	7.96	10.9	BLQ	BLQ	BLD	5.12	BLQ	BLQ	BLQ	BLQ
Spleen	78.4	188	333	276	314	337	296	472	NA	280	106
Stomach cutaneous	75.0	226	248	176	80.2	50.3	48.0	33.1	NM	27.9	NM
Stomach glandular	113	96.6	298	160	86.8	45.2	76.6	57.7	NA	24.4	14.1
Testis	7.24	25.9	41.0	27.9	27.6	18.7	16.2	15.9	NA	10.3	11.7

Study title:	Tissue distribution following an subcutaneous dose of [^{14}C]SOM230 in the rat										
Time point	0.25 h	1 h	3 h	5 h	8 h	24 h	48 h	72 h	168 h	168 h	2 week
	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6	Rat #7	Rat #8	Rat #9	Rat #10	Rat #11
Sample	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(LEH)	(HW)	(LEH)
Thymus	35.8	64.9	106	78.8	86.0	75.4	146	91.1	NA	42.5	83.8
Thyroid gland	65.1	124	312	93.8	104	96.3	97.8	84.8	NM	NM	22.2
Trachea	90.3	375	594	414	254	87.6	127	39.1	NM	NM	34.2
Uveal tract	119	263	235	134	132	51.0	40.6	106	NM	NM	NM
White fat	BLD	20.8	BLD	BLD	BLD	NM	15.2	10.5	BLQ	NM	NM
LOD (ngEq/g)	3.32	3.04	4.50	3.41	4.53	7.87	1.39	3.26	3.94	2.52	4.04
LOQ (ngEq/g)	6.64	6.08	9.01	6.81	9.07	15.7	2.79	6.53	7.88	5.03	8.07

[a] Theoretical QC concentration was 2310 ngEq/g for this study

LEH = Long Evans Hooded pigmented rats; HW = HanWistar albino rats

N.S. = no sample; NM = not measured, tissue concentration not distinguishable from surrounding tissues and/or background

BLQ = concentration below the limit of quantification and greater than the limit of detection

BLD = Below limit of detection (LOD)

NA = Not analyzed

Tissue	Tmax	Cmax[a]		AUCinf[a]	Tlast	t1/2	Tissue: blood ratio	
	(h)	(ngEq/mL)	(µmol/mL)	(µgEq•h/mL)	(h)	(h)	Cmax, tissue	AUCinf
Adrenal cortex	72	415	396	1640	336	2750	1.1	588
Adrenal medulla	3	405	387	166	336	521	1.1	59
Bile	3	12500	11900	164	336	67	33	59
Blood	3	380	363	2.79	48	11	1.0	1.0
Blood vessel wall	3	2150	2050	416	336	393	5.7	149
Bone marrow	3	230	220	486	336	2900	0.6	174
Bone mineral	3	49.8	47.6	5.12	168	243	0.1	1.8
Brain	NA	NA	NA	NA	NA	NA	NA	NA
Brown fat	0.25	19700	18800	28.4	336	182	52	10
Cartilage	5	2760	2640	111	336	139	7.3	40
Colon wall	8	539	515	17.0	168	54	1.4	6.1
Dosing site	1	190000	181000	12400	168	211	500	4440
Epididymis	3	87.5	83.6	13.3	336	258	0.2	4.8
Esophagus	3	231	221	21.6	336	218	0.6	7.7
Harderian gland	3	125	119	19.5	336	378	0.3	7.0
Heart	1	151	144	7.56	168	112	0.4	2.7
Kidney cortex	3	5870	5610	625	336	75	15	224
Kidney medulla	3	815	778	39.7	336	156	2.1	14
Kidney pelvis	3	1310	1250	45.8	336	131	3.4	16
Lachrymal gland	5	152	145	15.4	336	340	0.40	5.5
Liver	3	1760	1680	155	336	148	4.6	56
Lung	3	543	519	54.1	336	411	1.4	19
Lymph node	48	1150	1100	260	336	167	3.0	93
Muscle	3	48.1	45.9	11.0	72	436	0.13	3.9
Pancreas	3	188	180	18.9	336	134	0.49	6.8
Pituitary gland	1	249	238	117	336	587	0.66	42
Salivary gland	3	175	167	33.9	336	374	0.46	12

Tissue	Tmax	Cmax[a]		AUCinf[a]	Tlast	t1/2	Tissue: blood ratio	
	(h)	(ngEq/mL)	(µmol/mL)	(µgEq•h/mL)	(h)	(h)	Cmax, tissue	AUCinf
Seminal vesicles	5	10.8	10.3	3.06	72	191	0.03	1.1
Skin	3	279	266	25.5	336	202	0.73	9.1
Small intestine wall	3	1700	1620	98.1	336	198	4.5	35
Spinal cord	3	10.9	10.4	0.718	48	57	0.03	0.3
Spleen	72	472	451	127	336	171	1.2	46
Stomach cutaneous	3	248	237	7.31	72	57	0.65	2.6
Stomach glandular	3	298	285	17.4	336	123	0.78	6.2
Testis	3	41.0	39.2	15.3	336	606	0.11	5.5
Thymus	48	146	139	97.0	336	550	0.38	35
Thyroid gland	3	312	298	25.8	336	135	0.82	9.2
Trachea	3	594	567	31.5	336	230	1.6	11
Uveal tract	1	263	251	47.8	72	275	0.69	17
White fat	1	20.8	19.9	2.30	72	75	0.05	0.8

NA = not applicable, PK parameters were not calculated due to below LOQ values at all time points.

[a] Assuming 1 g = 1 mL for the PK parameter calculation

2.6.5.6 薬物動態試験：たん白結合

Test article: [^{14}C]SOM230

Study title:	In vitro blood distribution and plasma protein binding of ^{14}C-labeled SOM230			
Study number:	[DMPK(CH) R99-2082]			
GLP compliance:	not required			
Location in CTD:	4.2.2.3-1			
Study system:	Rat (Han:Wist), dog (Beagle) and human			
Radionuclide:	[^{14}C]			
Specific activity:	0.75 MBq/mg			
Method:	Ultrafiltration			
Analyte / Assay:	Radioactivity / LSC			
Species:	Concentration tested (ng/mL)	% Bound in plasma		
Rat (pooled, n=3)	25	93.0		
	100	94.4		
	1000	94.6		
	10000	94.5		
Dog (pooled, n=3)	25	91.9		
	100	93.3		
	1000	93.6		
	10000	92.0		
Human	Subject	1 (No. 3425641)	2 (No. 3108334)	3 (No. 3089839)
	25	83.1	85.4	89.6
	100	88.5	85.9	91.1
	1000	88.9	85.4	91.8
	10000	90.4	84.3	91.8

Study title:	In vitro blood distribution and plasma protein binding of ^{14}C-labeled pasireotide						
Test article: [^{14}C]SOM230							
Species:	Concentration tested (ng/mL)	F_{plasma} (mean ± SD)			C_b/C_p		
Rat (pooled, n=3)	100	106.6 ± 6.2			0.5		
Hematocrit: 48	1000	95.3 ± 2.2			0.5		
	10000	94.0 ± 2.5			0.6		
Dog (pooled, n=3)	100	88.9 ± 4.4			0.6		
Hematocrit: 51	1000	85.5 ± 2.8			0.6		
	10000	85.4 ± 2.0			0.6		
Human	Subject	1 (No. 3425641)	2 (No. 3108334)	3 (No. 3089839)	1	2	3
Hematocrit: (1) 44	100	90.7 ± 4.9	88.7 ± 3.4	96.7 ± 6.6	0.6	0.6	0.5
(2) 43	1000	92.2 ± 0.5	88.2 ± 1.6	93.8 ± 1.5	0.6	0.6	0.6
(3) 48	10000	85.8 ± 2.6	87.9 ± 1.9	92.9 ± 2.3	0.7	0.6	0.6

F_{plasma}: Fraction in the plasma

Note: Anticoagulant for human subjects 1 and 2 was citrate and heparin for subject 3.

2.6.5.7A 薬物動態試験：妊娠動物における試験（ラット）

Toxicokinetics: embryo-fetal development

	Rat		
Study number:	[0470017]		
GLP compliance:	Yes		
Location in CTD:	4.2.3.5.2-2		
Gender(M/F) / Number of animals:	F / 5/group (20 total)		
Study conditions:	Dosed between gestation day 6 and 17		
Vehicle / Formulation:	Solution in saline		
Method of Administration:	Once daily by s.c. injection		
Dose (mg/kg/day):	0, 1, 5 and 10 mg/kg		
Sample	Plasma		
Analyte:	SOM230		
Assay:	ELISA		
PK parameters:	mean ± SD	mean ± SD	mean ± SD
Dose (mg/kg/day)	1.0	5.0	10.0
Tmax (h)	1 – 2[a]	2	1 - 2 [a]
Cmax (ng/mL)	1100 ± 111	3100 ± 867	3220 ± 1140
Cmax /Dose (ng/mL)/(mg/kg/day)	1100 ± 111	619 ± 173	322 ± 114
AUC0-24 h (ng•h/mL)	4930 ± 1060	25600 ± 5050	42200 ± 15200
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	4930 ± 1060	5120 ± 1010	4220 ± 1520

[a] Tmax given as range (h)

2.6.5.7B 薬物動態試験：妊娠動物における試験（ウサギ）

Toxicokinetics: embryo-fetal development

	Rabbit		
Study number:	[0470018]		
GLP compliance:	Yes		
Location in CTD:	4.2.3.5.2-4		
Gender(M/F) / Number of animals:	F / 5/group; 3/group for 5.0 mg/kg/day		
Study conditions:	Dosed between gestation day 7 and 20		
Vehicle / Formulation:	Solution in saline		
Method of Administration:	Once daily by s.c. injection		
Dose (mg/kg/day):	0, 0.05, 1 and 5 mg/kg		
Sample	Plasma and fetus tissue		
Analyte:	SOM230		
Assay:	ELISA		
PK parameters:	mean ± SD	mean ± SD	mean ± SD
Dose (mg/kg/day)	0.05	1.0	5.0
Tmax (h)	1	1	1
Cmax (ng/mL)	45.0 ± 4.6	753 ± 150	2710 ± 456
Cmax /Dose (ng/mL)/(mg/kg/day)	901 ± 114	753 ± 150	542 ± 91.0
AUC0-24 h (ng•h/mL)	114 ± 26.7	1910 ± 363	11800 ± 2870
AUC0-24 h/Dose (ng•h/mL)/(mg/kg/day)	2280 ± 533	1910 ± 363	2350 ± 573
Cfetus/Cp, maternal	0.0	0.46	1.0

2.6.5.8 薬物動態試験：その他の分布試験（胎仔移行性）

Test article: [^{14}C]SOM230

Study title:	Embryo-fetal transfer in pregnant rats after a single 10 mg/kg subcutaneous dose of [^{14}C]SOM230 (12.5 mg/kg of [^{14}C]SOM230 bis-aspartate)							
GLP compliance:	not required							
Study Number:	[DMPK R0201643]							
Location in CTD:	4.2.2.3-3							
Species:	Rat (Han:WIST)							
Gender(M/F) / number of animals:	F/18 pregnant Han:WIST CR WIGA rats on day 13 or day 18 of gestation, n=1/time point							
Feeding condition:	Free access							
Vehicle / formulation:	Solution in saline							
Method of administration:	s.c. injection							
Dose (mg/kg):	10							
Radionuclide:	[^{14}C]							
Specific activity:	7.86 MBq/mg, purity 98.3%							
Analyte:	Radioactivity, [^{14}C]							
Sampling time:	1, 2, 8 and 24 h p.d. on day 13 and day 18 of gestation							
	Gestation. Day 13; Concentration (nmol/g)				Gestation. Day 18; Concentration (nmol/g)			
Tissues / organs:	1 h	2 h	8 h	24 h	1 h	2 h	8 h	24 h
Adrenal	0.19	0.67	1.4	2.4	ns	ns	ns	ns
Adrenal (cortex)	ns	ns	ns	ns	0.52	0.48	1.6	5.0
Adrenal (medulla)	ns	ns	ns	ns	0.45	0.28	0.60	2.1
Amnion	ns	ns	ns	ns	T	0.25	0.41	0.76
Amniotic fluid	ns	ns	ns	ns	nd	nd	nd	nd
Application site	ns	ns	ns	ns	546	641	485	719
Bile	ns	ns	ns	ns	3.9	3.9	21	nd
Blood	0.20	0.44	0.35	0.18	0.55	0.39	0.90	0.86
Blood vessel wall	ns	ns	ns	ns	0.77	1.0	2.8	6.8

	Gestation. Day 13; Concentration (nmol/g)				Gestation. Day 18; Concentration (nmol/g)			
Tissues / organs:	1 h	2 h	8 h	24 h	1 h	2 h	8 h	24 h
Bone marrow	0.19	0.41	1.0	0.76	T	T	0.56	1.4
Bone mineral	ns	ns	ns	ns	nd	nd	nd	nd
Bone periost	ns	ns	ns	ns	0.22	T	0.31	0.46
Brain	0.054	0.076	0.039	0.024	T	nd	nd	nd
Fat (brown)	ns	ns	ns	ns	nm	nm	nm	0.76
Fat (white)	0.10	0.10	0.12	0.11	nd	nd	nd	nd
Cartilage	ns	ns	ns	ns	0.46	0.50	3.7	8.0
Choroid plexus	ns	ns	ns	ns	nd	nd	nd	nd
Collagen	ns	ns	ns	ns	T	0.27	0.29	0.53
Eye	0.058	0.10	0.079	0.14	ns	ns	ns	ns
Eye (choroid)	ns	ns	ns	ns	0.22	T	0.44	0.61
Eye (lens)	ns	ns	ns	ns	nd	nd	nd	nd
Eye (vitreous body)	ns	ns	ns	ns	nd	nd	nd	nd
Harderian gland	0.10	0.30	0.42	0.31	nd	T	T	0.42
Heart	0.14	0.17	0.20	0.22	T	T	0.27	0.32
Intestinal wall (colon)	0.092	0.20	0.35	0.42	T	0.22	T	0.78
Intestinal wall (small)	0.42	1.3	1.7	1.1	ns	ns	ns	ns
Intestinal wall (duodenum)	ns	ns	ns	ns	0.23	T	2.4	1.5
Kidney	1.8	3.1	6.4	28	ns	ns	ns	ns
Kidney (CM junction)	ns	ns	ns	ns	nm	nm	11	45
Kidney (cortex)	ns	ns	ns	ns	4.6	4.5	11	38
Kidney (medulla)	ns	ns	ns	ns	0.46	1.42	0.97	23
Kidney (pelvis)	ns	ns	ns	ns	1.5	1.3	1.9	2.0
Lachrymal gland	0.18	0.27	0.40	0.28	T	nd	0.26	0.39
Liver	0.62	1.9	4.1	7.2	1.1	1.4	5.4	15
Lung	0.32	0.60	0.90	1.0	0.60	0.47	1.1	1.8

	Gestation. Day 13; Concentration (nmol/g)				Gestation. Day 18; Concentration (nmol/g)			
Tissues / organs:	1 h	2 h	8 h	24 h	1 h	2 h	8 h	24 h
Lymph nodes	0.10	0.39	0.66	0.95	0.36	0.45	1.6	4.6
Mouth (mucosa)	ns	ns	ns	ns	0.42	0.40	0.72	0.80
Mammary gland	0.092	0.20	0.21	0.37	ns	ns	ns	ns
Muscle	0.039	0.068	0.10	0.077	T	T	T	T
Nasal turbinates	ns	ns	ns	ns	nd	nd	nd	nd
Nerves	ns	ns	ns	ns	1.1	1.1	5.0	14
Oesophageus	ns	ns	ns	ns	nd	0.26	0.31	2.3
Ovary	0.12	0.22	0.37	0.70	ns	ns	ns	ns
Pancreas	0.10	0.28	0.23	0.34	T	T	0.34	0.66
Pineal gland	ns	ns	ns	ns	nd	nd	nd	0.64
Pituitary gland	0.14	0.57	0.37	0.58	0.21	0.68	0.53	1.1
Plasma	0.33	0.78	0.49	0.54	ns	ns	ns	ns
Salivary gland	0.11	0.21	0.19	0.30	T	T	0.33	0.60
Skin	1.3	0.66	0.89	1.2	T	T	0.46	0.68
Skin (subcutis)	ns	ns	ns	ns	0.68	0.46	0.74	0.86
Spleen	0.19	0.47	1.1	3.0	0.39	0.30	1.5	5.3
Spleen (red pulp)	ns	ns	ns	ns	nm	nm	1.8	6.6
Spleen (white pulp)	ns	ns	ns	ns	nm	nm	0.47	2.3
Stomach (glandular)	0.15	0.30	0.35	0.39	0.29	T	0.41	0.80
Stomach (non-glandular)	0.13	0.30	0.44	0.37	0.29	0.22	0.39	1.0
Thymus	0.12	0.16	0.34	0.50	T	T	0.40	1.2
Thyroid gland	0.14	0.50	0.42	0.37	T	0.25	0.71	0.68
Tongue	ns	ns	ns	ns	0.23	T	0.39	0.59
Tooth (enamel)	ns	ns	ns	ns	T	0.26	0.57	0.72
Tooth (pulp)	ns	ns	ns	ns	0.24	0.22	0.70	1.7

	Gestation. Day 13; Concentration (nmol/g)				Gestation. Day 18; Concentration (nmol/g)			
Tissues / organs:	1 h	2 h	8 h	24 h	1 h	2 h	8 h	24 h
Fetus (mean)	0.014	0.021	0.016	0.020	nd	nd	nd	nd
Uterus	0.12	0.23	0.43	0.51	ns	ns	ns	ns
Placenta (mean)	0.074	0.16	0.28	0.55	0.31	T	0.70	0.96

ns = no sample

nd < LOD (0.07 nmol/g)

nm = not measured; tissue concentration not distinguishable from surrounding tissues and/or background

T = trace, concentration below the limit of quantification and greater than the limit of detection

2.6.5.9A 薬物動態試験：*in vivo* における代謝（ラット血漿，肝臓及び腎臓）

Test article: [^{14}C]SOM230

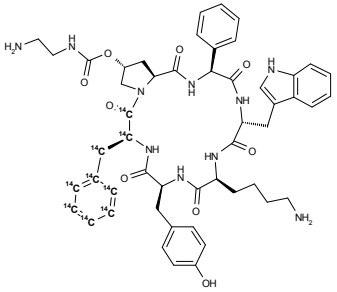
Study title: Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1 mg/kg)	
Study Number:	[DMPK (CH) R01-0388]
GLP compliance:	not required
Location in CTD:	4.2.2.4-1
Gender(M/F) / Number of animals:	M / 9
Feeding condition:	Fed
Formulation:	Solution in sterile saline
Method of Administration:	Subcutaneous injection
Dose (mg/kg):	1.0
Radionuclide:	[^{14}C]
Specific activity / purity:	318 µCi/mg / >98% radiochemical purity
Analyte/Assay (unit):	HPLC with on-line radioactivity detection

	Plasma concentrations (nmol/L)[b] - 1 mg/kg subcutaenous dose				
Sampling time (h)	Total (LSC)	Total (HPLC)	P1	SOM230	Sum of trace peaks
1	427	417	20	375	22
2	506	496	18	446	32
4	609	590	11	552	28
8	114	99	2	93	4
24	19	5	[a]	5	[a]
48	11	2	[a]	2	[a]
72	8	1	[a]	1	[a]

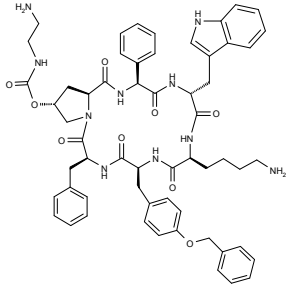
[a] Not applicable or not determined

[b] Values are rounded to three significant figures or to the nearest nmol/L; pooled samples from 3 animals per timepoint; metabolite and SOM230 concentrations were determined by HPLC with on-line radioactivity monitoring

Study title: Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1 mg/kg)		
Plasma Exposure		
1 mg/kg subcutaneous dose		
Plasma component	$AUC_{1\text{-}72\ h}$ (nmol•h/L)	(%)*
P1	87	2
SOM230	3610	77
Sum of trace peaks	183	4
* The values were not corrected for the recovery		



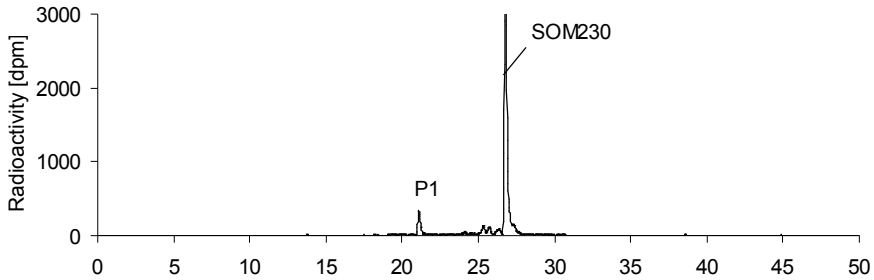
P1 (impurity)



SOM230

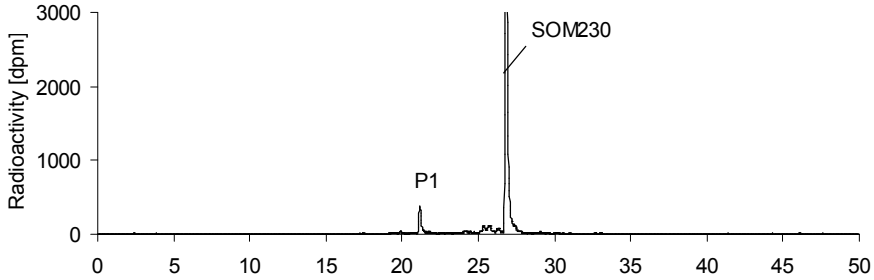
Kidney : Radio-chromatograms

24 h post dose

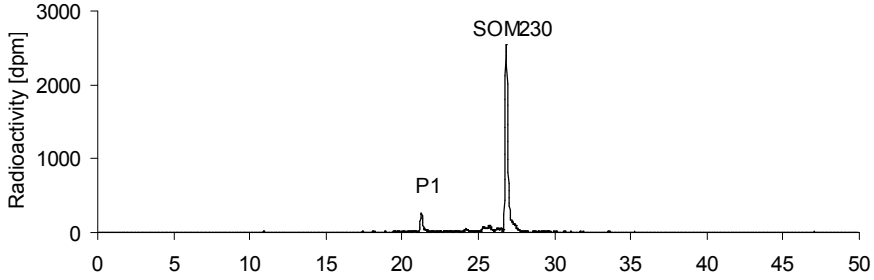


P1: impurity

48 h post dose

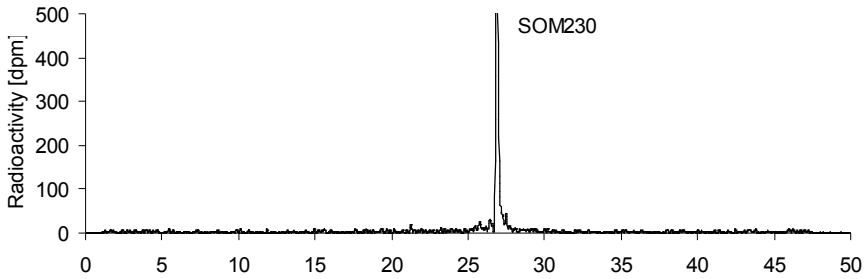


72 h post dose

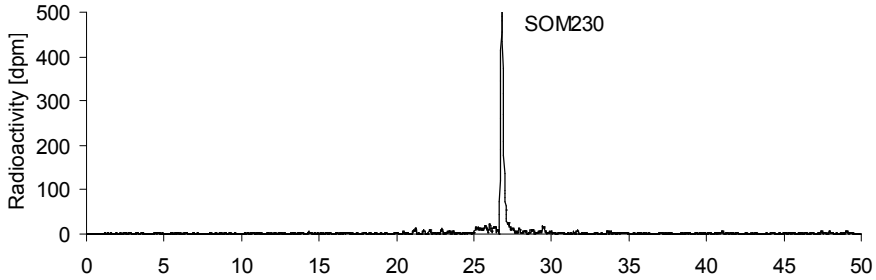


Liver : Radio-chromatograms

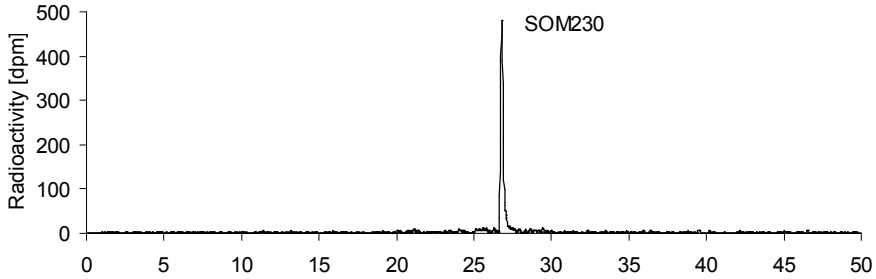
24 h post dose



48 h post dose



72 h post dose



2.6.5.9B 薬物動態試験：*in vivo* における代謝（ラット尿及び糞）

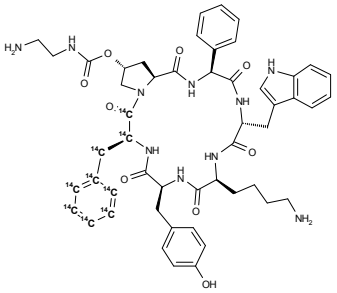
Test article: [^{14}C]SOM230

Study title: Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1 mg/kg)			
Study Number:	[DMPK (CH) R01-0388]		
GLP compliance:	not required		
Location in CTD:	4.2.2.4-1		
Gender(M/F) / Number of animals:	M / 3 (pooled)		
Feeding condition:	Fed		
Formulation:	Solution in saline		
Method of Administration:	Subcutaneous injection		
Dose (mg/kg):	1.0		
Radionuclide:	[^{14}C]		
Specific activity:	318 µCi/mg / >98% radiochemical purity		
Analyte/Assay:	HPLC with on-line radioactivity detection		
Metabolite	Urinary metabolites (%, 0-48 h)	Fecal metabolites (%, 0-48 h)	Total Excretion (%, 0-48 h)
P1	1.5	1.3	2.8
SOM230	4.2	48.0	52.3
P3	0.0	3.4	3.4
Sum of trace peaks	2.8	9.5	12.4
Total of peaks/recovered ^{14}C	8.6	62.3	70.9
Not recovered from sample	[a]	11.0	11.0
Total analyzed (pool 0-48 h)	8.6	73.3	81.9
Total excretion (0-72 h)	8.9	74.8	83.7

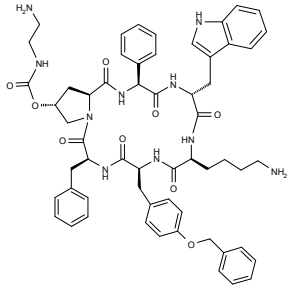
[a] Not detected or not quantifiable

Study title: Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1 mg/kg)

Metabolite structures



P1



SOM230

2.6.5.9C 薬物動態試験：*in vivo* における代謝（ラット乳汁及び血漿）

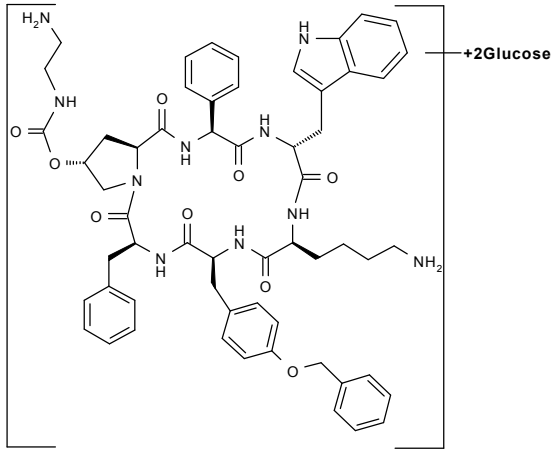
Test article: [^{14}C]SOM230

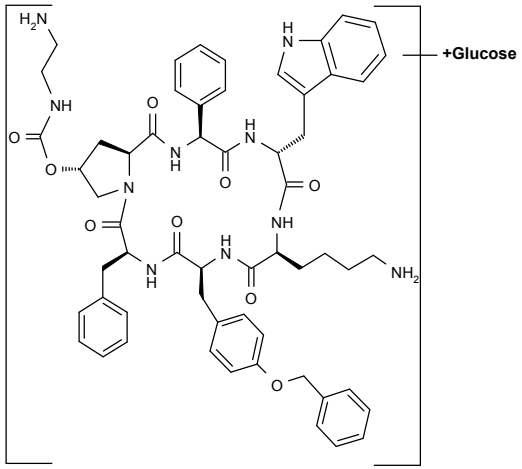
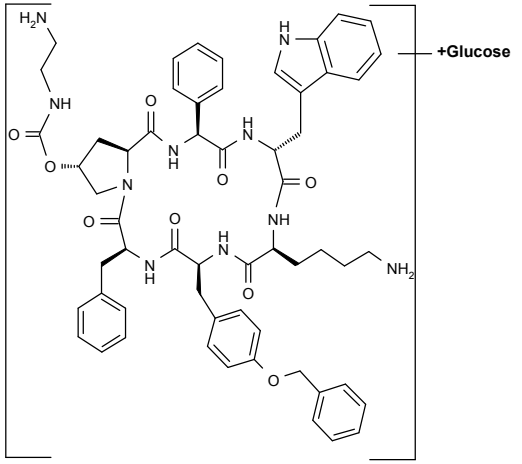
Study title: Excretion in milk after a single subcutaneous dose of [^{14}C]SOM230 in the rat				
Study Number:	[DMPK R0900555]			
GLP compliance:	not required			
Location in CTD:	4.2.2.5-1			
Gender(M/F) / Number of animals:	F / 15 (3 per timepoint); lactating, 8-9 days post-parturition; HanWistar			
Feeding condition:	fed			
Formulation:	Solution in saline			
Method of Administration:	s.c. injection			
Dose (mg/kg):	1.0			
Radionuclide:	[^{14}C]			
Specific activity:	125.8 µCi/mg / 97.9% radiochemical purity			
Analyte/Assay:	Liquid scintillation counting; metabolite profiles by HPLC with off-line radioactivity detection; metabolite identification by LC-MS/MS			
	Plasma (ng/mL or ngEq/mL)		Milk (ng/mL or ngEq/mL)	
Time (h)	SOM230	Others (A22.3, A27.2, A28)	SOM230	Others (A22.3, A27.2, A28)
1	361	25.0	80.1	9.65
2	302	25.1	66.4	0
4	268	21.1	56.2	6.67
8	157	0	49.1	0
24	6.28	2.31	-	-
Cmax (ngEq/mL)	361	25.1	80.1	9.65
tmax (h)	1	2	1	1
AUC0-24h (ngEq•h/mL)	3240	144	447	29.7
AUC%	95.7*	4.27**	93.8*	6.23**

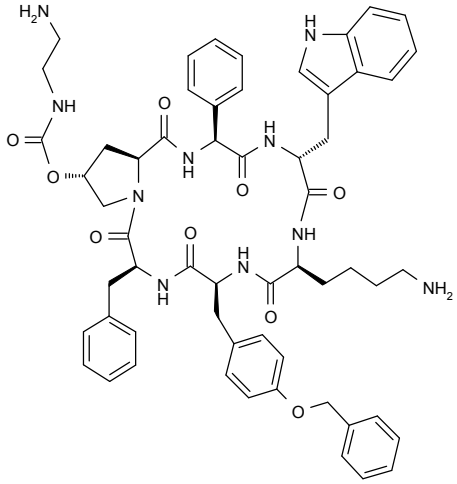
*The %AUC for SOM230 comprises SOM230, A22.7, A23.5, and A23.9. These were the identified glucose adducts introduced *ex vivo* during sample processing.

**The %AUC for others comprises A22.3, A27.2, and A28. These were the unidentified peaks which were partially introduced *ex vivo* during sample processing.

Metabolite structures

Peak ID	Measured mass (MH^+) (delta massExact mass)	Retention time t_R (min)	Matrix	Proposed structures
A22.7	1371.6151 (0.549 ppm 1371.6143)	22.7	Plasma	

A23.5	1209.5624 (0.725 ppm 1209.5615)	23.5	Plasma	
A23.9	1209.5619 (0.311 ppm 1209.5615)	23.9	Plasma, Milk	

SOM230	1047.5095 (0.764 ppm 1047.5087)	24.8	Plasma, Milk	
A22.3	Unknown	22.3	Plasma	unknown
A27.2	Unknown	27.2	Plasma, Milk	unknown
A28	Unknown	28	Plasma, Milk	unknown

2.6.5.9D 薬物動態試験：*in vivo* における代謝（サル血漿，尿及び糞）

Test article: [^{14}C]SOM230

Study title: Absorption, metabolism and excretion following a single subcutaneous dose of [^{14}C]SOM230 in monkeys			
Study Number:	[DMPK R0900554]		
GLP compliance:	not required		
Location in CTD:	4.2.2.4-2		
Gender(M/F) / Number of animals:	M / 3		
Feeding condition:	Fed		
Formulation:	Solution in saline		
Method of Administration:	s.c. injection		
Dose (mg/kg):	0.6 mg/kg		
Radionuclide:	[^{14}C]		
Specific activity:	61.05 µCi/mg as salt / 98.8% radiochemical purity		
Analyte/Assay:	Liquid scintillation counting; metabolite profiles by HPLC with off-line radioactivity detection; metabolite identification by LC-MS/MS		
	Plasma (ngEq/mL)		
Time (h)	SOM230*	M27	Others (A25.5 & A28)**
0.25	865	26.9	52.7
0.5	1092	30.1	58.1
1	1180	43.4	56.8
2	1039	30.1	40.4
4	298	8.89	15.6
8	106	3.68	10.6
12	53.5	0.0	0.0
24	11.2	0.0	0.0

tmax (h)	1	2	0.5
Cmax (ngEq/mL)	1180	43.4	58.1
AUC0-24h (ngEq•h/mL)	4881	137	227
AUC %	93.1	2.68	4.45

*The %AUC for SOM230 comprises SOM230, A22.7, A23.5, and A23.9. These were the identified glucose adducts introduced *ex vivo* during sample processing.

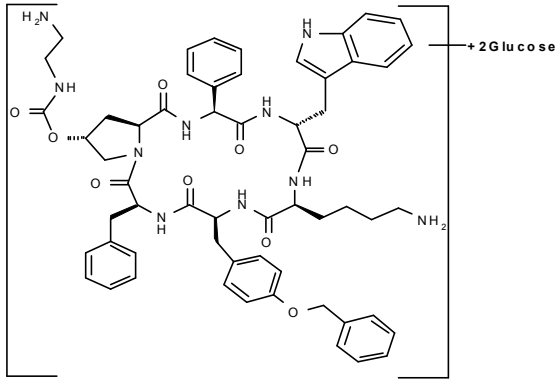
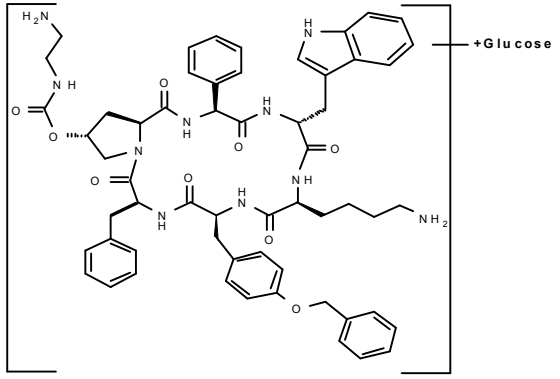
**The %AUC for Others comprises A25.5 and A28. These were the unidentified peaks which were partially introduced *ex vivo* during sample processing.

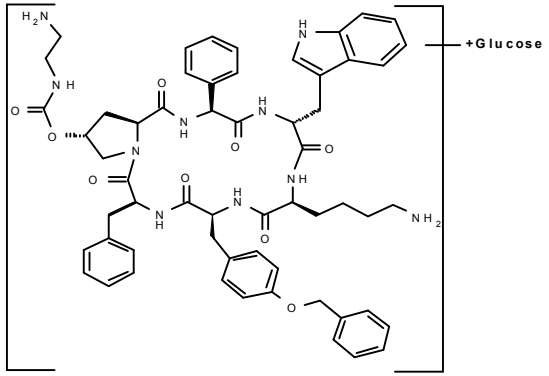
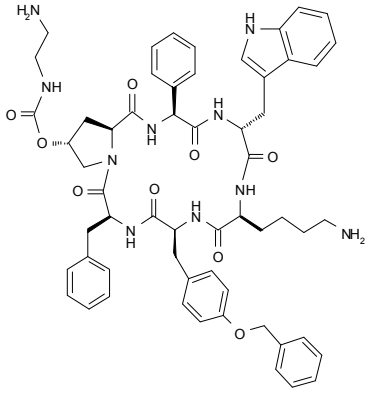
	SOM230	M27	Others (A25.5, A26.7 and A28)
Urine (0–24 h)	3.52*	not detected	not detected
Feces (0-72 h)	77.6**	8.47	8.47***
Sum Excreta (0-72 h)	81.1	8.47	8.47

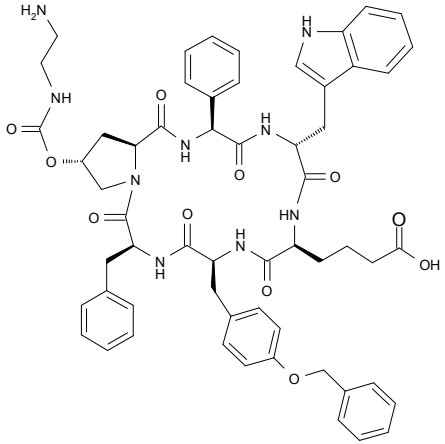
*The 3.52% of SOM230 detected in the urine comprises only SOM230. No other peaks were detected.

** The 77.6% of SOM230 detected in the feces includes A22.7, and A23.5 as these were identified as glucose adducts introduced *ex vivo* during sample processing.

***The 8.47% of dose for Others comprises A25.5, A26.7 and A28. These were the unidentified peaks which were partially introduced ex vivo during sample processing.

Peak ID	Measured mass (MH+ m/z) (delta mass exact mass)	Retention time t_R (min)	Matrix	Proposed structures
A22.7	1371.6151 (0.549 ppm 1371.6143)	22.7	Plasma (trace) Feces	
A23.5	1209.5624 (0.725 ppm 1209.5615)	23.5	Plasma Feces	

Peak ID	Measured mass (MH+ m/z) (delta mass exact mass)	Retention time t_R (min)	Matrix	Proposed structures
A23.9	1209.5619 (0.311 ppm 1209.5615)	23.9	Plasma Feces	
SOM230	1047.5095 (0.764 ppm 1047.5087)	24.8	Plasma Feces Urine	
A25.5	unknown		Plasma	unknown
A26.7	unknown		Feces	unknown

Peak ID	Measured mass (MH+ m/z) (delta mass exact mass)	Retention time t_R (min)	Matrix	Proposed structures
M27 (P30 in vitro report) (DMPK-R0400850)	1062.4728 (0.753 ppm 1062.4720)	27.35	Plasma Feces	
A28	unknown		Plasma Feces	unknown

2.6.5.9E 薬物動態試験：*in vivo* における代謝（ヒト血漿）

Test article: [^{14}C]SOM230

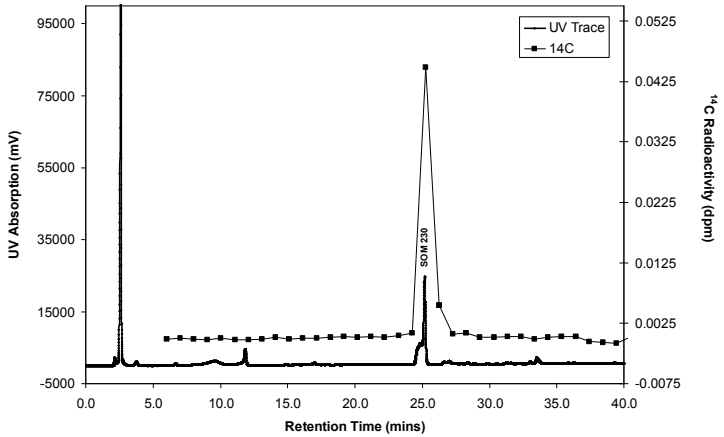
Study title: An open-label, single center study to determine absorption, distribution, metabolism and excretion (ADME) of pasireotide (SOM230) following a single subcutaneous injection of [14C]pasireotide (600 µg) in healthy subjects

Study Number:	[CSOM230B2112]
GLP compliance:	not required
Location in CTD:	5.3.3.1-3
Gender(M/F) / Age range / Number of subjects:	M / 18-25 yrs/ 4
Formulation:	Sterile aqueous drug solution
Method of Administration:	Subcutaneous injection
Dose (µg):	600 (0.232 µCi)
Radionuclide:	[^{14}C]
Analyte/Assay (unit):	HPLC with offline AMS detection

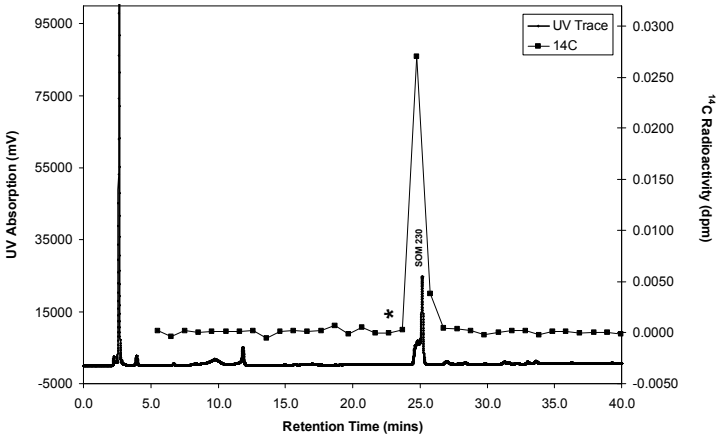
	Ratio of plasma pasireotide to plasma radioactivity				
Parameter	Subject USA/0501/ 00002	Subject USA/0501/ 00003	Subject USA/0501/ 00005	Subject USA/0501/ 00014	Mean
Plasma pasireotide					
AUC24h (ng•h/mL)	78.7	50.9	51.9	90.6	68.0
Plasma radioactivity					
AUC24h (ngEq•h/mL)	73.4	46.4	49.3	82.5	62.9
AUC ratio					
(pasireotide /radioactivity)	1.07	1.10	1.05	1.10	1.08
	Mean concentration of pasireotide and its metabolite(s) in plasma (Mean ± SD)				
Theoretical concentration in pooled sample (ngEq/mL, 0-12h)	5.52	3.81	4.03	5.97	4.84 ± 1.07
Pasireotide (ng/mL)	5.52	3.81	4.03	5.97	4.84 ± 1.07
Pasireotide (% of total radioactivity)	100	100	100	100	-
Other peak (% of total radioactivity)	Below detection	Below detection	Below detection	Below detection	Below detection

Representative metabolite profile in plasma (0-12 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00002

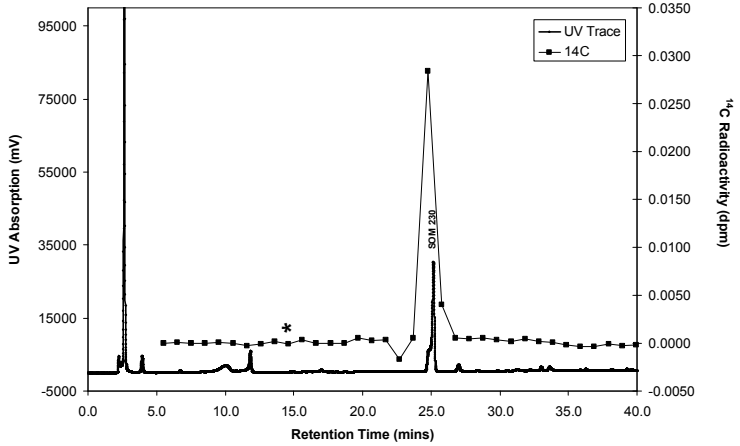


Subject USA/0501/00003

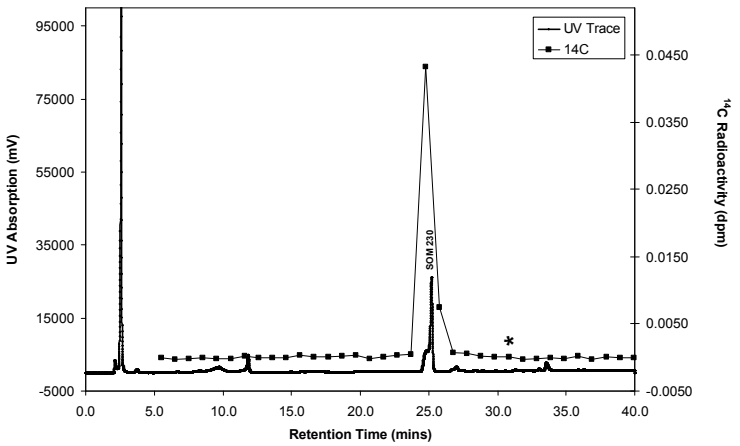


Representative metabolite profile in plasma (0-12 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00005



Subject USA/0501/00014



2.6.5.9F　薬物動態試験：*in vivo* における代謝（ヒト尿及び糞）

Test article: [^{14}C]SOM230

Study title: An open-label, single center study to determine absorption, distribution, metabolism and excretion (ADME) of pasireotide (SOM230) following a single subcutaneous injection of [14C]pasireotide (600 µg) in healthy subjects

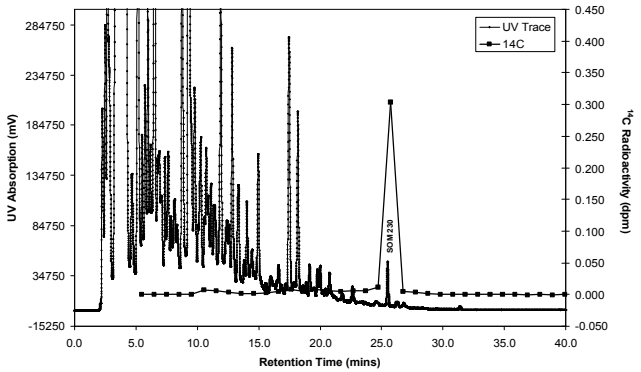
Study Number:	[CSOM230B2112]
GLP compliance:	not required
Location in CTD:	5.3.3.1-3
Gender(M/F) / Number of animals:	M / 18-25 yrs / 4
Formulation:	Sterile aqueous drug solution
Method of Administration:	Subcutaneous injection
Dose (µg/ subject):	600 (0.232 µCi)
Radionuclide:	[^{14}C]
Analyte/Assay:	HPLC with offline AMS detection

Urine pooled (0-144 h)	Total % of dose in pooled sample [a]	Pasireotide (% of dose)	Other peaks (% of dose)	
			Unknown 1 (P10)	Unknown 2 (P19)
USA/0501/00002	8.87	8.06	0.425	0.386
USA/0501/00003	6.52	5.61	0.525	0.376
USA/0501/00005	4.84	4.16	0.349	0.335
USA/0501/00014	7.97	5.78	0.339	1.85
Mean ± SD		5.90 ± 1.61	0.410 ± 0.086	0.737 ± 0.742
Feces pooled (0-168 h)			P28	
USA/0501/00002	34.2	31.1	3.16	-
USA/0501/00003	44.6	41.3	3.26	-
USA/0501/00005	53.4	30.0	23.4	-
USA/0501/00014	48.8	46.2	2.59	-
Mean ± SD		37.2 ± 7.89	8.10 ± 10.2	-

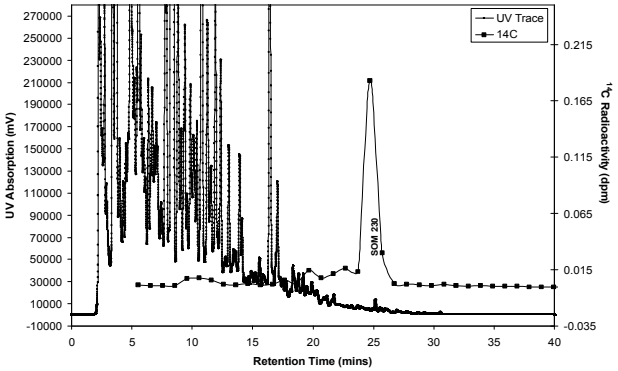
[a] Determined by AMS. Urine (0-144 hours) and feces samples (0-168 hours) were pooled (separately to encompass ≥90% of the total excretion for each subject).

Representative metabolite profile in urine (0-144 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00002

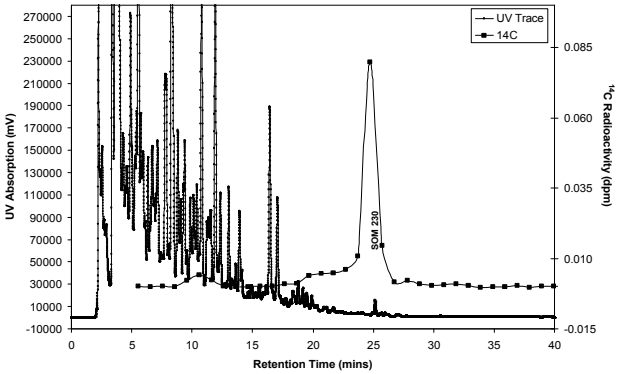


Subject USA/0501/00003

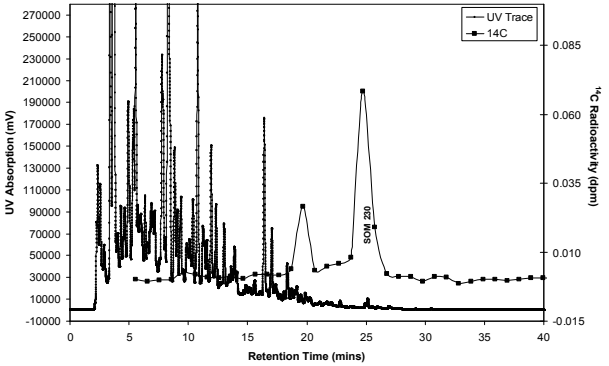


Representative metabolite profile in urine (0-144 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00005

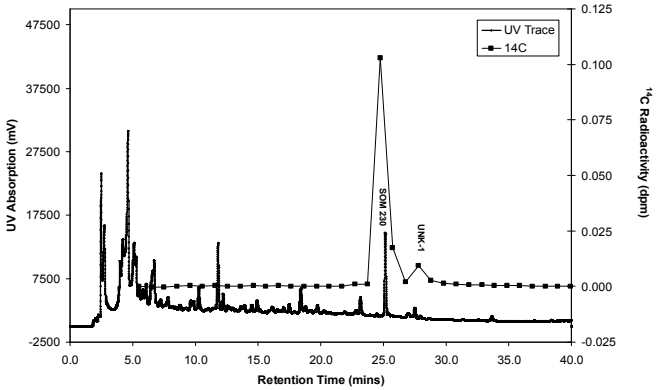


Subject USA/0501/00014

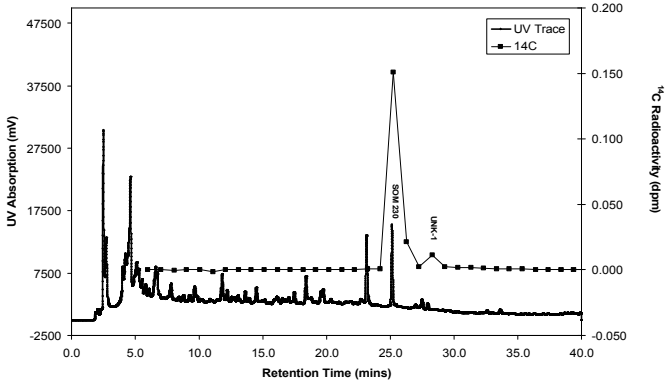


Representative metabolite profile in feces (0-168 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00002

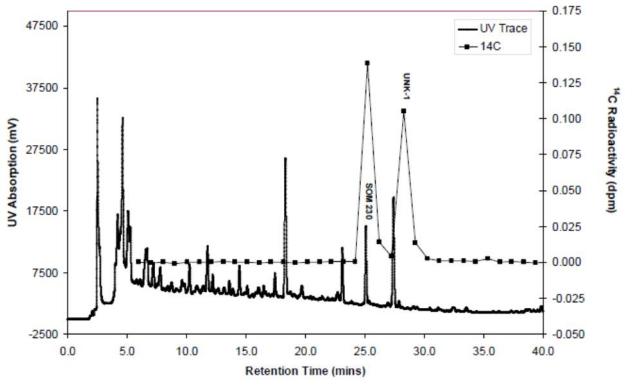


Subject USA/0501/00003

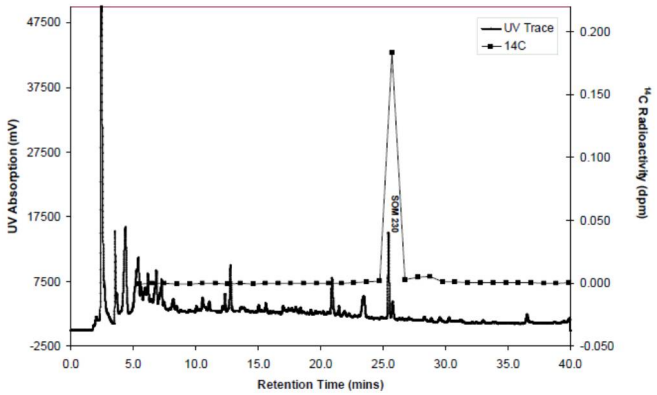


Representative metabolite profile in feces (0-168 hours pooled sample) by subject following a single s.c. dose of 600 micrograms [^{14}C]pasireotide

Subject USA/0501/00005



Subject USA/0501/00014



2.6.5.10A 薬物動態試験：*in vitro* における代謝（ラット，サル及びヒト）

Test article: [^{14}C]SOM230

Study Title: *In vitro* biotransformation of SOM230: Species comparison using liver fractions from rat, cynomolgus monkey and man	
Study Number:	[DMPK(CH) R01-389]
GLP compliance:	not required
Location in CTD:	4.2.2.4-3
Study System:	Incubations with liver microsomes or hepatocytes (only rat) to investigate the patterns and the nature of metabolites. In addition, human kidney microsomes were used. Tissue source: Liver microsomes of rat, cynomolgus monkey and man, human kidney liver microsomes and cryopreserved rat hepatocytes were purchased from In Vitro Technologies (IVT).
Initial Concentration(s):	1.0 µmol/L [^{14}C]SOM230
Radionuclide:	[^{14}C]
Specific activity / purity:	11.78 MBq/mg, radiochemical purity ca 90%
Analyte/Assay:	Total radioactivity was measured by liquid scintillation counting. Unchanged [^{14}C]SOM230 and patterns of metabolites were determined by HPLC with on-line radiodetection.

		Radioactivity in HPLC peak (% of total)			
Incubation	Incubation time (min)	On pellet	P1 (21.4 min)	P2 (24.9 min)	SOM230 (27.1 min)
Rat liver microsomes:	0	0.4	4.2	nd	88.7
	10	1.1	4.2	nd	84.1
	20	1.3	4.1	nd	84.9
	30	1.4	4.3	nd	84.6
	60	1.9	4.3	nd	85.4
	120	2.1	3.7	nd	86.5
	120 (control 1)	2.5	4.1	nd	83.2
	120 (control 2)	1.9	3.2	nd	87.0

nd = not detected

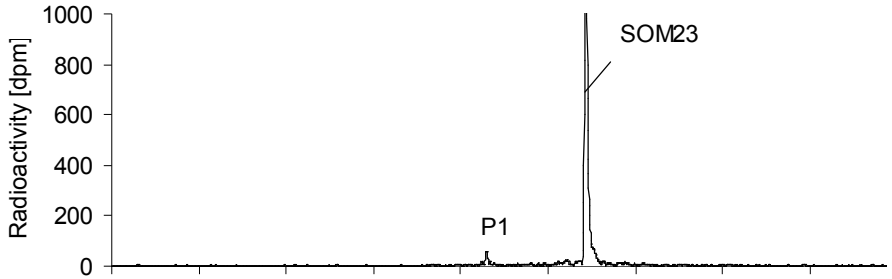
		Radioactivity in HPLC peak (% of total)			
Incubation	Incubation time (min)	On pellet	P1 (21.4 min)	P2 (24.9 min)	SOM230 (27.1 min)
Monkey liver microsomes:	0	1.1	3.1	nd	89.6
	30	1.5	3.6	nd	87.3
	60	1.7	3.8	1.9	85.2
	120	3.6	3.9	4.0	81.1
	120 (control 1)	1.0	3.8	nd	89.8
Human liver microsomes:	0	0.8	4.1	nd	87.3
	30	1.8	3.5	nd	84.6
	60	2.5	-	sample lost	-
	120	1.9	4.3	nd	86.7
	120 (control 1)	1.4	3.4	nd	91.8
Human kidney microsomes:	0	0.9	4.3	nd	90.5
	30	1.2	3.6	nd	90.0
	60	1.3	3.4	nd	92.5
	120	2.1	3.3	nd	90.5
	120 (control 1)	1.7	4.7	nd	89.4
Rat hepatocytes	0	2.4	3.3	nd	87.6
	15	3.1	4.0	nd	89.2
	30	2.4	6.3	nd	88.2
	60	4.1	3.5	nd	87.4
	120	6.0	4.7	nd	82.9
	240	8.6	5.9	nd	77.1
	240 (stability control)	1.5	4.7	nd	86.5

Control 1 - control incubation (120 min) without NADPH added.

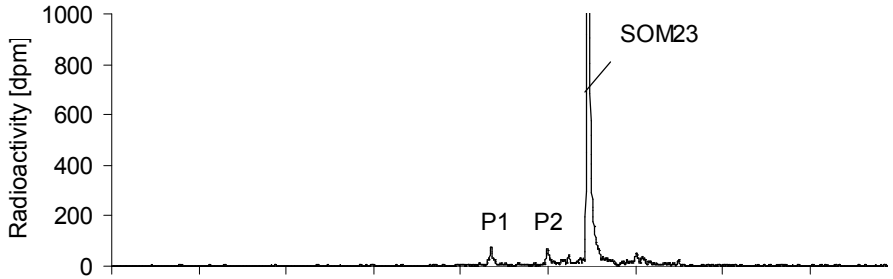
Control 2 – control incubation (120 min) with heat inactivated microsomes.

Stability control – control incubation (240 min) of 1 µmol/L [^{14}C]SOM230 in incubation medium only.

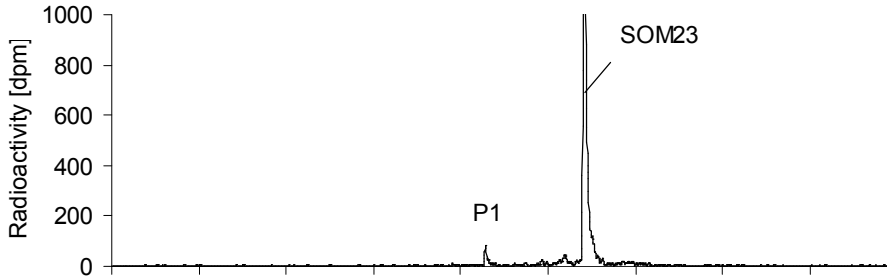
Rat liver microsomes (0.2 mg/mL), 120 min incubation:



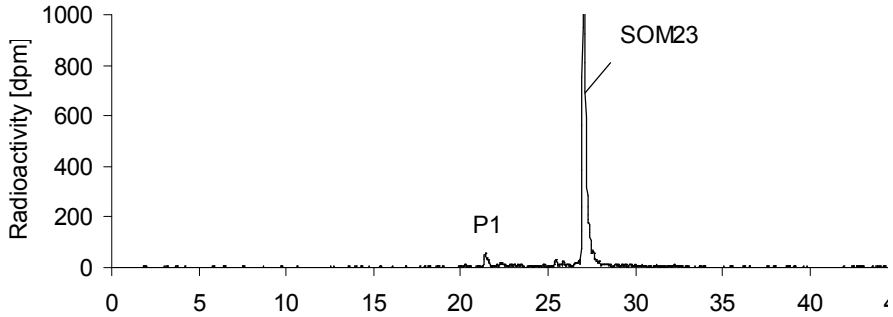
Cynomolgus monkey liver microsomes (0.5 mg/mL), 120 min incubation:



Human liver microsomes (0.5 mg/mL), 120 min incubation:

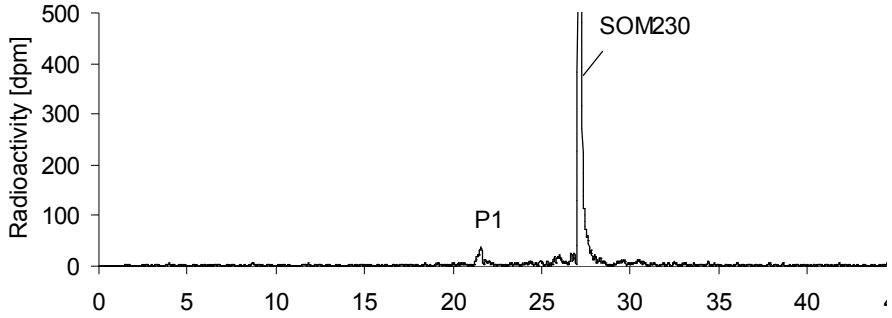


Human liver microsomes (0.5 mg/mL), zero time incubation:

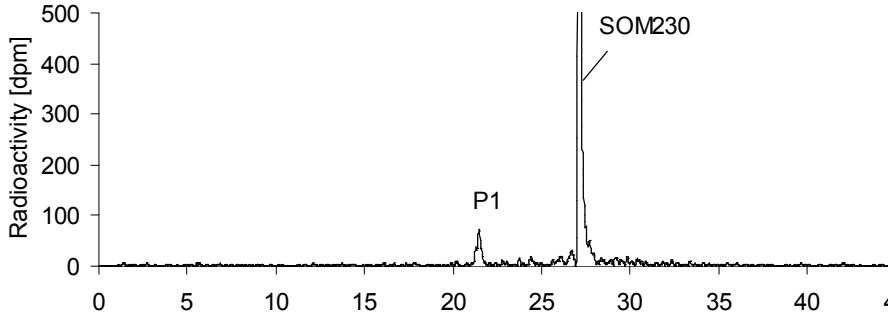


Patterns of metabolites by HPLC analysis of supernatant from 120 min incubations of 1.0 µmol/L [^{14}C]SOM230 with liver microsomes of rat (0.2 mg/mL), cynomolgus monkey (0.5 mg/mL), and man (0.5 mg/mL).

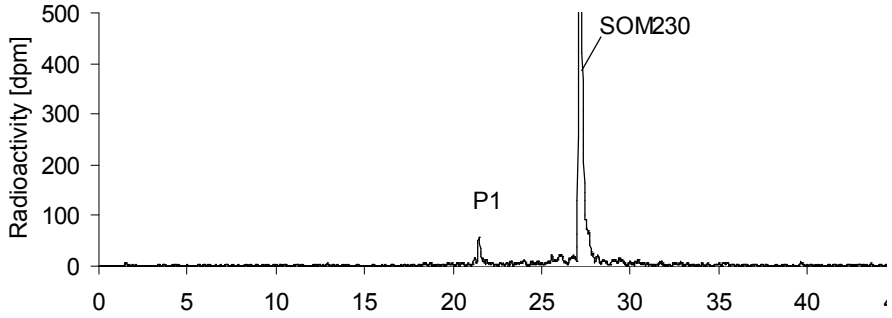
Rat hepatocytes, 0 hours incubation:



Rat hepatocytes, 4 hours incubation:



Control 4 hours incubation in medium:



Patterns of metabolites by HPLC analysis of supernatant from incubations of 1.0 µmol/L [^{14}C]SOM230 using cryopreserved hepatocytes of rat. In addition, HPLC analysis of a control incubation of 1.0 µmol/L [^{14}C]SOM230 performed 4 hours in incubation medium.

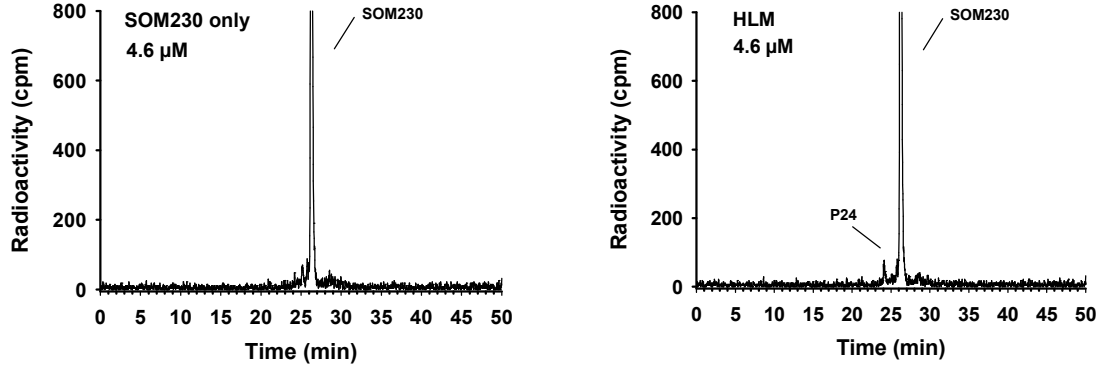
2.6.5.10B　薬物動態試験：*in vitro* における代謝（ヒト肝ミクロソーム）

Test article: [^{14}C]SOM230

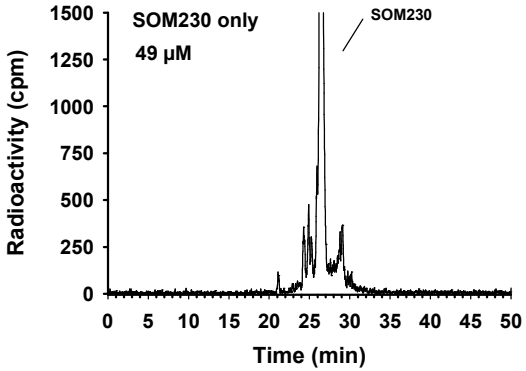
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism	
Study Number:	[DMPK R0400850]
GLP compliance:	not required
Location in CTD:	5.3.2.2-4
Study System:	Pooled human liver microsomes (n = 22 donors, 13 male and 9 female) were purchased from Gentest, BD Biosciences Co. (Woburn, Massachusetts). Microsomal preparations from baculovirus-infected insect cells expressing recombinant human cytochrome P450 [co-expressed with P450 oxidoreductase (OR)]: CYP1A1, CYP1A2, CYP1B1, CYP2C18, CYP2D6, CYP3A5, or CYP4A11, and recombinant human cytochrome P450s [co-expressed with P450 oxidoreductase and cytochrome b_5 (cytb_5)]: CYP2A6, CYP2B6, CYP2C8, CYP2C9 (Arg_{144},Ile_{359}), CYP2C19, CYP2E1, CYP2J2, or CYP3A4, as well as control P450 microsomes were purchased from Gentest, BD Biosciences.
Radionuclide:	^{14}C (167.59 mCi·mmol^{-1}, 94.2% radiochemical purity)
Analyte/Assay:	Radioactivity / HPLC with radioactivity detection Metabolite structure elucidation by LC-MS/MS

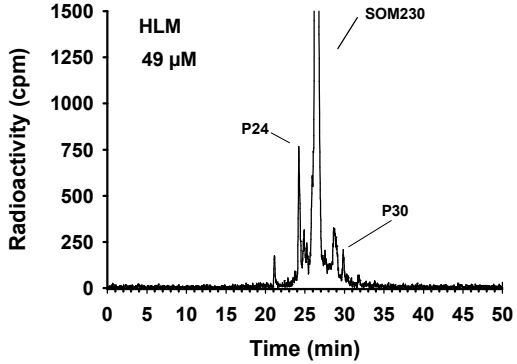
Metabolism of [^{14}C]Pasireotide in human liver microsomes

[^{14}C]SOM230 4.6 µM or 49 µM was incubated with or without human liver microsomes (1 mg protein·mL^{-1}) in the presence of NADPH. The reactions were incubated at 37°C for 30 min, quenched with acetonitrile, and the products were analyzed by HPLC.



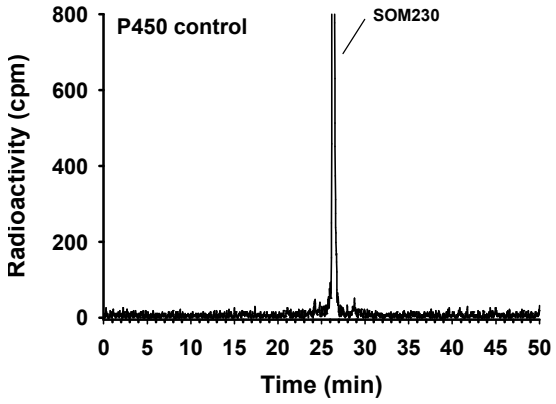
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism

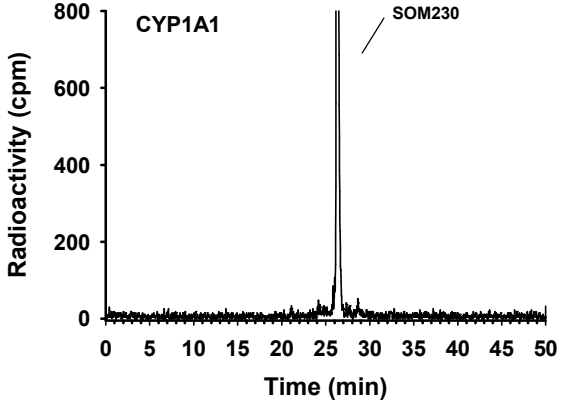


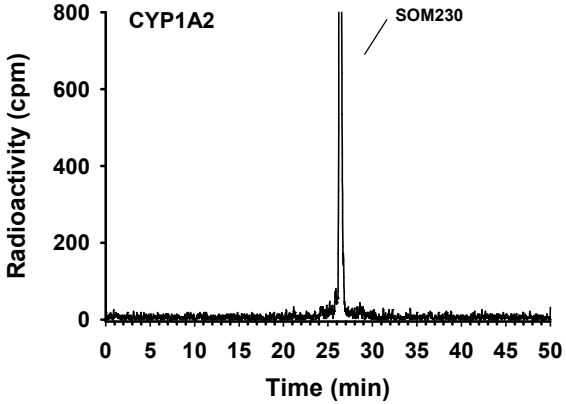


Metabolism of [^{14}C]SOM230 by human CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, and CYP4A11

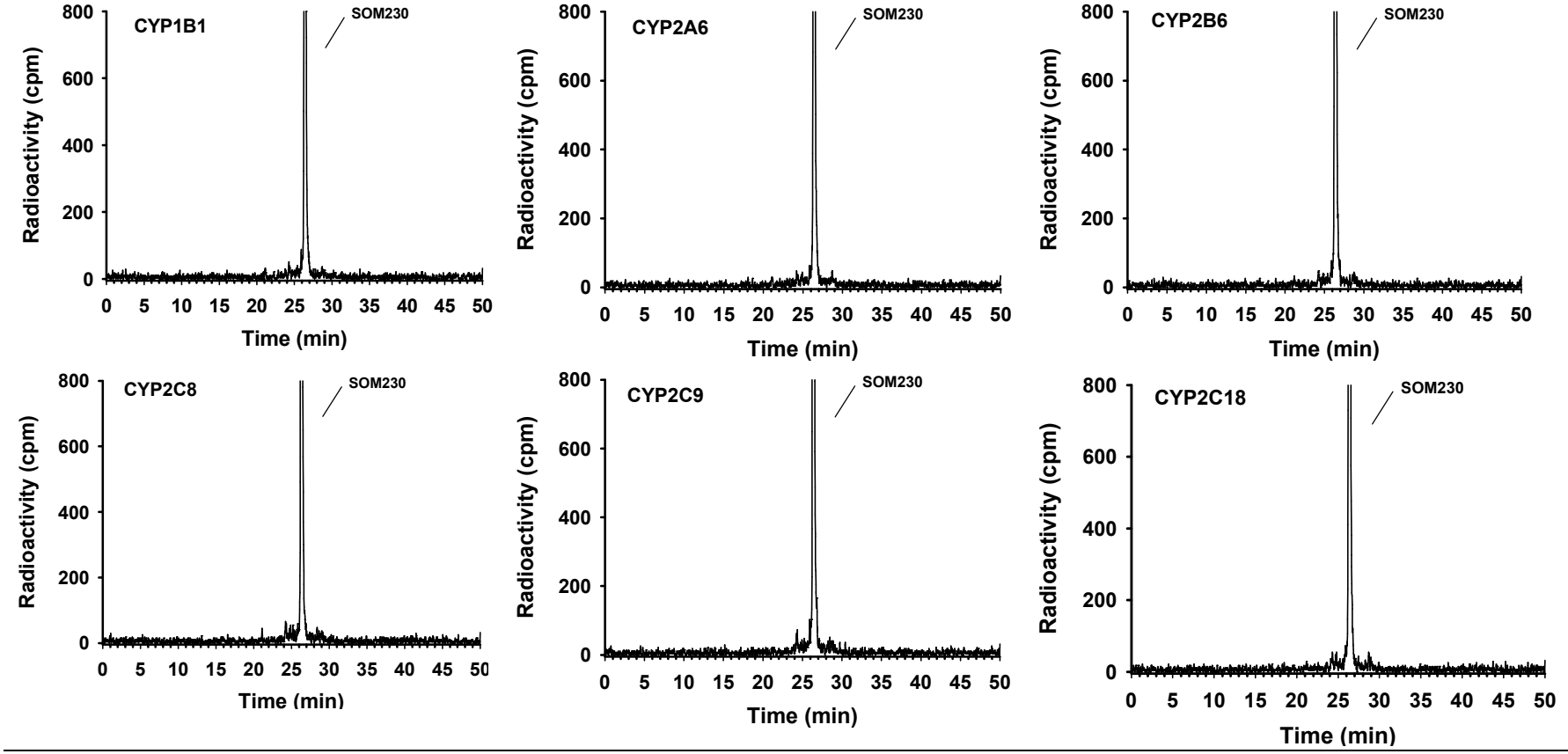
[^{14}C]SOM230 (4.6 µM) was incubated with human recombinant cytochrome P450 enzymes (100 pmol P450·mL^{-1}) or control microsomes in the presence of NADPH. The reactions were incubated at 37°C for 30 min, quenched with acetonitrile, and the products were analyzed by HPLC.



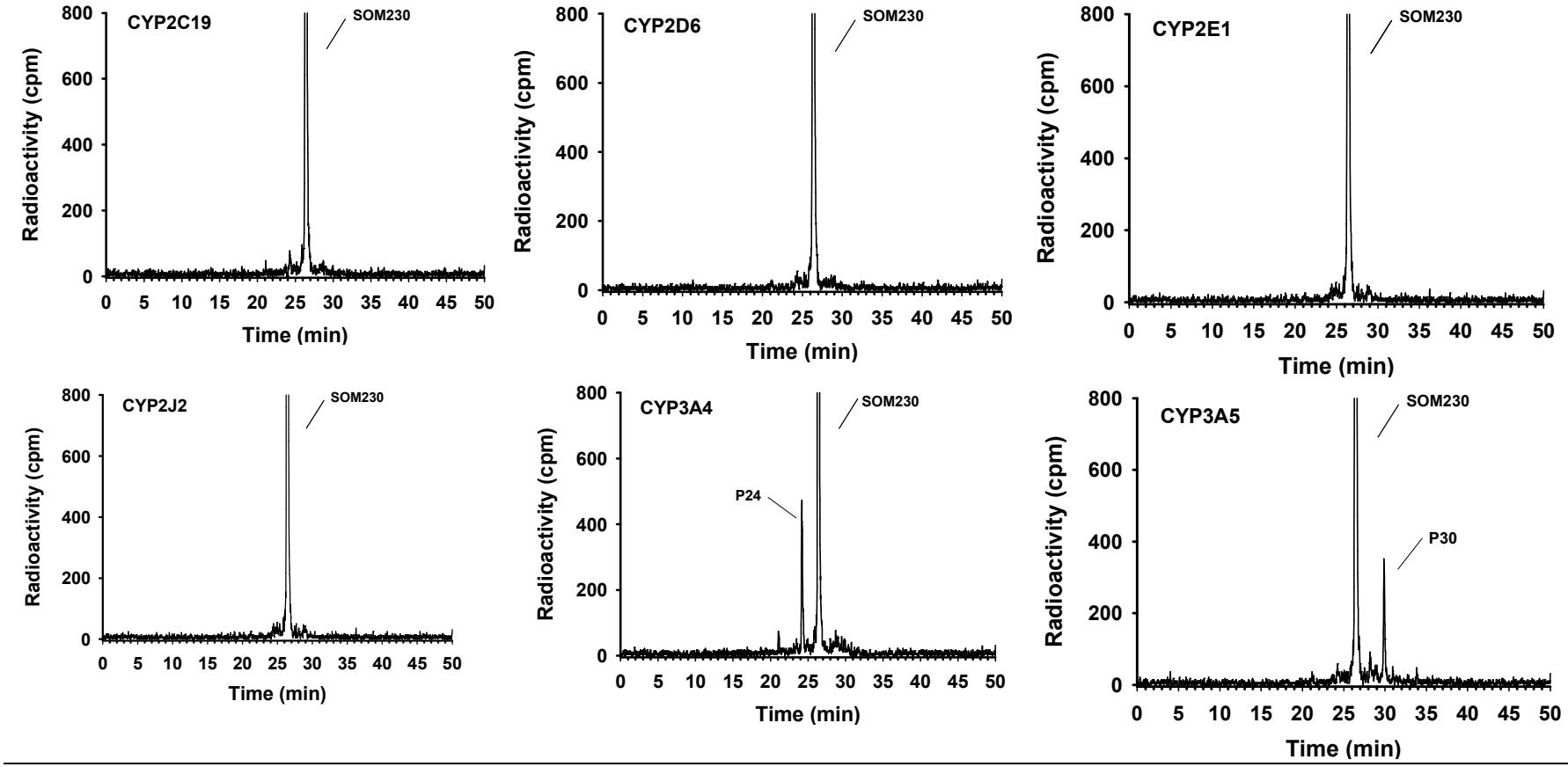




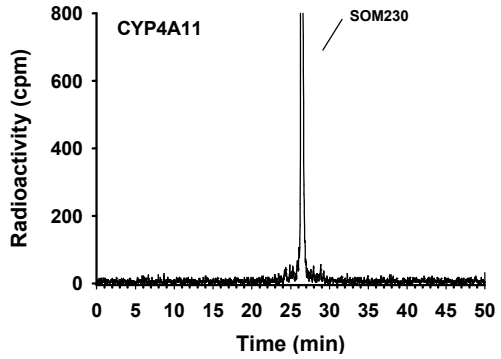
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism



Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism

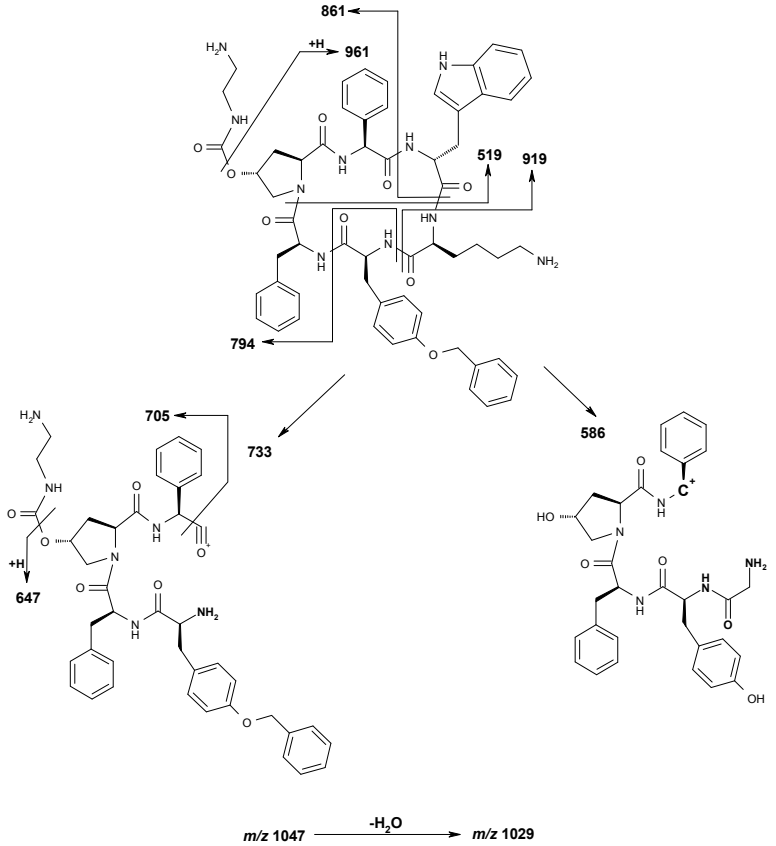


Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism



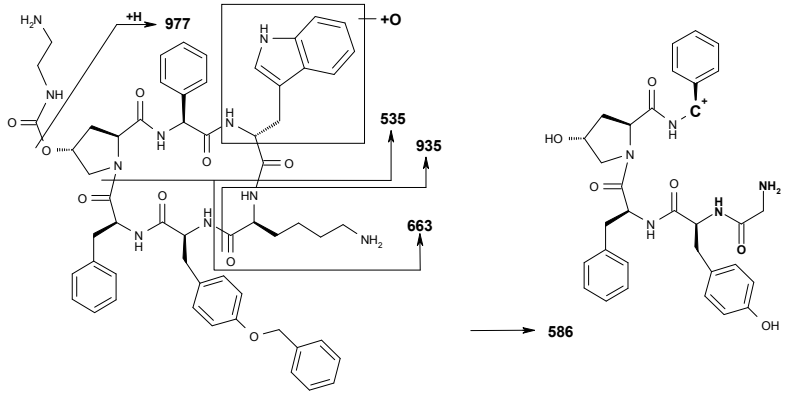
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism

Positive ion mass spectrum and proposed fragmentation of SOM230 (MH+ 1047) from an incubation with CYP3A4



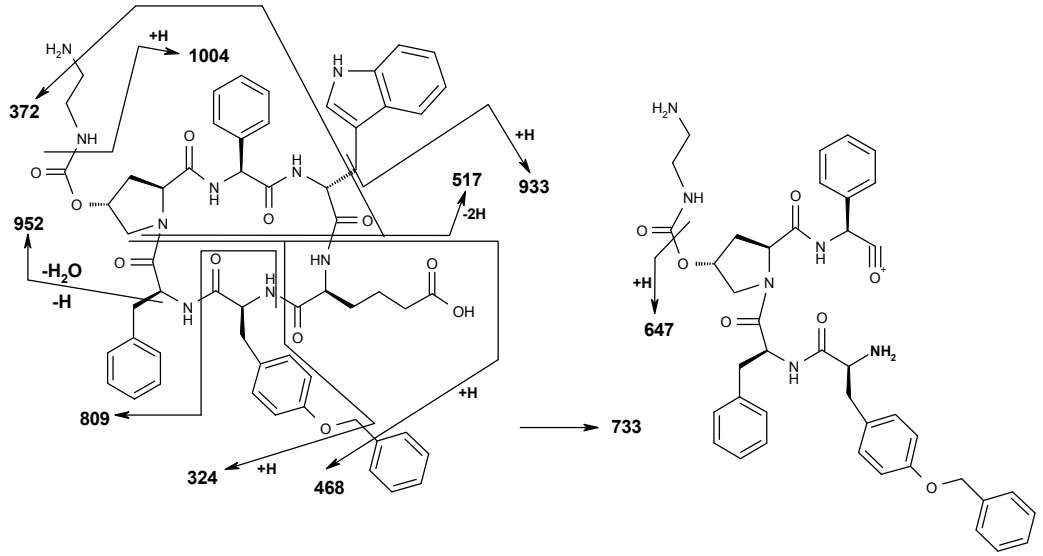
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism

Positive ion mass spectrum and proposed fragmentation of SOM230 metabolite, P24 (MH+ 1063) from an incubation with CYP3A4



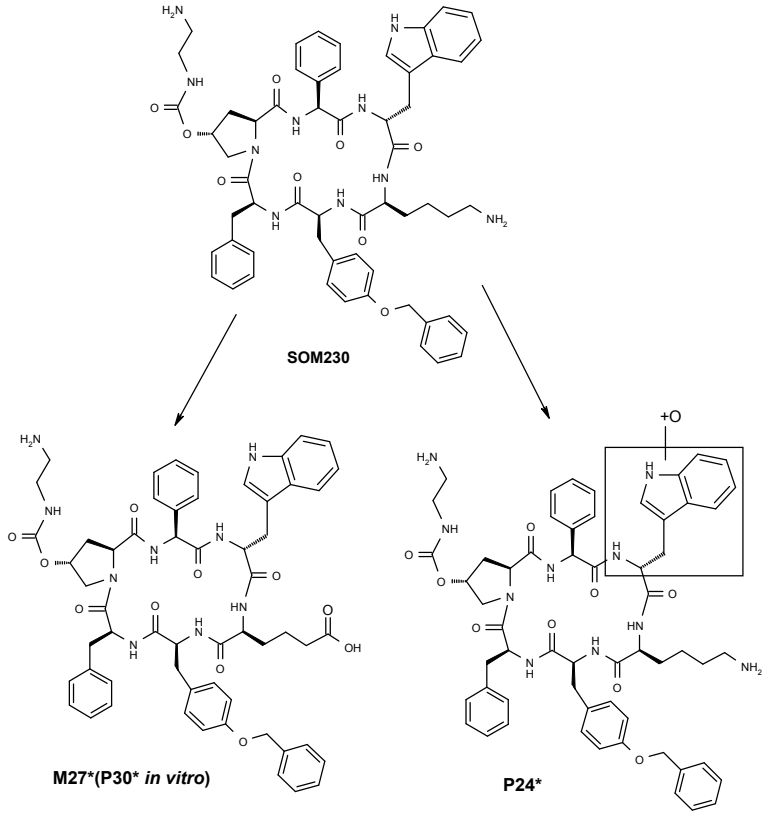
Study Title: [^{14}C]SOM230: Metabolic profile in human liver microsomes and identification of cytochrome P450s involved in the metabolism

Positive ion mass spectrum and proposed fragmentation of SOM230 metabolite, P30 (MH+ 1062) from an incubation with CYP3A5



Conclusions: The major metabolic pathways of [^{14}C]SOM230 in human liver microsomes were formation of metabolites P24 (mono oxidation on the phenylglycine moiety of SOM230) and P30 formation (deamination on the lysine moiety of SOM230). [^{14}C]SOM230 was metabolized mainly by CYP3A4 (formation of P24) and CYP3A5 (formation of P30). Low turnover of SOM230 was observed in human liver microsomes and the linearity observed in the activity of the two concentrations tested suggested that the Km for the metabolism was high (~ ≥ 49 µM). There is a potential that inhibitors of CYP3A4/5 may affect the hepatic oxidative clearance of SOM230 clinically, but the magnitude of interactions would be dependent upon the contributions of other SOM230 clearance pathways in humans.

2.6.5.11 薬物動態試験：推定代謝経路



M27* was found in monkey plasma (<3% of total AUC) [2.6.5.9D-DMPK R0900554]

P30* was trace amount in human microsomes [2.6.5.10B-DMPK R0400850] but not found in human plasma *in vivo* [2.6.5.9E-CSOM230B2112]

P24* was trace amount in human microsomes [2.6.5.10B-DMPK R0400850] but not found in human plasma *in vivo* [2.6.5.9E-CSOM230B2112]

2.6.5.12A 薬物動態試験：薬物代謝酵素の誘導／阻害（ヒト肝細胞による代謝酵素及びトランスポーターの誘導）

Test article: SOM230

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes	
Study Number:	[DMPK R0800722]
GLP compliance:	not required
Location in CTD:	5.3.2.2-5
Study System:	Primary human hepatocytes
Analyte/Assay:	Induction of mRNA, relative to the vehicle control, was determined by real-time PCR and evaluation of changes in enzyme activities were assessed after the induction period by quantitative LC-MS/MS analysis of enzyme-selective probe substrate metabolism

SOM230 was examined for its potential to induce cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferase (UGT) UGT1A1 mRNA and activities, as well as mRNAs of P-glycoprotein (P-gp, ABCB1) and the multidrug resistance-associated protein-2 (MRP2, ABCC2) transporters in primary human hepatocytes of three individual donors after 48 h of treatment.

Induction of mRNA, relative to the vehicle control, was determined by real-time PCR and evaluation of changes in enzyme activities were assessed after the induction period by quantitative LC-MS/MS analysis of enzyme-selective probe substrate metabolism. Human hepatocytes were treated with SOM230 at a concentration range of 0.005-1 µM. The 1 µM dose was >10-fold above the mean highest serum concentration of SOM230 observed in the clinic at the highest administered dose. Rifampicin (RIF) and phenobarbital (PB) were used as positive controls for induction of the majority of these genes. β-napthoflavone (BNF) was included as positive control for CYP1A and UGT1A1 induction in human hepatocytes.

SOM230 (up to 1 µM) did not induce the mRNA levels or activities of CYP1A2, CYP2B6, CYP2C8, CYP2C19 or CYP3A in all three livers. SOM230 was also not found to be an *in vitro* inducer of CYP1A1, CYP1B1, CYP2J2, P-gp or MRP2 mRNAs. CYP2C9 mRNA levels were induced 2.81- to 4.97-fold (at 0.005 to 0.1 µM) in only one liver, but not the other two livers. However, SOM230 did not induce CYP2C9 activity in any of the livers. UGT1A1 activity was induced 2.15-fold (0.1 µM) in one liver, but not in the other two livers. UGT1A1 mRNA levels were not induced by SOM230. The criteria for classification as a non-inducer were that activity or mRNA levels increased less than two-fold with respect to the vehicle control and/or were less than 40% of the maximal positive control responses.

Taken together, it is unlikely that SOM230 would cause relevant increases in the clearance of co-administered compounds by an induction mechanism.

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 1) 72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP1A1	CYP1A2	CYP1B1	CYP2B6	CYP2C8	CYP2C9	CYP2C19
DMSO (0.1%) Control	1.00 (0.702-1.43)[b]	1.00 (0.703-1.42)	1.00 (0.843-1.19)	1.00 (0.669-1.5)	1.00 (0.701-1.43)	1.00 (0.716-1.40)	1.00 (0.711-1.41)
SOM230, 0.005 μM	0.680 (0.569-0.813)	1.27 (1.04-1.55)	2.64 (2.12-3.29)	1.34 (1.16-1.54)	2.27 (1.77-2.9)	2.81 (2.33-3.39)	1.93 (1.65-2.26)
SOM230, 0.01 μM	0.720 (0.491-1.06)	1.34 (0.918-1.96)	1.66 (1.4-1.95)	2.42 (1.49-3.92)	2.91 (1.92-4.41)	3.94 (2.69-5.75)	3.04 (2.06-4.47)
SOM230, 0.1 μM	0.837 (0.562-1.25)	1.54 (1.1-2.17)	1.91 (1.54-2.37)	1.82 (1.27-2.59)	3.05 (2.13-4.37)	4.97 (3.51-7.06)	3.35 (2.36-4.76)
SOM230, 1 μM	0.536 (0.462-0.623)	1.30 (1.12-1.49)	8.37 (5.89-11.9)	1.17 (0.939-1.46)	2.35 (1.96-2.81)	2.77 (2.29-3.35)	2.39 (2.00-2.85)
RIF[c], 0.01 μM	1.47 (0.541-3.98)	2.65 (0.996-7.06)	2.87 (2.35-3.51)	2.41 (0.848-6.86)	5.04 (1.83-13.9)	3.75 (2.74-5.15)	5.10 (1.91-13.6)
RIF, 0.1 μM	2.00 (1.27-3.13)	3.55 (2.37-5.33)	96.2 (83.5-111)	4.99 (3.09-8.04)	12.0 (7.81-18.4)	8.86 (5.97-13.2)	4.95 (3.29-7.46)
RIF, 1 μM	1.93 (1.3-2.88)	2.02 (1.41-2.89)	54.8 (46.5-64.5)	17.3 (11.4-26.3)	23.5 (16-34.5)	10.5 (7.32-14.9)	8.66 (6.07-12.4)
RIF, 10 μM	2.95 (2.26-3.86)	2.01 (1.57-2.57)	139 (99.6-194)	21.6 (15.9-29.1)	21.6 (16.8-27.8)	10.5 (8.20-13.3)	10.7 (8.34-13.8)
PB[d], 1000 μM	2.05 (1.75-2.40)	1.77 (1.66-1.88)	123 (105-145)	28.3 (23.1-34.6)	14.1 (12.1-16.4)	6.61 (6.26-6.98)	6.94 (6.22-7.74)
BNF[e], 10 μM	9.26 (6.74-12.7)	18.1 (13.8-23.8)	2.94 (2.26-3.82)	3.09 (2.2-4.34)	1.21 (0.925-1.58)	1.71 (1.32-2.22)	1.49 (1.15-1.94)

[a] Calculated from quadruplicate real-time PCR reactions

[b] Values in parenthesis are the range of fold difference

[c] RIF, rifampicin

[d] PB, phenobarbital

[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 1)

72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP2J2	CYP3A4	CYP3A5	UGT1A1	P-gp (MDR1)	MRP2
DMSO (0.1%) Control	1.00 (0.828-1.21)[b]	1.00 (0.756-1.32)	1.00 (0.676-1.48)	1.00 (0.812-1.23)	1.00 (0.815-1.23)	1.00 (0.836-1.20)
SOM230, 0.005 μM	1.12 (0.943-1.32)	6.25 (4.88-8.00)	2.91 (1.91-4.44)	1.05 (0.858-1.28)	1.57 (1.35-1.83)	1.31 (1.11-1.54)
SOM230, 0.01 μM	1.73 (1.50-1.99)	7.88 (5.88-10.6)	2.89 (2.05-4.08)	1.13 (1-1.28)	1.77 (1.52-2.05)	1.58 (1.44-1.74)
SOM230, 0.1 μM	1.23 (1.10-1.38)	7.11 (5.26-9.61)	3.29 (2.39-4.52)	1.20 (1.06-1.36)	1.51 (1.33-1.71)	1.39 (1.2-1.61)
SOM230, 1 μM	1.39 (1.14-1.7)	5.37 (4.30-6.72)	3.01 (2.21-4.11)	1.12 (0.92-1.37)	1.56 (1.26-1.94)	1.47 (1.18-1.84)
RIF[c], 0.01 μM	1.22 (1.06-1.41)	10.7 (9.62-11.9)	3.28 (2.96-3.64)	0.933 (0.823-1.06)	1.23 (1.02-1.49)	1.47 (1.3-1.66)
RIF, 0.1 μM	1.57 (1.33-1.86)	90.9 (75.2-110)	6.46 (5.52-7.56)	1.94 (1.65-2.27)	1.83 (1.55-2.15)	2.07 (1.78-2.42)
RIF, 1 μM	2.01 (1.75-2.31)	313 (230-427)	6.68 (5.77-7.73)	4.19 (3.62-4.84)	3.09 (2.46-3.89)	2.14 (1.90-2.40)
RIF, 10 μM	0.995 (0.851-1.16)	178 (152-208)	5.16 (3.45-7.70)	4.12 (3.53-4.81)	3.31 (2.88-3.8)	2.41 (2.09-2.78)
PB[d], 1000 μM	1.53 (1.22-1.92)	189 (153-232)	9.41 (8.05-11.0)	4.93 (4.49-5.40)	3.13 (2.77-3.54)	2.95 (2.62-3.33)
BNF[e], 10 μM	1.60 (1.34-1.92)	4.65 (3.65-5.93)	3.54 (2.78-4.52)	2.85 (2.42-3.35)	1.21 (1.01-1.46)	1.35 (1.15-1.60)

[a] Calculated from quadruplicate real-time PCR reactions
[b] Values in parenthesis are the range of fold difference
[c] RIF, rifampicin
[d] PB, phenobarbital
[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 2)

72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP1A1	CYP1A2	CYP1B1	CYP2B6	CYP2C8	CYP2C9	CYP2C19
DMSO (0.1%) Control	1.00 (0.942-1.06)[b]	1.00 (0.933-1.07)	1.00 (0.815-1.23)	1.00 (0.921-1.09)	1.00 (0.817-1.22)	1.00 (0.933-1.07)	1.00 (0.925-1.08)
SOM230, 0.005 μM	1.17 (1.01-1.34)	1.11 (1.02-1.2)	1.98 (1.69-2.32)	0.759 (0.611-0.943)	0.877 (0.808-0.951)	1.12 (1.04-1.21)	1.08 (1-1.17)
SOM230, 0.01 μM	0.897 (0.814-0.988)	1.00 (0.972-1.03)	1.91 (1.73-2.12)	0.883 (0.749-1.04)	0.805 (0.732-0.885)	1.05 (1.02-1.09)	1.00 (0.961-1.05)
SOM230, 0.1 μM	0.925 (0.712-1.20)	0.847 (0.803-0.893)	2.08 (1.77-2.43)	0.853 (0.795-0.915)	0.796 (0.677-0.937)	0.981 (0.906-1.06)	0.935 (0.88-0.992)
SOM230, 1 μM	2.64 (2.45-2.84)	1.57 (1.43-1.72)	3.85 (3.07-4.82)	0.659 (0.584-0.744)	1.06 (0.919-1.22)	1.06 (0.932-1.2)	1.01 (0.961-1.06)
RIF[c], 0.01 μM	1.01 (0.915-1.12)	0.855 (0.776-0.942)	2.89 (2.44-3.43)	0.583 (0.546-0.623)	0.652 (0.588-0.724)	0.986 (0.947-1.03)	0.864 (0.826-0.903)
RIF, 0.1 μM	2.09 (1.65-2.65)	2.42 (2.14-2.74)	49.1 (34.5-70)	1.05 (0.872-1.25)	2.33 (1.7-3.2)	1.19 (1.1-1.3)	0.979 (0.887-1.08)
RIF, 1 μM	1.82 (1.54-2.16)	1.61 (1.4-1.86)	41.8 (35.4-49.4)	2.04 (1.72-2.42)	4.82 (4.36-5.33)	1.62 (1.45-1.81)	1.09 (0.983-1.21)
RIF, 10 μM	1.24 (1.09-1.40)	0.894 (0.798-1.00)	69.6 (61.0-79.4)	4.27 (3.54-5.15)	5.14 (4.54-5.81)	1.46 (1.3-1.64)	1.00 (0.882-1.14)
PB[d], 1000 μM	2.10 (1.64-2.68)	1.87 (1.49-2.35)	86.2 (73.6-101)	6.12 (4.88-7.69)	8.86 (6.96-11.3)	1.64 (1.26-2.12)	1.06 (0.843-1.33)
BNF[e], 10 μM	24.8 (20.1-30.6)	18.1 (16-20.5)	1.96 (1.72-2.23)	1.79 (1.60-1.99)	0.269 (0.244-0.297)	0.534 (0.491-0.581)	0.450 (0.415-0.487)

[a] Calculated from quadruplicate real-time PCR reactions

[b] Values in parenthesis are the range of fold difference

[c] RIF, rifampicin

[d] PB, phenobarbital

[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 2)

72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP2J2	CYP3A4	CYP3A5	UGT1A1	P-gp (MDR1)	MRP2
DMSO (0.1%) Control	1.00 (0.859-1.16)[b]	1.00 (0.829-1.21)	1.00 (0.882-1.13)	1.00 (0.89-1.12)	1.00 (0.873-1.15)	1.00 (0.757-1.32)
SOM230, 0.005 μM	0.272 (0.253-0.291)	0.202 (0.177-0.229)	0.286 (0.246-0.331)	0.476 (0.428-0.528)	0.53 (0.507-0.554)	0.651 (0.584-0.727)
SOM230, 0.01 μM	2.13 (1.71-2.64)	0.835 (0.753-0.926)	1.17 (0.977-1.41)	0.835 (0.75-0.928)	0.732 (0.701-0.764)	0.681 (0.632-0.733)
SOM230, 0.1 μM	1.29 (1.14-1.46)	0.725 (0.611-0.861)	0.69 (0.532-0.895)	0.687 (0.573-0.824)	0.594 (0.536-0.659)	0.653 (0.57-0.749)
SOM230, 1 μM	0.73 (0.536-0.995)	0.262 (0.233-0.294)	0.554 (0.496-0.619)	0.548 (0.494-0.608)	0.526 (0.501-0.552)	0.57 (0.54-0.603)
RIF[c], 0.01 μM	0.648 (0.499-0.842)	0.28 (0.233-0.336)	0.401 (0.328-0.49)	0.601 (0.527-0.685)	0.559 (0.506-0.618)	0.688 (0.609-0.777)
RIF, 0.1 μM	0.78 (0.561-1.08)	0.943 (0.856-1.04)	0.799 (0.651-0.981)	0.56 (0.53-0.592)	0.496 (0.467-0.527)	0.622 (0.584-0.663)
RIF, 1 μM	0.982 (0.853-1.13)	5.34 (4.51-6.33)	0.872 (0.721-1.05)	0.807 (0.715-0.911)	0.706 (0.641-0.777)	0.782 (0.74-0.827)
RIF, 10 μM	0.66 (0.587-0.741)	7.54 (5.85-9.72)	0.913 (0.795-1.05)	0.971 (0.868-1.09)	0.826 (0.741-0.921)	0.917 (0.83-1.01)
PB[d], 1000 μM	0.899 (0.785-1.03)	11.5 (10.6-12.6)	1.27 (1.15-1.41)	1.19 (1.14-1.25)	0.893 (0.858-0.929)	1.06 (0.981-1.15)
BNF[e], 10 μM	0.474 (0.413-0.543)	0.0584 (0.052-0.0655)	0.368 (0.295-0.459)	1.28 (1.17-1.40)	0.374 (0.349-0.401)	0.715 (0.679-0.753)

[a] Calculated from quadruplicate real-time PCR reactions
[b] Values in parenthesis are the range of fold difference
[c] RIF, rifampicin
[d] PB, phenobarbital
[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 3)

72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP1A1	CYP1A2	CYP1B1	CYP2B6	CYP2C8	CYP2C9	CYP2C19
DMSO (0.1%) Control	1.00 (0.933-1.07)[b]	1.00 (0.941-1.06)	1.00 (0.844-1.19)	1.00 (0.899-1.11)	1.00 (0.827-1.21)	1.00 (0.877-1.14)	1.00 (0.910-1.10)
SOM230, 0.005 μM	1.35 (1.19-1.52)	0.868 (0.772-0.977)	3.65 (3.25-4.11)	1.16 (0.917-1.46)	0.848 (0.764-0.940)	0.948 (0.788-1.14)	1.09 (0.977-1.22)
SOM230, 0.01 μM	1.72 (1.5-1.97)	1.08 (0.893-1.30)	4.15 (3.5-4.92)	1.17 (0.904-1.51)	0.880 (0.780-0.994)	1.03 (0.936-1.12)	1.20 (1.07-1.34)
SOM230, 0.1 μM	1.02 (0.86-1.21)	0.807 (0.705-0.925)	3.97 (3.2-4.92)	1.09 (0.876-1.35)	0.664 (0.526-0.838)	0.846 (0.746-0.96)	1.10 (1.01-1.20)
SOM230, 1 μM	1.14 (0.978-1.33)	0.752 (0.687-0.823)	4.32 (3.34-5.58)	0.883 (0.772-1.01)	0.624 (0.565-0.689)	1.49 (1.41-1.58)	1.24 (1.07-1.43)
RIF[c], 0.01 μM	0.833 (0.668-1.04)	0.912 (0.82-1.02)	6.57 (5.58-7.74)	0.664 (0.576-0.765)	1.02 (0.838-1.24)	1.39 (1.25-1.54)	1.05 (0.938-1.18)
RIF, 0.1 μM	2.46 (1.74-3.47)	1.25 (1.13-1.38)	40.2 (29.3-55.1)	1.61 (1.37-1.89)	1.77 (1.30-2.42)	1.04 (0.964-1.13)	1.04 (0.936-1.15)
RIF, 1 μM	1.72 (1.42-2.09)	0.732 (0.595-0.901)	110 (98.6-123)	6.89 (5.81-8.17)	2.07 (1.46-2.93)	1.48 (1.24-1.75)	1.32 (1.18-1.48)
RIF, 10 μM	1.47 (1.28-1.68)	0.428 (0.343-0.535)	151 (130-175)	10.5 (9.27-11.9)	1.93 (1.66-2.23)	1.62 (1.43-1.82)	1.36 (1.22-1.52)
PB[d], 1000 μM	2.16 (1.77-2.65)	0.847 (0.678-1.06)	173 (146-205)	24.3 (20.5-28.9)	2.94 (2.47-3.51)	2.06 (1.79-2.38)	1.39 (1.21-1.59)
BNF[e], 10 μM	2.80 (2.2-3.56)	0.846 (0.735-0.974)	2.70 (2.14-3.41)	0.771 (0.606-0.981)	0.414 (0.373-0.460)	0.658 (0.611-0.708)	1.54 (1.32-1.79)

[a] Calculated from quadruplicate real-time PCR reactions
[b] Values in parenthesis are the range of fold difference
[c] RIF, rifampicin
[d] PB, phenobarbital
[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

mRNA fold induction (Liver 3)

72h treatment of human hepatocytes

mRNA Fold induction[a]

Treatment	CYP2J2	CYP3A4	CYP3A5	UGT1A1	P-gp (MDR1)	MRP2
DMSO (0.1%) Control	1.00 (0.785-1.27)[b]	1.00 (0.81-1.24)	1.00 (0.817-1.22)	1.00 (0.937-1.07)	1.00 (0.904-1.11)	1.00 (0.896-1.12)
SOM230, 0.005 μM	0.917 (0.782-1.08)	0.674 (0.558-0.815)	1.10 (0.931-1.31)	0.972 (0.895-1.06)	1.10 (1.00-1.20)	1.08 (0.997-1.17)
SOM230, 0.01 μM	0.889 (0.781-1.01)	0.708 (0.591-0.847)	1.07 (0.833-1.37)	1.25 (1.2-1.31)	1.22 (1.16-1.30)	1.14 (1.02-1.27)
SOM230, 0.1 μM	0.872 (0.783-0.971)	0.61 (0.539-0.69)	0.827 (0.693-0.987)	1.07 (0.953-1.21)	1.12 (1.01-1.24)	1.10 (1.00-1.20)
SOM230, 1 μM	0.728 (0.536-0.99)	0.524 (0.415-0.662)	0.736 (0.628-0.863)	1.02 (0.964-1.09)	1.06 (0.955-1.17)	1.13 (1.05-1.21)
RIF[c], 0.01 μM	1.10 (0.914-1.33)	1.00 (0.918-1.10)	0.742 (0.605-0.911)	0.991 (0.847-1.16)	0.94 (0.876-1.01)	1.03 (0.972-1.08)
RIF, 0.1 μM	1.22 (1.09-1.35)	3.92 (3.24-4.76)	0.929 (0.81-1.07)	1.32 (1.22-1.43)	1.14 (1.05-1.24)	1.30 (1.15-1.47)
RIF, 1 μM	1.26 (0.895-1.78)	6.89 (5.58-8.52)	0.722 (0.633-0.825)	1.88 (1.62-2.17)	1.41 (1.30-1.52)	1.69 (1.59-1.8)
RIF, 10 μM	0.825 (0.492-1.38)	6.78 (5.10-9.01)	0.625 (0.552-0.707)	2.23 (2.02-2.47)	1.94 (1.79-2.11)	1.79 (1.66-1.94)
PB[d], 1000 μM	1.54 (1.31-1.80)	9.38 (8.12-10.8)	0.986 (0.926-1.05)	3.19 (2.94-3.45)	1.91 (1.79-2.05)	2.31 (2.18-2.44)
BNF[e], 10 μM	0.657 (0.600-0.72)	0.143 (0.127-0.161)	0.377 (0.319-0.446)	1.02 (0.942-1.10)	0.867 (0.816-0.922)	0.818 (0.756-0.885)

[a] Calculated from quadruplicate real-time PCR reactions
[b] Values in parenthesis are the range of fold difference
[c] RIF, rifampicin
[d] PB, phenobarbital
[e] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

P450 activity fold induction (Liver 1)

48h treatment of human hepatocytes

P450 activity Fold induction

Treatment	CYP1A2[a]	CYP2B6[b]	CYP2C8[c]	CYP2C9[d]	CYP2C19[e]	CYP3A[f]	UGT1A1[g]
DMSO (0.1%) Control	0	0	0	0	0	0	0
SOM230, 0.005 μM	3.15 ± 0.26	-2.62 ± -0.31	-5.72 ± -0.91	-8.17 ± -0.59	-1.09 ± -0.11	-1.53 ± -0.081	22.2 ± 3.4
SOM230, 0.01 μM	4.04 ± 0.34	-3.79 ± -0.45	-3.36 ± -0.54	-3.08 ± -0.23	0.102 ± 0.028	-2.27 ± -0.12	5.60 ± 0.89
SOM230, 0.1 μM	6.50 ± 0.54	-5.55 ± -0.65	-4.51 ± -0.72	-14.8 ± -1.1	-10.3 ± -1.0	-3.95 ± -0.20	13.9 ± 2.2
SOM230, 1 μM	6.69 ± 0.56	-5.33 ± -0.63	-5.45 ± -0.87	-6.17 ± -0.44	-7.85 ± -0.78	-3.56 ± -0.18	5.11 ± 0.80
RIF[h], 0.01 μM	-2.02 ± -0.17	-9.79 ± -1.1	0.448 ± 0.086	2.66 ± 0.20	-2.78 ± -0.28	0.145 ± 0.036	-7.73 ± -1.2
RIF, 0.1 μM	4.34 ± 0.36	7.61 ± 0.89	14.4 ± 2.3	13.1 ± 0.94	20.8 ± 2.1	33.5 ± 1.6	-28.3 ± -4.4
RIF, 1 μM	5.05 ± 0.42	53.5 ± 6.3	61.5 ± 9.8	79.8 ± 5.7	97.1 ± 9.6	100 ± 4.9	-21.2 ± -3.3
RIF, 10 μM	5.13 ± 0.43	58.9 ± 6.9	94.2 ± 15	100 ± 7.2	100 ± 9.9	90.7 ± 4.4	-7.76 ± -1.2
PB[i], 1000 μM	5.50 ± 0.46	100 ± 12	100 ± 16	91.8 ± 6.6	51.2 ± 5.1	99.4 ± 4.9	14.2 ± 2.2
BNF[j], 10 μM	100 ± 8.3	1.46 ± 0.18	-9.33 ± -1.5	10.6 ± 0.76	-5.02 ± -0.50	-6.69 ± -0.33	100 ± 15

[a] Fold increase in phenacetin *O*-deethylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[b] Fold increase in bupropion hydroxylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[c] Fold increase in amodiaquine *N*-desethylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[d] Fold increase in estradiol 3' glucuronidation activity with respect to vehicle control treated cells ± standard deviation.

[e] Fold increase in *S*-mephenytoin 4' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[f] Fold increase in midazolam 1' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[g] Fold increase in estradiol 3' glucuronidation activity with respect to vehicle control treated cells ± standard deviation.

[h] RIF, rifampicin [i] PB, phenobarbital [j] BNF, β-napthoflavone

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

P450 activity fold induction (Liver 2)

48h treatment of human hepatocytes

P450 activity Fold induction

Treatment	CYP1A2[a]	CYP2B6[b]	CYP2C8[c]	CYP2C9[d]	CYP2C19[e]	CYP3A[f]	UGT1A1[g]
DMSO (0.1%) Control	0	0	0	0		0	0
SOM230, 0.005 μM	3.39 ± 0.27	-0.439 ± -0.062	126 ± 122	-0.451 ± -0.11	-	-7.33 ± -1.1	30.9 ± 3.6
SOM230, 0.01 μM	4.52 ± 0.35	12.2 ± 0.99	151 ± 146	19.9 ± 2.5	-	1.54 ± 0.24	76.3 ± 8.8
SOM230, 0.1 μM	5.33 ± 0.41	19.3 ± 1.6	114 ± 110	17.6 ± 2.2	-	0.347 ± 0.079	85.6 ± 9.9
SOM230, 1 μM	8.78 ± 0.68	17.4 ± 1.4	-52.4 ± -51	28.0 ± 3.6	-	2.17 ± 0.34	57.3 ± 6.6
RIF[h], 0.01 μM	0.817 ± 0.073	15.9 ± 1.3	-191 ± -180	27.7 ± 3.5	-	0.442 ± 0.079	59.5 ± 6.9
RIF, 0.1 μM	5.02 ± 0.39	47.2 ± 3.8	-26.7 ± -26	34.3 ± 4.4	-	21.6 ± 3.3	61.0 ± 7.0
RIF, 1 μM	6.32 ± 0.49	51.6 ± 4.2	100 ± 97	55.0 ± 7.0	-	62.3 ± 9.6	60.4 ± 7.0
RIF, 10 μM	6.66 ± 0.52	100 ± 8.0	53.4 ± 52	74.2 ± 9.4	-	99.3 ± 15	48.2 ± 5.6
PB[i], 1000 μM	3.68 ± 0.29	78.5 ± 6.3	-8.89 ± -8.7	100 ± 13	-	100 ± 16	81.9 ± 9.4
BNF[j], 10 μM	100 ± 7.7	22.4 ± 1.8	-75.7 ± -73	54.6 ± 6.9	-	-9.32 ± -1.4	100 ± 12

[a] Fold increase in phenacetin *O*-deethylation activity with respect to vehicle control treated cells ± standard deviation

[b] Fold increase in bupropion hydroxylation activity with respect to vehicle control treated cells ± standard deviation

[c] Fold increase in amodiaquine *N*-desethylation activity with respect to vehicle control treated cells ± standard deviation

[d] Fold increase in diclofenac 4' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[e] Fold increase in *S*-mephenytoin 4' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[f] Fold increase in midazolam 1' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[g] Fold increase in estradiol 3' glucuronidation activity with respect to vehicle control treated cells ± standard deviation.

[h] RIF, rifampicin [i] PB, phenobarbital [j] BNF, β-napthoflavone

-: Data not show; the level of CYP2C19 activity in Liver 2 was too low to quantify, even for the positive control treatments.

Study title: Evaluation of SOM230 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes

P450 activity fold induction (Liver 3)

48h treatment of human hepatocytes

P450 activity Fold induction

Treatment	CYP1A2[a]	CYP2B6[b]	CYP2C8[c]	CYP2C9[d]	CYP2C19[e]	CYP3A[f]	UGT1A1[g]
DMSO (0.1%) Control	0	0	0	0	0	0	0
SOM230, 0.005 μM	1.45 ± 0.17	-9.60 ± -1.1	6.56 ± 0.98	10.4 ± 1.5	1.16 ± 0.11	0.760 ± 0.050	-26.5 ± -8.9
SOM230, 0.01 μM	0.0113 ± 0.025	-1.53 ± -0.18	13.7 ± 2.0	11.5 ± 1.6	-2.94 ± -0.27	0.357 ± 0.025	-56.8 ± -19
SOM230, 0.1 μM	2.92 ± 0.33	3.28 ± 0.39	6.98 ± 1.0	4.00 ± 0.56	-3.31 ± -0.30	-0.103 ± -0.010	-42.0 ± -14
SOM230, 1 μM	-0.565 ± -0.069	12.3 ± 1.5	2.97 ± 0.45	23.0 ± 3.2	0.213 ± 0.022	0.381 ± 0.026	-62.0 ± -21
RIF[h], 0.01 μM	4.36 ± 0.50	42.2 ± 5.0	13.5 ± 2.0	29.8 ± 4.2	7.04 ± 0.64	2.37 ± 0.15	6.20 ± 2.1
RIF, 0.1 μM	3.81 ± 0.44	43.9 ± 5.2	8.81 ± 1.3	19.0 ± 2.6	15.9 ± 1.4	9.69 ± 0.63	-82.3 ± -27
RIF, 1 μM	2.04 ± 0.23	61.0 ± 7.2	69.4 ± 10	72.0 ± 10	41.2 ± 3.7	60.5 ± 3.9	-102 ± -34
RIF, 10 μM	-4.15 ± -0.47	65.6 ± 7.8	83.9 ± 12	100 ± 14	100 ± 9.1	97.9 ± 6.3	-90.9 ± -30
PB[i], 1000 μM	23.2 ± 2.6	100 ± 12	100 ± 15	94.0 ± 13	64.1 ± 5.8	100 ± 6.5	-142 ± -47
BNF[j], 10 μM	100 ± 11	17.6 ± 2.1	0.981 ± 0.16	21.7 ± 3.0	15.8 ± 1.4	-1.95 ± -0.13	100 ± 33

[a] Fold increase in phenacetin *O*-deethylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[b] Fold increase in bupropion hydroxylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[c] Fold increase in amodiaquine *N*-desethylation activity with respect to vehicle control treated cells ± standard deviation of quadruplicate wells

[d] Fold increase in diclofenac 4' hydroxylation activity with respect to vehicle control treated cells ± standard deviation

[e] Fold increase in *S*-mephenytoin 4' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[f] Fold increase in midazolam 1' hydroxylation activity with respect to vehicle control treated cells ± standard deviation.

[g] Fold increase in estradiol 3' glucuronidation activity with respect to vehicle control treated cells ± standard deviation.

[h] RIF, rifampicin [i] PB, phenobarbital [j] BNF, β-napthoflavone

2.6.5.12B 薬物動態試験：薬物代謝酵素の誘導／阻害（CYP に対する阻害）

Test article: SOM230

Study Title(s):	*In vitro* assessment of cytochrome P450 enzyme inhibition by NVP-SOM230
Study Number:	[ADME(US) R0300356]
GLP compliance:	not required
Location in CTD:	5.3.2.2-1
Study System:	Pooled human liver microsomes (source: Xenotech LLC)
Probe substrate/Assay:	Phenacetin, Paclitaxel, Diclofenac, S-mephenytoin, Bufuralol, Chlorzoxazone, Midazolam; LC-MS/MS analysis of specific metabolite formations from probe substrates by cytochrome P450

CYP Enzyme	Probe reaction(s)	Pasireotide IC_{50} value[a] (μM)
1A2	phenacetin *O*-deethylation	ca. 10
2C8	paclitaxel 6α-hydroxylation	ca. 50
2C9	diclofenac 4′-hydroxylation	ca. 5
2C19	*S*-mephenytoin 4′-hydroxylation	ca. 25
2D6	bufuralol 1′-hydroxylation	ca. 5
2E1	chlorzoxazone 6-hydroxylation	> 100
3A4/5	midazolam 1′-hydroxylation	ca. 15
3A4/5	testosterone 6β-hydroxylation	ca. 10

[a] SOM230 concentration producing 50% inhibition of the probe substrate reaction

SOM230 showed low to moderate inhibitory potential for CYP enzymes with IC_{50} values ranging from 5 to >100 μM. Inhibition of CYP2C9 and CYP2D6 activities was associated with the lowest (5 μM) IC_{50} values. However, based on these in vitro inhibition results and anticipated low therapeutic SOM230 plasma concentrations (ca. 15 nM, [Study 2101]), it is concluded that SOM230 is unlikely to inhibit the metabolic clearance of comedications metabolized by CYP enzymes, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5.

2.6.5.12C　薬物動態試験：薬物代謝酵素の誘導／阻害（CYP2B6 に対する阻害）

Test article: SOM230

Study Title(s):	*In vitro* assessment of cytochrome P450 2B6 enzyme inhibition by SOM230
Study Number:	[DMPK R1100187]
GLP compliance:	not required
Location in CTD:	5.3.2.2-2
Study System:	Pooled human liver microsomes (source: BD Biosciences)
Probe substrate/Assay:	Bupropion; LC-MS/MS analysis of specific metabolite formations from probe substrate by cytochrome P450 2B6 (CYP2B6)

CYP Enzyme	Probe reaction(s)	Pasireotide IC_{50} value[a] (μM)
2B6	bupropion hydroxylation	ca. 80

[a] SOM230 concentration producing 50% inhibition of the probe substrate reaction

SOM230 showed low inhibitory potential for CYP2B6 with IC_{50} value ~80 μM. Based on this in vitro inhibition result and anticipated low therapeutic SOM230 plasma concentrations (ca. 15 nM, [Study 2101]), it is concluded that SOM230 is unlikely to inhibit the metabolic clearance of comedications metabolized by CYP2B6.

2.6.5.12D 薬物動態試験：薬物代謝酵素の誘導／阻害（UGT1A1 に対する阻害）

Test article: SOM230

Study Title(s):	In vitro assessment of UGT1A1 enzyme inhibition by SOM230
Study Number:	[DMPK R1100760]
GLP compliance:	not required
Location in CTD:	5.3.2.2-3
Study System:	Pooled human liver microsomes and human Supersomes® UGT1A1 (source: BD Biosciences)
Probe substrate/Assay:	β-estradiol; LC-MS/MS analysis of specific metabolite (estradiol 3-β-glucuronide) formations from probe substrate by UTG1A1

Test compound	Probe reaction	IC_{50} value[a] (µM)	
		HLM[b]	UGT1A1[c]
SOM230	estradiol-3β-glucuronidation	> 100	ca. 59
genistein[d]		ca. 5	ca. 1.2

[a] test compound concentration estimated to inhibition probe substrate reaction by 50%.

[b] human liver microsomes

[c] recombinant UGT1A1

[d] positive inhibitor control

SOM230 showed very weak inhibition using pooled human liver microsomes or recombinant UGT1A1 at test concentrations of up to 100 µM. Based on these *in vitro* inhibition results and anticipated low therapeutic SOM230 plasma concentrations (<0.1 µM), it is concluded that SOM230 is unlikely to inhibit the metabolic clearance of comedications metabolized by UGT1A1 *in vivo*.

2.6.5.13A 薬物動態試験：累積排泄（ラット）

Test article: [^{14}C]SOM230

Study Title		Disposition in the rat after subcutaneous administration of [^{14}C]SOM230 (1mg/kg)				
Study number:		[DMPK (CH) R01-0388]				
GLP compliance:		not required				
Location in CTD		4.2.2.4-1				
Gender(M/F) / Number of animals:		M / 3 for urine and feces collection (Han Wistar)				
Feeding condition:		Fed				
Vehicle / Formulation		Solution in saline				
Method/ Route / Duration of administration:		Subcutaneous injection				
Dose (mg/kg):		1.0				
Specific activity		318 µCi/mg / >98% radiochemical purity				
Analyte / Radionuclide:		Radioactivity / ^{14}C				
Assay:		Liquid scintillation counting (LSC) or LSC after solubilization				
Excretion route:		Urine	Feces	Cage wash	Carcass	Recovery
		(%, mean ± SD)	(%, mean ± SD)	(%, mean ± SD)	(%, mean ± SD)	(%, mean ± SD)
Interval (h)	0 – 24	8.3 ± 1.3	66.6 ± 2.1	-	-	-
	0 – 48	8.6 ± 1.2	73.3 ± 1.2	-	-	-
	0 – 72	8.9 ± 1.2	74.8 ± 1.3	-	-	-
	72			0.5 ± 0.2	8.3 ± 1.1	92.5 ± 0.8

2.6.5.13B 薬物動態試験：累積排泄（ラット乳汁）

Test article: [^{14}C]SOM230

Study title: Excretion in milk after a single subcutaneous dose of [^{14}C]SOM230 in the rat		
Study number:	[DMPK R0900555]	
GLP compliance:	not required	
Location in CTD:	4.2.2.5-1	
Gender(M/F) / Number of animals:	F / 15 (3 per timepoint); lactating, 8-9 days post-parturition; HanWistar	
Feeding condition:	fed	
Vehicle / Formulation	Solution in saline	
Method / Route:	s.c.	
Dose (mg/kg):	1	
Specific activity / radiochemical purity:	125.8 µCi/mg / 97.9% radiochemical purity	
Analyte / Radionuclide:	Radioactivity / ^{14}C	
Assay:	Liquid scintillation counting; metabolite profiles by HPLC with off-line radioactivity detection; metabolite identification by LC-MS/MS	
	Plasma	Milk
Cmax (ngEq/mL)	386	89.8
Tmax (h)	1.0	1.0
AUC0-24 (ngEq•h/mL):	3390	914
AUCinf (ngEq•h/mL):	3430	958

Conclusions:

After a single 1 mg/kg [^{14}C]SOM230 subcutaneous dose to lactating rats, the transfer of parent drug and its metabolites into milk was observed. The overall milk:plasma (M/P) exposure ratio of total radioactivity was 0.28, based on AUCinf values. Projecting the rat data to humans, it is estimated that the maximum amount of SOM230 and/or its metabolites that a breast-fed infant could be exposed to by ingesting 1 L of milk daily is low accounting for 0.18% of an adult bid dose (600, 900 or 1200 µg). Metabolite profiles in plasma and milk were similar. Unchanged SOM230 was present at lower concentrations in rat milk compared to that observed in plasma.

2.6.5.13C 薬物動態試験：累積排泄（サル）

Test article: [^{14}C]SOM230

Study Title		Absorption, metabolism and excretion following a single subcutaneous dose of [^{14}C]pasireotide in the monkey	
Study number:		[DMPK R0900554]	
GLP compliance:		not required	
Location in CTD		4.2.2.4-2	
Gender(M/F) / Number of animals:		M/3	
		cynomolgus	
Feeding condition:		Fed	
Vehicle / Formulation		Solution in saline	
Method/ Route / Duration of administration:		Subcutaneous injection	
Dose (mg/kg):		0.6 mg/kg	
Specific activity /radiochemical purity:		61.05 µCi/mg as salt / 98.8% radiochemical purity	
Analyte / Radionuclide:		Radioactivity / [^{14}C]	
Assay:		Liquid scintillation counting (LSC) or LSC after solubilization	
Excretion route:		Urine (% of dose ± SD)	Feces (% of dose ± SD)
Interval (h)	0 – 24	4.48 ± 1.98	-
	0 – 72	-	80.5 ± 15.8
	0 – 168	6.27 ± 2.21	94.5 ± 7.98
SOM230	0 – 24	3.52	-
SOM230	0 – 72	-	77.6
Cage wash	0 – 168	1.42 ± 0.283	
Total	0 – 168	102 ± 5.84	
Absorption (%)		100*	
Bioavailability (%)		100*	

* Based on the total radioactivity recovered in excreta (100% of dose), the absorption was judged to be completed. The s.c. bioavailability of SOM230 in monkey is expected to be 100% as its absorption was 100% and no first pass effect is expected as seen in rats which had a s.c. bioavailability of 100% [DMPK R00-2234].

2.6.5.13D 薬物動態試験：累積排泄（ヒト）

Test article: [^{14}C]SOM230

Study Title	An open-label, single center study to determine absorption, distribution, metabolism and excretion (ADME) of pasireotide (SOM230) following a single subcutaneous injection of [14C]pasireotide (600 µg) in healthy subjects
Study number:	[CSOM230B2112]
GLP compliance:	not required
Location in CTD	5.3.3.1-3
Gender(M/F) / Age range / Number of subjects:	M / 18-25 yrs / 4
Vehicle / Formulation	Sterile aqueous drug solution
Route of administration:	Subcutaneous injection
Dose (µg/kg):	600 (0.232 µCi)
Analyte / Radionuclide:	Radioactivity / ^{14}C
Assay:	AMS detection

Excretion route:	Subject USA/0501/ 00002	Subject USA/0501/ 00003	Subject USA/0501/ 00005	Subject USA/0501/ 00014	Mean ± SD
Urine (0-240 hours)	9.88	6.92	5.18	8.53	7.63 ± 2.03
Feces (0-240 hours)	38.1	46.2	57.2	51.8	48.3 ± 8.16
Dose recovery (%)	48.0	53.1	62.4	60.3	55.9 ± 6.63

[a] Subject 00003 withdrew from the study at 216 hours postdose

2.6.5.14 薬物動態試験：胆汁中排泄

該当なし

2.6.5.15 薬物動態試験：薬物相互作用（イヌにおけるシクロスポリン A と SOM230 の相互作用）

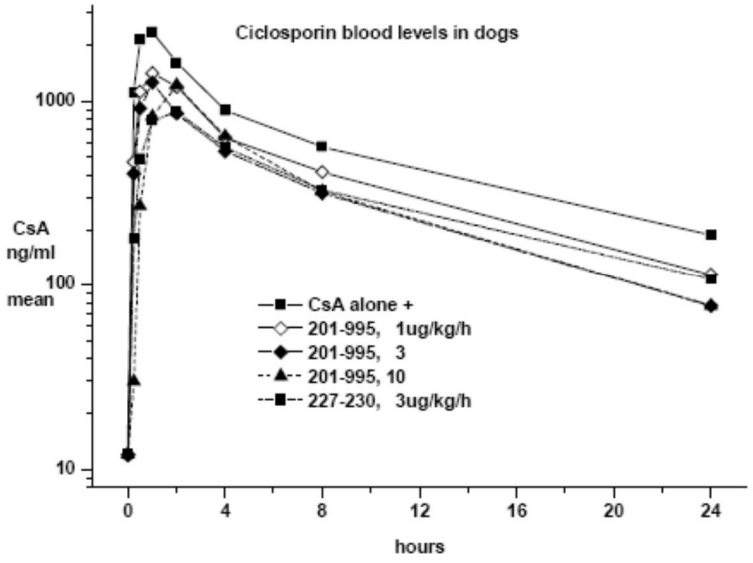
Study Title:	Pharmacokinetic interaction of ciclosporin A (Neoral®) and SMS 201-995 (Sandostatin®) or SOM230 in the dog
Study number:	[RD-2001-01165]
GLP compliance:	not required
Location in CTD:	4.2.2.6-2
Study System:	SMS 201-995 and SOM230 were administered to Beagle dogs via s.c. infusion by an osmotic Alzet pump, implanted 3 to 4 days before a single p.o. administration of CsA.
Analyte/Assay:	The blood and plasma levels of CsA, IGF-1 and SMS 201-995 were determined by RIA using the appropriate antisera, antibodies, labels and standards:

Compound	Dose	CsA, $AUC_{0\text{-}24h}$ (ng·h/mL) Mean, (SEM)	SMS 201-995, $AUC_{0\text{-}24h}$ (ng·h/mL) Mean, (SEM)	IGF1 (ng/mL) Mean, (SEM)
CsA, (Neoral) alone	10 mg/kg	15300, (13800-16900)	-	36.9, (28-50)
SOM230+ CsA	3 µg/kg/h + 10 mg/kg	8160, (6700-9510)	-	15.4, (15-16)
SMS 201-995 + CsA	1 µg/kg/h + 10 mg/kg	10500, (9300-11800)	196, (154-250)	41.4, (33-52)
SMS 201-995 + CsA	3 µg/kg/h + 10 mg/kg	8130, (7200-9190)	552, (486-927)	29.4, (22-39)
SMS 201-995 + CsA	10 µg/kg/h + 10 mg/kg	8420, (6690-10600)	2270, (2210-2340)	19.3, (15-25)

All PK values were rounded up to 3 significant figures

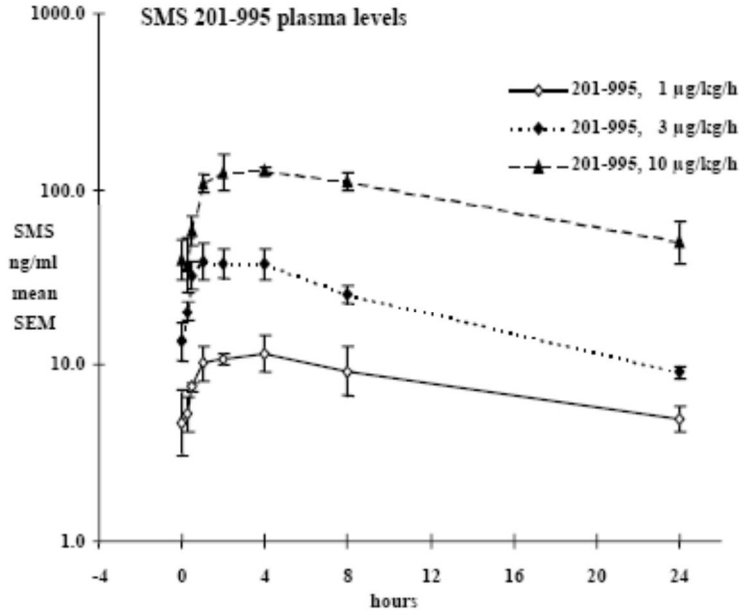
Pharmacokinetic interaction of Neoral® CsA, 10 mg/kg p.o., with SMS 201-995 and SDZ 227-230 during continuous s.c. infusion in beagle dogs.

CsA alone n = 6, combinations n = 3 - 4, Mean

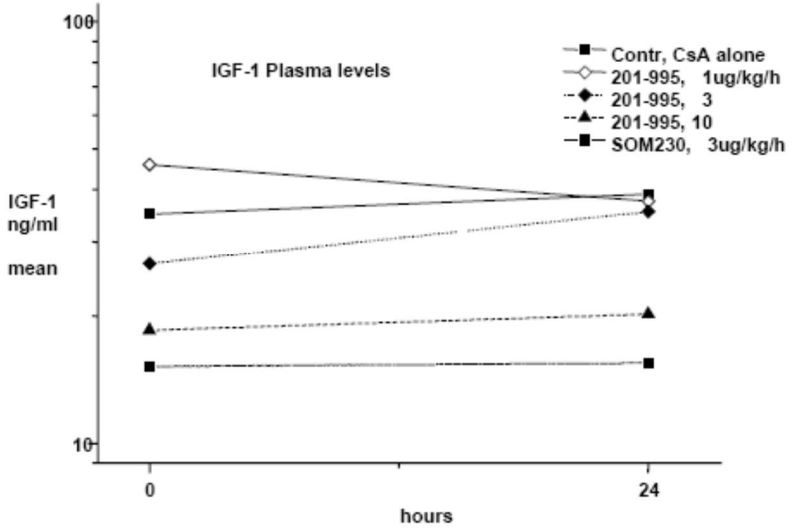


Plasma levels of SMS 201-995 during continuous s.c. infusion of SMS combined with oral administration of CsA, Neoral®, 10 mg/kg, given at t0.

n = 3 - 4, Mean, SEM.



IGF-1 plasma levels under continuous treatment with SMS 201-995 and SOM230 before (t0) and 24 hours after a single administration of CsA (Neoral®, 10 mg/kg), Control n = 6, combinations n = 3 - 4, Mean



CsA = Cyclosporin A

Additional information:

SMS 201-995 delayed the enteral absorption of CsA and suppressed IGF-1 plasma levels dose dependently. SOM230 had a similar effect on reduction of CsA level but was at least three times more active at lowering plasma IGF-1 levels when compared to SMS 201-995.

CsA led to an increase of the steady state plasma level of SMS 201-995.

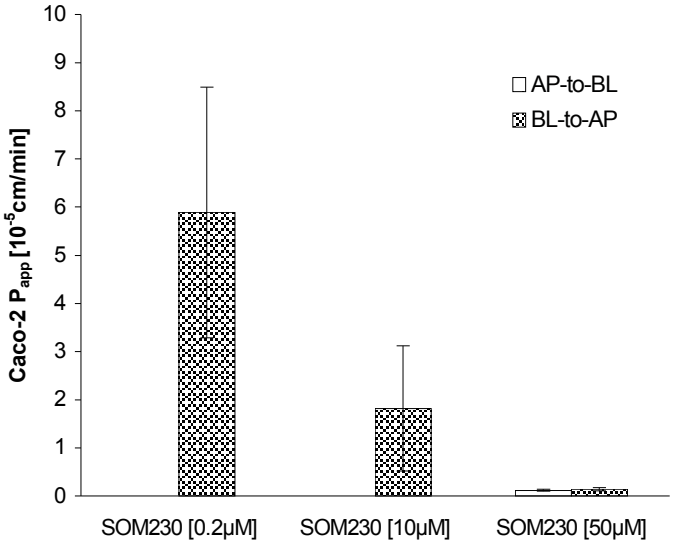
2.6.5.16A 薬物動態試験：その他（Caco-2 透過性試験）

Test article: [^{14}C]SOM230

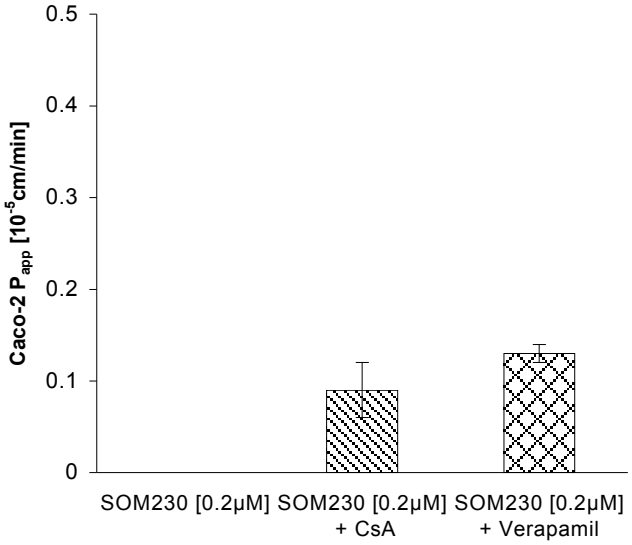
Study Titles:	Mechanistic transport studies across Caco-2 cell monolayers
Study number:	[DMPK(CH) R99-2281]
GLP compliance:	not required
Location in CTD:	5.3.2.3-1
Study System:	Human intestinal cell line Caco-2 grown on permeable filter support
Analyte/Assay:	0.2 – 50 µM [^{14}C]SOM230, radiolabeled (specific activity 0.75 MBq/mg; radiochemical purity ≥98%)/ liquid scintillation counting

Compound		Caco-2 permeability	
	Conc. [µM]	P_{app} (x 10^{-5} cm/min) Apical to Basolateral	P_{app} (x 10^{-5} cm/min) Basolateral to Apical
SOM230	0.2	0.00 ± 0.00	5.89 ± 5.89
SOM230	10	0.00 ± 0.00	1.82 ± 1.3
SOM230	50	0.12 ± 0.02	0.14 ± 0.03
SOM230+ Cyclosporin A	0.2/10	0.09 ± 0.03	-
SOM230+ Verapamil	0.2/100	0.13 ± 0.01	-
Mannitol	0.01	1.9 ± 0.3	-
Propranolol	0.01	22.0 ± 2.0	-

Concentration-dependent transport of SOM230 across Caco-2 cell monolayers measured in the AP-to-BL and BL-to-AP direction.



The role of the efflux pump inhibitors CsA and Verapamil on the transport of SOM230 [0.2 µM] across Caco-2 cell monolayers measured in the AP-to-BL direction.



CsA = Cyclosporin A

Additional information:

No SOM230 (0.2 µM) apical to basolateral transport was detectable within a time period of 120 minutes. Basolateral to apical transport (~ 6×10^{-5} cm/min) was significantly higher than apical to basolateral transport.

No increase of apical to basolateral transport was observed with SOM230 (10 µM). However, basolateral to apical transport decreased significantly ($P_{app} \cong 2\times10^{-5}$ cm/min). For SOM230 (50 µM), a significant increase of apical to basolateral and a significant decrease of basolateral to apical transport, respectively, was observed. The permeability values in both transport directions converged completely at 50 µM concentrations ($P_{app} \cong 0.1\times10^{-5}$ cm/min).

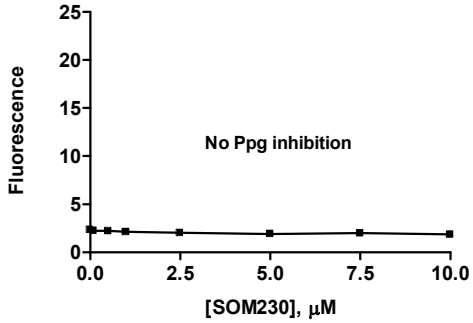
Addition of CsA and Verapamil, respectively, resulted in a significant increase of apical to basolateral transport of SOM230 (0.2 µM), closely approaching the bidirectional permeability data determined for SOM230 (50 µM).

2.6.5.16B 薬物動態試験：その他（P-gp の阻害）

Test article: SOM230

Study Titles:	The potential of SOM230 to inhibit P-glycoprotein in cells determined by flow cytometry
Study number:	[DMPK R0600583]
GLP compliance:	not required
Location in CTD:	5.3.2.3-2
Study System:	Rho123 efflux in MDA435 T0.3 cells
Analyte/Assay:	0.1 µM Rho123 efflux / fluorescence by flow cytometry

SOM230 (µM)	Rho123 fluorescence (geometric mean)	% events (of 10,000)
0	2.36	85.8
0.1	2.27	84.1
0.5	2.24	80.6
1.0	2.14	84.4
2.5	2.06	83.1
5	1.92	83.5
7.5	2.01	84.0
10	1.89	82.0
CsA (10 µM)	211	89.3



CsA = Cyclosporin A

Additional information:

SOM230 (up to 10 µM) was not found to inhibit Pgp-mediated efflux of Rho123 in MDA435 T0.3 cells

2.6.5.16C 薬物動態試験：その他（BCRP を介した透過性と相互作用）

Test article: SOM230

Study Title:	[^{14}C]SOM230: *In vitro* permeability and potential interaction with breast cancer resistance protein (BCRP) of across Caco-2 and MDCK/mBCRP cell monolayers
Study number:	[DMPK R1000737]
GLP compliance:	not required
Location in CTD:	4.2.2.6-1
Study System:	Caco-2 and MDCK/mBCRP cell monolayers
Analyte/Assay:	2.1 – 13 µM [^{14}C]SOM230, radiolabeled (specific activity 131 mCi/mmol; radiochemical purity 97.5%)/ liquid scintillation counting 33-36 nM [^{3}H]E3S (Estrone-3-sulfate), radiolabeled (specific activity 50.3 Ci/mmol)/ liquid scintillation counting

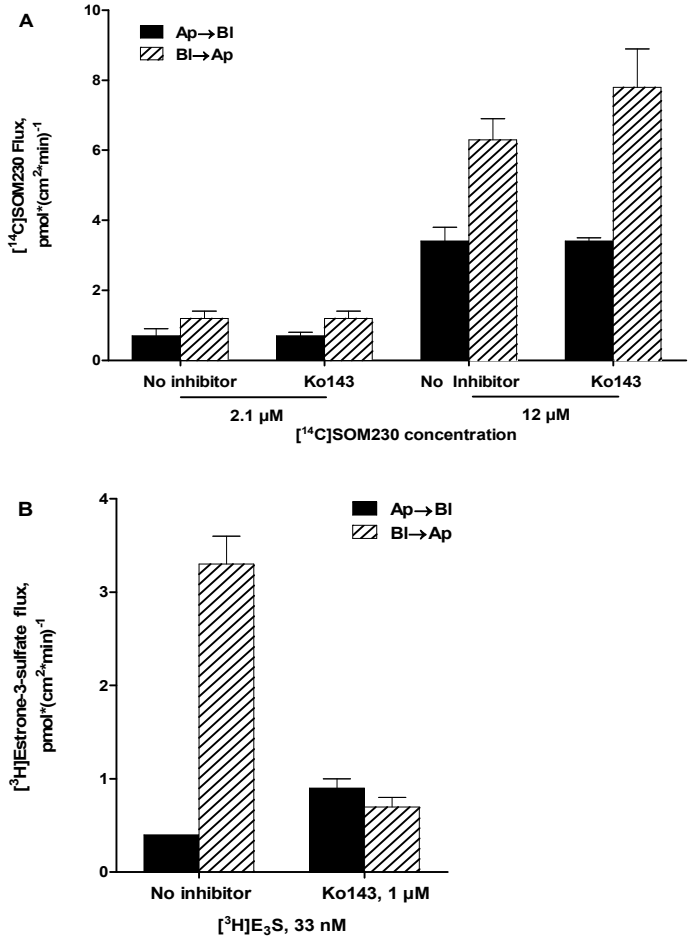
Compound (concentration)	Inhibitor [a]	**Caco-2 permeability**		
		P_{app} (x 10^{-5} cm/min) Apical to Basolateral (Ap→Bl) [b]	P_{app} (x 10^{-5} cm/min) Basolateral to Apical (Bl→Ap) [b]	P_{app} Ratio (Bl→Ap/ Ap→Bl)
[^{14}C]SOM230 (2.1 µM)	None	0.54 ± 0.2	0.96 ± 0.2	1.8 ± 0.6
	Ko143	0.52 ± 0.1	0.93 ± 0.1	1.8 ± 0.4
[^{14}C]SOM230 (12 µM)	None	0.48 ± 0.1	0.88 ± 0.1	1.8 ± 0.3
	Ko143	0.48 ± 0.22	1.1 ± 0.2	2.3 ± 0.3
[^{3}H]E_3S (33 nM)	None	22.2 ± 2.0	165 ± 13	7.4 ± 0.9
	Ko143	42.6 ± 2.7	34.5 ± 2.9	0.81 ± 0.08
[^{14}C]mannitol (3.9 µM)		4.0 ± 0.3	3.8 ± 0.7	
[^{3}H]propranolol (4.5 µM)		79.2 ± 6.0	110 ± 3.5	

[a] Final concentration of Ko143 was 1.0 µM.
[b] Values represent the average ± standard deviation of quadruplicate measurements.

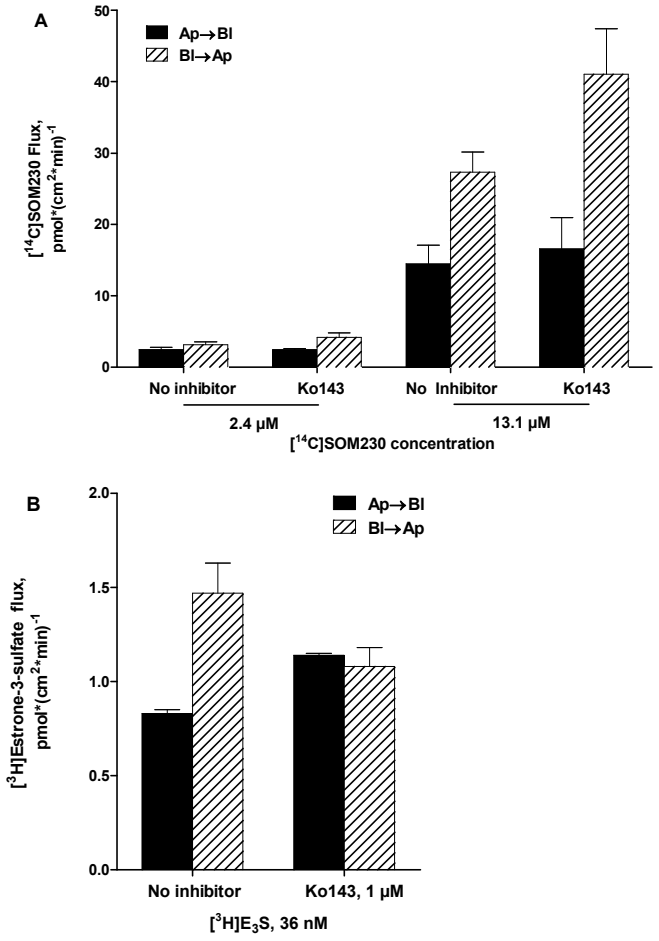
Study Title:	[^{14}C]SOM230: *In vitro* permeability and potential interaction with breast cancer resistance protein (BCRP) of across Caco-2 and MDCK/mBCRP cell monolayers			
Compound		**MDCK/mBCRP permeability**		
(concentration)	Inhibitor [a]	P_{app} (x 10^{-5} cm/min) Apical to Basolateral (Ap→Bl) [b]	P_{app} (x 10^{-5} cm/min) Basolateral to Apical (Bl→Ap) [b]	P_{app} Ratio (Bl→Ap/ Ap→Bl)
[^{14}C]SOM230 (2.4 µM)	None	1.70 ± 0.2	2.17 ± 0.3	1.3 ± 0.2
	Ko143	1.70 ± 0.1	2.88 ± 0.4	1.7 ± 0.3
[^{14}C]SOM230 (13 µM)	None	1.84 ± 0.3	3.47 ± 0.3	1.9 ± 0.4
	Ko143	2.11 ± 0.6	5.21 ± 0.8	2.5 ± 0.8
[^{3}H]E_3S (36 nM)	None	38.6 ± 0.82	68.6 ± 7.6	1.8 ± 0.2
	Ko143	53.4 ± 0.50	50.3 ± 4.7	0.94 ± 0.09

[a] Final concentrations for Ko143 was 1.0 µM.
[b] Values represent the average ± standard deviation of quadruplicate measurements.

[^{14}C]SOM230 or [^{3}H]Estrone-3-sulfate transport rates across Caco-2 cell monolayers and the effect of the BCRP inhibitor



[^{14}C]SOM230 or [^{3}H]estrone-3-sulfate flux across MDCK/mBCRP cell monolayers



[^{14}C]SOM230 (panel A) or [^{3}H]estrone-3-sulfate (positive control, panel B) flux across Caco-2 cell monolayers was estimated by measuring the amount of radioactivity that crossed the monolayer in the Ap→Bl direction (solid bars) or in the Bl→Ap direction (hatched bars) in 120 min at 37°C in the absence or presence of the BCRP inhibitor Ko143 (1 μM).	[^{14}C]SOM230 (panel A) or [^{3}H]Estrone-3-sulfate (positive control, panel B) flux across MDCK/mBCRP cell monolayers was estimated by measuring the amount of radioactivity that crossed the monolayer in the Ap→Bl direction (solid bars) or in the Bl→Ap direction (hatched bars) in 120 min at 37°C in the absence or presence of the BCRP inhibitor Ko143 (1 μM)

Additional information:

The apparent SOM230 permeability classifies this compound as a poorly passive permeability compound when compared to the low permeability marker mannitol ($4.0 \pm 1.0 \times 10^{-5}$ cm·min^{-1}) and high permeability marker propranolol ($79.2 \pm 18 \times 10^{-5}$ cm·min^{-1}).

The presence of the BCRP inhibitor Ko143 (1.0 μM) had little effect on the P_{app} in either direction of Caco-2 monolayers, indicating that BCRP is unlikely to transport SOM230. The flux values were unchanged across MDCK/mBCRP monolayers in the presence of Ko143 further confirming that SOM230 is unlikely to be transported by BCRP.

2.6.5.16D 薬物動態試験：その他（ヒト肝細胞への SOM230 の取り込み及び OATP の阻害）

Test article: SOM230

Study Title:	Assessment of SOM230 uptake into primary human hepatocytes and as an inhibitor of the hepatic organic anion transport polypeptide transporters, OATP1B1 and OATP1B3
Study number:	[DMPK R1000572]
GLP compliance:	not required
Location in CTD:	5.3.2.3-3
Study System:	Cryopreserved pooled human hepatocytes(20-donor), control human embryonic kidney cell (HEK293), and HEK stably expressing OATP1B1 or OATP1B3
Analyte/Assay:	1.0 µM [^{14}C]SOM230, radiolabeled (specific activity 131 mCi/mmol; radiochemical purity 97.5%)/ liquid scintillation counting [^{3}H]estradiol-17β*D*-glucuronide ([^{3}H]E$_2$17βG), radiolabeled (specific activity 50.3 Ci/mmol)/ liquid scintillation counting; [^{14}C]tetraethylammonium ([^{14}C]TEA), radiolabeled (specific activity 53 mCi/mmol)/ liquid scintillation counting; [^{3}H]CCK8, radiolabeled (specific activity 37.8 Ci/mmol)/ liquid scintillation counting;

Uptake of [^{14}C]SOM230 or the positive control OATP ([^{3}H]E$_2$17βG) or OCT1 ([^{14}C]TEA) substrates into human hepatocytes in suspension

Substrate	Substrate concentration, µM	Human hepatocytes		
		Cellular uptake (pmol·mg protein^{-1})		Fold stimulation in uptake caused by active transport[b]
		Control[a]	With Inhibitor Cocktail	
[^{14}C]SOM230	1.0	118 ± 19	112 ± 11	1.1
[^{3}H]E$_2$17βG	1.5	46.5 ± 5.4	15.2 ± 1.4*	3.0
[^{14}C]TEA	29.7	154 ± 14	89 ± 7.0*	1.7

[a] Control refers to uptake in the absence of transport protein inhibitors; [b] fold stimulation in uptake caused by active transport was calculated by dividing uptake in the absence of transport protein inhibitors (control) by uptake in the presence of transport protein inhibitors (with inhibitor cocktail); *Significantly different from control, P<0.05, two-tailed *t*-test.

Study Title:	Assessment of SOM230 uptake into primary human hepatocytes and as an inhibitor of the hepatic organic anion transport polypeptide transporters, OATP1B1 and OATP1B3

Effect of SOM230 and rifamycin SV on the accumulation of the model OATP1B1 substrate [^{3}H]E$_2$17βG in control or OATP1B1-expressing cells

Inhibitor	Inhibitor concentration, µM	HEK control or OATP1-expressing cells		
		[^{3}H]E$_2$17βG accumulation, (pmol·mg protein^{-1}·min^{-1})		% Inhibition [a]
		Control cells	OATP1B1 cells	
None	-	0.410 ± 0.20	1.96 ± 0.21	-
Rifamycin SV	25	0.441 ± 0.01	0.344 ± 0.23	106
SOM230	0.25	0.486 ± 0.26	2.00 ± 0.26	1.79
	1.0	0.458 ± 0.12	2.00 ± 0.19	0.125

[a] % inhibition was calculated as described by Equation 1

$$\left(1-\left[\frac{(Accumulation)_{OATP,I}-(Accumulation)_{Control,I}}{(Accumulation)_{OATP,0}-(Accumulation)_{Control,0}}\right]\right)\times 100 \quad \text{Equation 1}$$

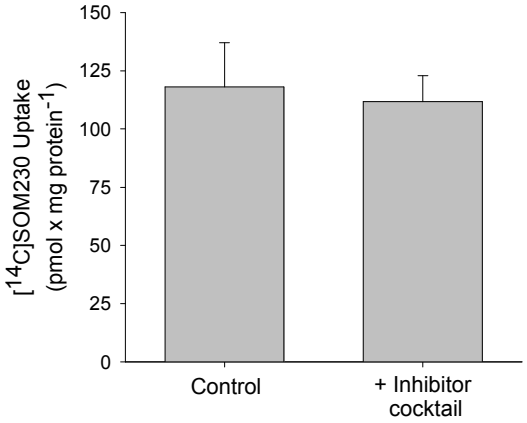
Effect of SOM230 and rifamycin SV on the accumulation of the model OATP1B3 substrate [^{3}H]CCK8 in control or OATP1B3-expressing cells

Inhibitor	Inhibitor concentration, µM	HEK control or OATP3-expressing cells		
		[^{3}H]CCK8 accumulation, (pmol·mg protein^{-1}·min^{-1})		% Inhibition [a]
		Control cells	OATP1B3 cells	
None	-	0.0844 ± 0.004	0.161 ± 0.014	-
Rifamycin SV	25	0.0615 ± 0.007	0.0423 ± 0.005	125
SOM230	0.25	0.0686 ± 0.007	0.140 ± 0.015	6.53
	1.0	0.0586 ± 0.008	0.129 ± 0.013	7.67

[a] % inhibition was calculated as described by Equation 1.

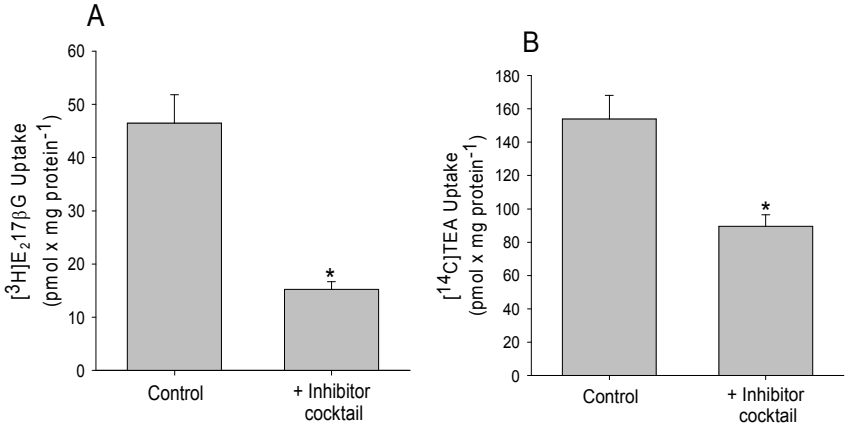
Study Title:	Assessment of SOM230 uptake into primary human hepatocytes and as an inhibitor of the hepatic organic anion transport polypeptide transporters, OATP1B1 and OATP1B3

Uptake of [^{14}C]SOM230 into human hepatocytes in suspension



The uptake of [^{14}C]SOM230 (1.0 μM) into human hepatocytes in suspension was done using the oil-centrifugation method. Uptake was done in the absence or presence of an inhibitor cocktail designed to completely inhibit uptake activity mediated by OCT1, OATP1B1, OATP1B3 and OATP2B1. The difference in uptake in the absence versus presence of the inhibitor cocktail represents transporter mediated uptake. The uptakes reported are means ± standard deviation of six replicates.

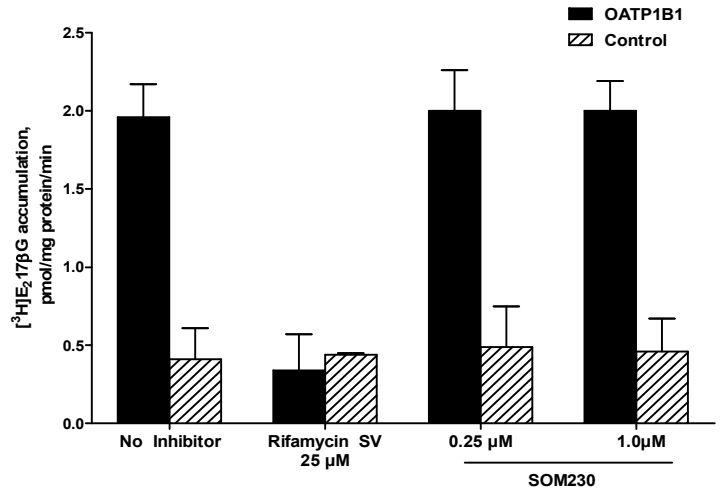
Uptake of probe substrates of OATPs ($E_2$17βG) and OCT1 (TEA)



The uptake of (A) [^{3}H]$E_2$17βG (1.5 μM) and (B) [^{14}C]TEA (29.7 μM) into human hepatocytes in suspension was done using the oil-centrifugation method. Uptake was done in the absence or presence of an inhibitor cocktail designed to completely inhibit uptake activity mediated by OCT1, OATP1B1, OATP1B3 and OATP2B1. The difference in uptake in the absence versus presence of the inhibitor cocktail represents transporter mediated uptake. The uptakes reported are means ± standard deviation of six replicates. *Significantly different from control, $P<0.05$, two-tailed t-test.

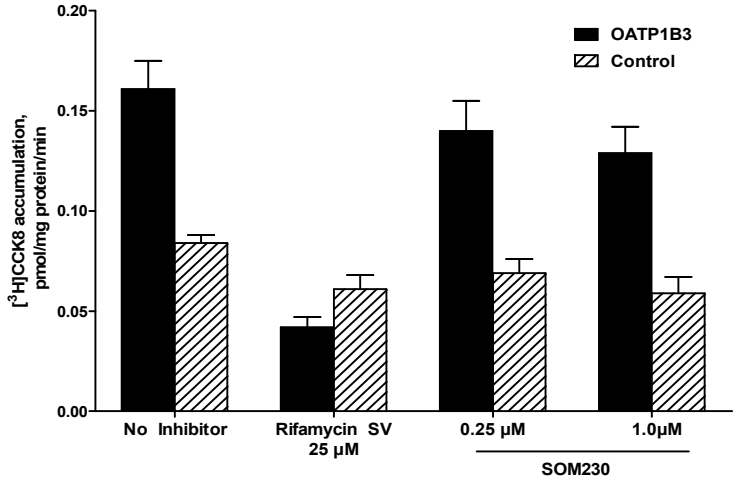
Study Title:	Assessment of SOM230 uptake into primary human hepatocytes and as an inhibitor of the hepatic organic anion transport polypeptide transporters, OATP1B1 and OATP1B3

Assessment of SOM230 as an inhibitor of OATP1B1



HEK293 cells stably expressing OATP1B1 (black bars), or control cells (hatched bars) were incubated with [^{3}H]$E_2$17βG (1.0 µM) in the presence or absence of rifamycin SV (25 µM; positive control inhibition) or SOM230 as indicated in the figure below. Each bar represents the average pmol [^{3}H]$E_2$17βG accumulation per mg cellular protein per min ± standard deviation of three separate wells.

Assessment of SOM230 as an inhibitor of OATP1B3



HEK293 cells stably expressing OATP1B3 (black bars), or control cells (hatched bars) were incubated with [^{3}H]CCK8 (46 nM) in the presence or absence of rifamycin SV (25 µM; positive control inhibition) or SOM230 as indicated in the figure below. Each bar represents the average pmol [^{3}H]CCK8 accumulation per mg cellular protein per min ± standard deviation of three separate wells.

Additional information:

The level of accumulation of [^{14}C]SOM230 in the absence of transport protein inhibitors was not significantly different in the presence of inhibitors of the major hepatic uptake transporters: organic cation transporter 1 (OCT1), OATP1B1, OATP1B3, and OATP2B1 suggesting that SOM230 is not actively taken up into human liver by the major hepatic uptake transporters.

SOM230 at concentrations up to 1 µM did not inhibit the transport activity of either OATP1B1 or OATP1B3, which were stably expressed in HEK cells.

2.6.5.16E 薬物動態試験：その他（MRP2 及び BSEP の阻害剤としての SOM230）

Test article: SOM230

Study Title:	Assessment of SOM230 as an inhibitor of human multidrug resistance-associated protein 2 (MRP2) and bile salt export pump (BSEP)
Study number:	[DMPK R1100482]
GLP compliance:	not required
Location in CTD:	5.3.2.3-4
Study System:	inside out membrane vesicles containing expressed hMRP2 or hBSEP (50 µg of protein per reaction).
Analyte/Assay:	[^{3}H]estradiol-17β-glucuronide ([^{3}H]E$_2$17βG), radiolabeled (25 µM, specific activity 0.18 Ci/mmol)/ liquid scintillation counting; [^{3}H]taurocholic acid, radiolabeled (0.25 µM, specific activity 5 Ci/mmol)/ liquid scintillation counting.

Study Title: Assessment of SOM230 as an inhibitor of human multidrug resistance-associated protein 2 (MRP2) and bile salt export pump (BSEP)

Effect of SOM230 and the model inhibitor MK571 on MRP2-mediated [^{3}H]estradiol 17-beta glucuronide transport

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	MRP2-mediated transport (pmol/mg protein/min)[a]	% inhibition
[^{3}H]$E_2$17βG	None	-	376 ± 2.4	0
25 µM	MK571	200	60.2 ± 9.1	84.0
	SOM230	0.1	326 ± 64	13.3
		0.5	324 ± 26	13.7
		2.5	298 ± 26	20.8
		5	228 ± 21	39.3
		10	188 ± 16	50.0

[a] MRP2 mediated activity was calculated as the average difference in [^{3}H]$E_2$17βG accumulation in vesicles in the presence ATP from that in the presence AMP

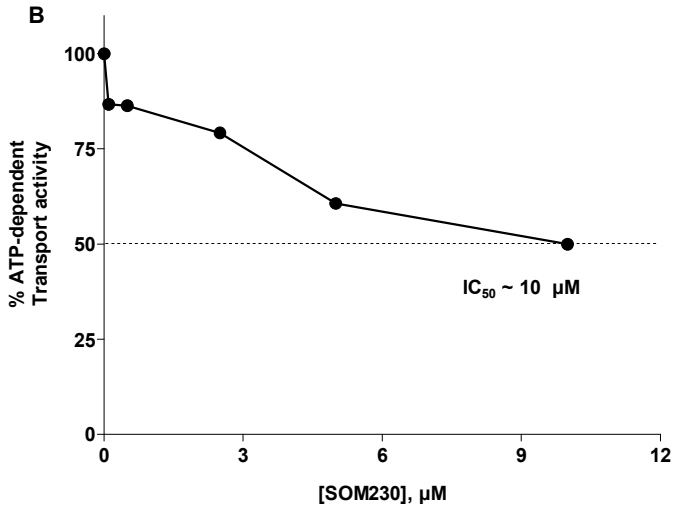
Effect of SOM230 and the model inhibitor Cyclosporin A on BSEP-mediated [^{3}H]taurocholic acid transport

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	BSEP mediated transport (pmol/mg protein/min) [a]	% Inhibition
[^{3}H]TC	None	-	1.78 ± 0.32	0
0.25 µM	CsA	40	0.304 ± 0.079	83.0
	SOM230	0.1	1.50 ± 0.32	16.0
		0.5	1.42 ± 0.15	20.5
		2.5	1.25 ± 0.098	29.8
		5	1.05 ± 0.16	41.4
		10	0.923 ± 0.062	48.4

[a] BSEP-mediated activity was calculated as the average difference in [^{3}H]TC accumulation in vesicles in the presence ATP from that in the presence AMP

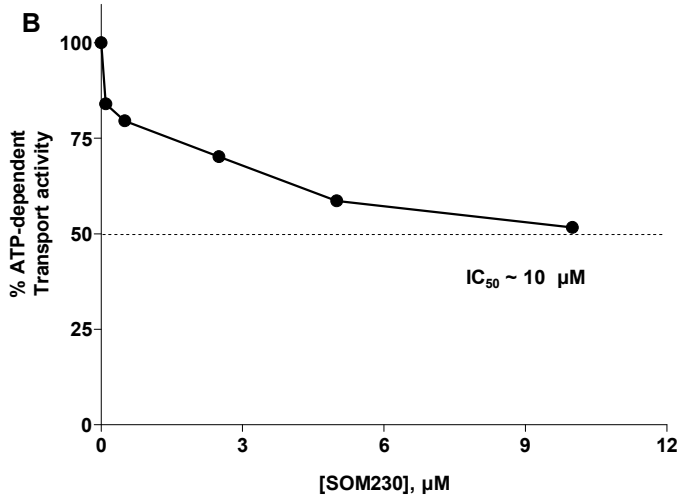
Study Title: Assessment of SOM230 as an inhibitor of human multidrug resistance-associated protein 2 (MRP2) and bile salt export pump (BSEP)

Assessment of SOM230 as an inhibitor of hMRP2



Inside-out membrane vesicles expressing hMRP2 were incubated with [^{3}H]E$_2$17βG (25 µM) in the presence of SOM230 (n = four separate samples).

Assessment of SOM230 as an inhibitor of hBSEP



Inside-out membrane vesicles expressing hBSEP were incubated with [^{3}H]TC (0.25 µmol/L) in the presence of SOM230 (n = four separate samples).

Additional information:

The likelihood of pasireotide to inhibit the activity of MRP2 and BSEP in human is low considering that $C_{max,ss}$ of pasireotide observed in human plasma is <0.1 µM and predicted $C_{max,ss}$ of pasireotide in human liver <0.23 µM (based on the rat tissue distribution [DMPK R0500319] and rat blood-to-plasma ratio [DMPK(CH) R99-2082] and assumed human would have the same ratio of 2.3 in rats), which are far much lower than IC_{50} values from *in vitro* study.

2.6.5.16F 薬物動態試験：その他（P-gp 及び BCRP の阻害剤としての SOM230）

Test article: SOM230

Study Title:	Assessment of SOM230 as an inhibitor of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)
Study number:	[DMPK R1200248-01]
GLP compliance:	not required
Location in CTD:	5.3.2.3-5
Study System:	inside out membrane vesicles containing expressed human P-gp or BCRP transporters (50 µg of protein per reaction).
Analyte/Assay:	[^{3}H]*N*-methyl verapamil ([^{3}H]NMV), radiolabeled (0.4 µM, specific activity 0.06 Ci/mmol)/ liquid scintillation counting; [^{3}H]estrone-3-sulfate (^{3}H]E_3S), radiolabeled (1 µM, specific activity 0.11 Ci/mmol)/ liquid scintillation counting.

Study Title: Assessment of SOM230 as an inhibitor of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)

Effect of SOM230 and the model inhibitor CsA on P-gp-mediated [^{3}H]NMV transport

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	P-gp-mediated transport (pmol/mg protein/min)[a]	% inhibition
[^{3}H]NMV, 0.4 µM	None	-	1.38 ± 0.34	0
	CsA	40 [b]	-0.160 ± 0.30	ca. 100%
	SOM230	0.50	1.04 ± 0.26	24.6
		1.0	0.471 ± 0.12	65.9
		2.5	0.425 ± 0.036	69.3
		5.0	0.229 ± 0.018	83.4
		10	0.124 ± 0.0080	91.0

[a] P-gp mediated activity was calculated as the average difference in [^{3}H]NMV accumulation in vesicles in the presence ATP from that in the absence ATP

[b] Nominal concentration

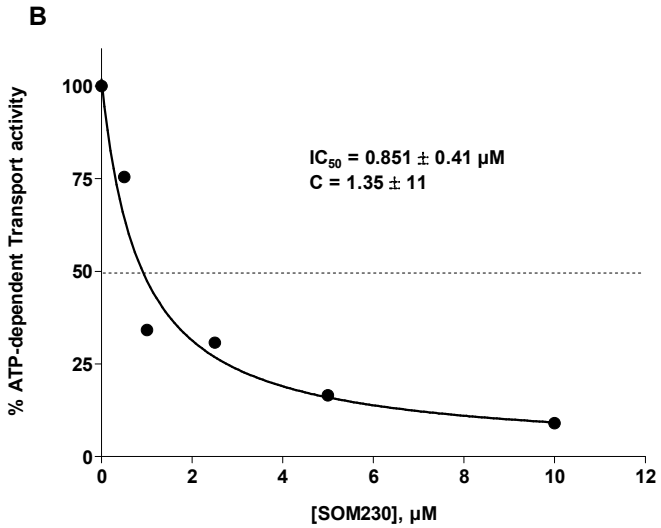
Effect of SOM230 and the model inhibitor FTC on BCRP-mediated [^{3}H]E_3S transport

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	BCRP mediated transport (pmol/mg protein/min) [a]	% Inhibition
[^{3}H] E_3S, 1 µM	None	-	114 ± 4.5	0
	FTC	10	2.44 ± 1.1	97.9
	SOM230	0.50	107 ± 13	6.28
		1.0	105 ± 16	7.80
		2.5	90.5 ± 2.4	20.6
		5.0	77.4 ± 2.3	32.1
		10	58.8 ± 0.93	48.4

[a] BCRP-mediated activity was calculated as the average difference in [^{3}H] E_3S accumulation in vesicles in the presence ATP from that in the presence AMP

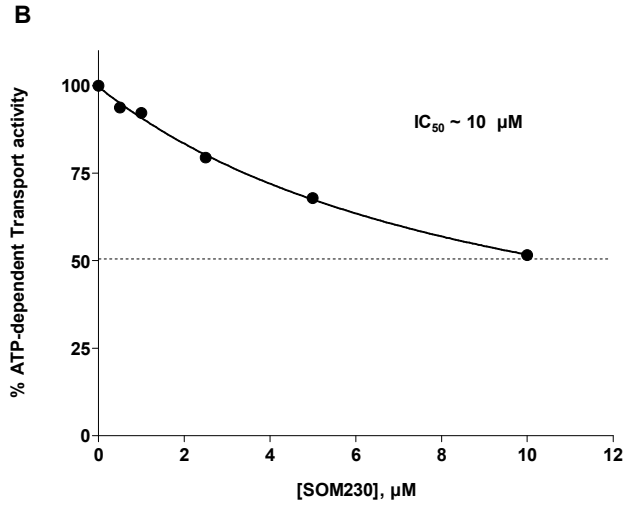
Study Title: Assessment of SOM230 as an inhibitor of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)

Assessment of SOM230 as an inhibitor of P-gp



Inside-out membrane vesicles expressing P-gp were incubated with [^{3}H]NMV (0.4 µM) in the presence of SOM230 (n = four separate samples).

Assessment of SOM230 as an inhibitor of hBCRP



Inside-out membrane vesicles expressing BCRP were incubated with [^{3}H] E_3S (1 µM) in the presence of SOM230 (n = four separate samples).

Additional information:

The likelihood of SOM230 to inhibit the activity of P-gp and BCRP in human is low considering that Cmax,ss of SOM230 observed in human plasma is <0.1 µM and predicted Cmax,ss of SOM230 in human liver <0.23 µM (based on the rat tissue distribution [DMPK R0500319] and rat blood-to-plasma ratio [DMPK(CH) R99-2082] and assumed human would have the same ratio of 2.3 in rats), which are lower than IC_{50} values from *in vitro* study. Note: No OATP uptake transport activity for SOM230 was detected in hepatocytes [DMPK R1000572]. Also, SOM230 did not inhibit P-gp-mediated efflux of Rho123 in MDA435 T0.3 cells (a P-gp over-expressing cell-line) [Table 2.6.5.16B-DMPK R0600583].

2.6.5.16G 薬物動態試験：その他（OCT1 及び OCT2 の阻害剤としての SOM230）

Test article: SOM230

Study Title:	Assessment of SOM230 as inhibitor of human organic cation transporters 1 and 2 (OCT1 & OCT2)
Study number:	[DMPK R1200761]
GLP compliance:	not required
Location in CTD:	5.3.2.3-6
Study System:	human embryonic kidney (HEK) cells stably expressing the human orthologs of OCT1 (HEK-OCT1) or OCT2 (HEK-OCT2)
Analyte/Assay:	[^{3}H]methyl-4-phenylpyridinium ([^{3}H]MPP$^+$), radiolabeled (7.9 nM, specific activity 80 Ci/mmol)/ liquid scintillation counting; [^{14}C]metformin, radiolabeled (10.5 µM, specific activity 107 mCi/mmol)/ liquid scintillation counting.

Effect of SOM230 and decynium 22 on [^{3}H]MPP$^+$ accumulation in control or OCT1-expressing cells

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	[^{3}H]MPP$^+$ accumulation, (fmol·mg protein^{-1}·min^{-1})[a]		% inhibition [b]
			OCT1 cells	Control cells	
[^{3}H]MPP$^+$ 7.9 nM	None	-	154 ± 4.6	16.6 ± 1.9	0.0
	Decynium 22	20	32.6 ± 1.4	11.3 ± 0.47	84.4
	SOM230	0.10	145 ± 1.0	16.5 ± 0.63	6.29
		0.50	149 ± 0.79	17.6 ± 0.25	3.98
		1.0	147 ± 6.1	17.5 ± 0.58	5.58
		5.0	156 ± 2.2	17.5 ± 1.3	NI [c]
		7.5	149 ± 4.2	18.0 ± 1.4	4.04
		10	155 ± 17	18.0 ± 0.51	NI

[a] [^{3}H]MPP$^+$ was added to a final concentration of 7.9 nM

[b] % inhibition was calculated as described by Equation

$$(1-[\frac{(Accumulation)_{OCT,I}-(Accumulation)_{Control,I}}{(Accumulation)_{OCT,0}-(Accumulation)_{Control,0}}])\times 100$$

[c] NI: No Inhibition

Study Title: Assessment of SOM230 as inhibitor of human organic cation transporters 1 and 2 (OCT1 & OCT2)

Effect of SOM230 and decynium 22 on [^{14}C]metformin accumulation in control or OCT2-expressing cells

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	[^{14}C]metformin accumulation, [a] (pmol·mg protein^{-1}·min^{-1})		% inhibition [b]
			OCT2 cells	Control cells	
[^{14}C]metformin, 10.5 µM	None	-	119 ± 7.9	2.89 ± 0.13	0.0
	Decynium 22	20	1.51 ± 0.25	1.20 ± 0.11	99.7
	SOM230	0.10	123 ± 4.5	2.89 ± 0.36	NI [c]
		0.50	115 ± 1.8	2.49 ± 0.15	3.12
		1.0	116 ± 4.5	2.46 ± 0.25	2.34
		5.0	111 ± 3.6	2.04 ± 0.40	6.45
		7.5	105 ± 1.4	1.81 ± 0.13	11.8
		10	106 ± 1.2	1.49 ± 0.16	10.7

[a] [^{14}C]Metformin was added to a final concentration of 10.5 µM

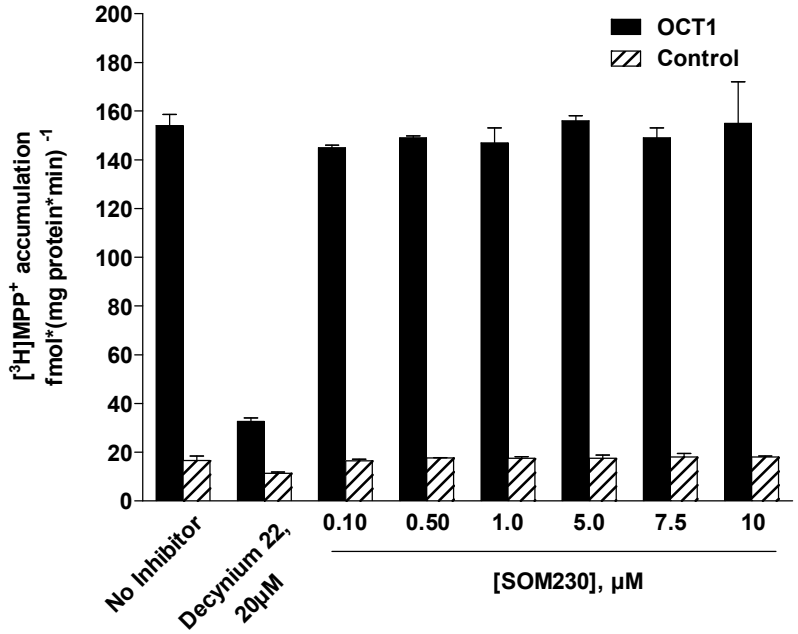
[b] % inhibition was calculated as described by Equation

$$(1-[\frac{(Accumulation)_{OCT,I}-(Accumulation)_{Control,I}}{(Accumulation)_{OCT,0}-(Accumulation)_{Control,0}}])\times 100$$

[c] NI: No Inhibition

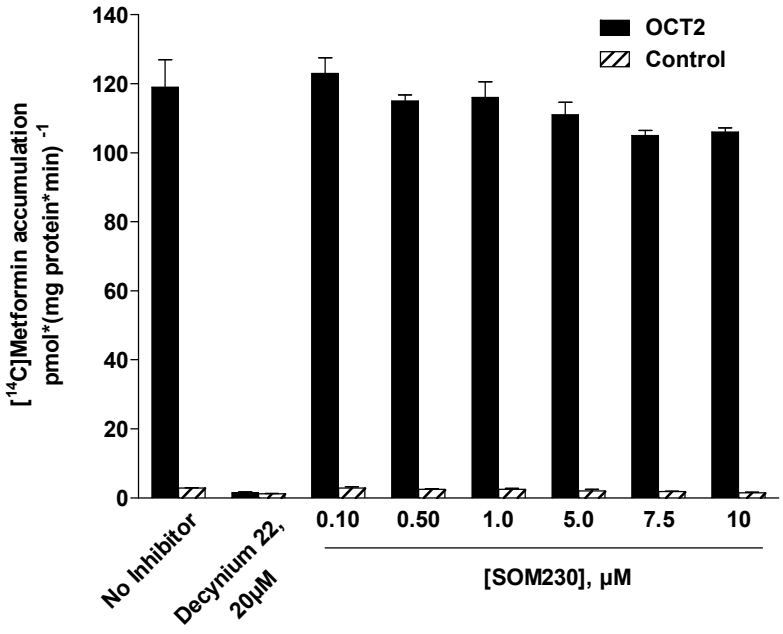
Study Title: Assessment of SOM230 as inhibitor of human organic cation transporters 1 and 2 (OCT1 & OCT2)

Assessment of SOM230 as an inhibitor of OCT1



HEK cells stably expressing OCT1 (black bars), or control cells (hatched bars) were incubated with [^{3}H]MPP$^+$ (7.9 nM) in the presence or absence of decynium 22 (20 µM; positive control inhibition) or SOM230 (0.10-10 µM). (n = three separate samples).

Assessment of SOM230 as an inhibitor of OCT2



HEK cells stably expressing OCT2 (black bars), or control cells (hatched bars) were incubated with [^{14}C]metformin (10.5 µM) in the presence or absence of decynium 22 (20 µM; positive control inhibition) or SOM230 (0.10-10 µM). (n = three separate samples).

Additional information:

The results of these studies demonstrated that SOM230 is not an *in vitro* inhibitor of human OCT1 or OCT2.

2.6.5.16H 薬物動態試験：その他（OAT1 及び OAT3 の阻害剤としての SOM230）

Test article: SOM230

Study Title:	Assessment of SOM230 as an inhibitor of human organic anion transporters 1 and 3
Study number:	[DMPK R1200835]
GLP compliance:	not required
Location in CTD:	5.3.2.3-7
Study System:	human embryonic kidney (HEK293) cells stably expressing OAT1 and OAT3
Analyte/Assay:	[^{3}H]Cidofovir, radiolabeled (1.6 µM, specific activity 36.7 Ci/mmol)/ liquid scintillation counting;
	[^{3}H]estrone-3-sulfate ([^{3}H]E_3S), radiolabeled (0.75 µM, specific activity 50 Ci/mmol)/ liquid scintillation counting.

Effect of SOM230 and the model inhibitor probenecid on [^{3}H]cidofovir accumulation in control or OAT1-expressing HEK293 cells

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	[^{3}H]cidofovir accumulation [a] (pmol/mg protein/min)		% inhibition [b]
			Control cells	OAT1 cells	
[^{3}H]Cidofovir 1.6 µM	None	0	0.0759 ± 0.021	9.38 ± 1.1	0
	Probenecid	100	0.0920 ± 0.034	0.879 ± 0.076	91.6
	SOM230	0.10	0.0558 ± 0.024	8.66 ± 0.071	7.60
		0.50	0.0576 ± 0.024	8.31 ± 0.49	11.3
		1.0	0.0323 ± 0.018	7.60 ± 0.26	18.6
		2.5	0.0447 ± 0.010	7.22 ± 0.35	22.9
		5.0	0.0547 ± 0.014	5.81 ± 0.35	38.1
		10	0.0438 ± 0.070	4.64 ± 0.54	50.6

[a] Final [^{3}H]cidofovir concentration in the incubation mixture was 1.6 µM

[b] % Inhibition was calculated from the effect of inhibitor concentration on the difference in level of [^{3}H]cidofovir accumulation in OAT1 cells compared to that in control cells relative to the same difference in the absence of inhibitors

Study Title:	Assessment of SOM230 as an inhibitor of human organic anion transporters 1 and 3

Effect of SOM230 and the model inhibitor probenecid on [^{3}H]estrone-3-sulfate accumulation in control or OAT3-expressing HEK293 cells

Substrate, concentration	Inhibitor	Inhibitor concentration, µM	[^{3}H]E_3S accumulation [a] (fmol/mg protein/min)		% inhibition [b]
			Control cells	OAT3 cells	
[^{3}H]estrone-3-sulfate, 0.75 µM	None	0	0.629 ± 0.024	6.28 ± 0.059	0
	Probenecid	100	0.579 ± 0.045	0.961 ± 0.068	93.2
	SOM230	0.10	0.614 ± 0.070	5.74 ± 0.32	9.19
		0.50	0.597 ± 0.056	4.63 ± 0.053	28.8
		1.0	0.565 ± 0.036	3.97 ± 0.13	39.7
		2.5	0.573 ± 0.0040	3.13 ± 0.026	54.7
		5.0	0.516 ± 0.031	1.87 ± 0.10	76.0
		10	0.498 ± 0.020	1.40 ± 0.011	84.0

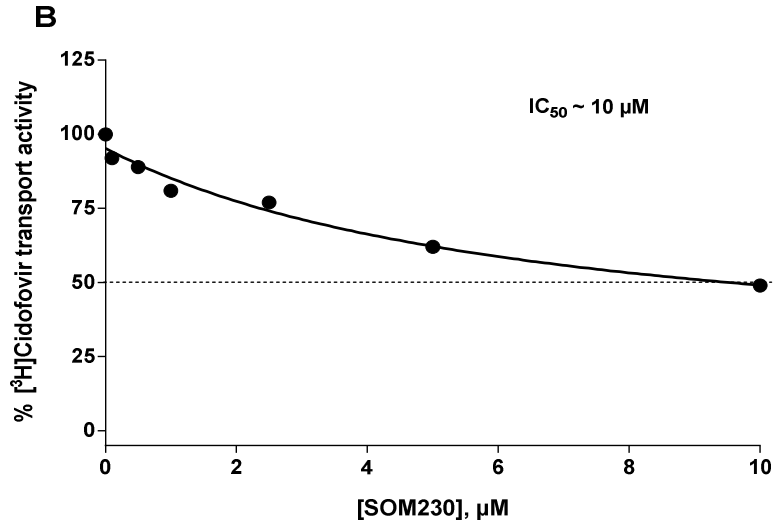
[a] Final [^{3}H]E3S concentration in the incubation mixture was 0.75 µM

[b] % inhibition was calculated as described by Equation

$$(1-[\frac{(Accumulation)_{OCT,I}-(Accumulation)_{Control,I}}{(Accumulation)_{OCT,0}-(Accumulation)_{Control,0}}])\times 100$$

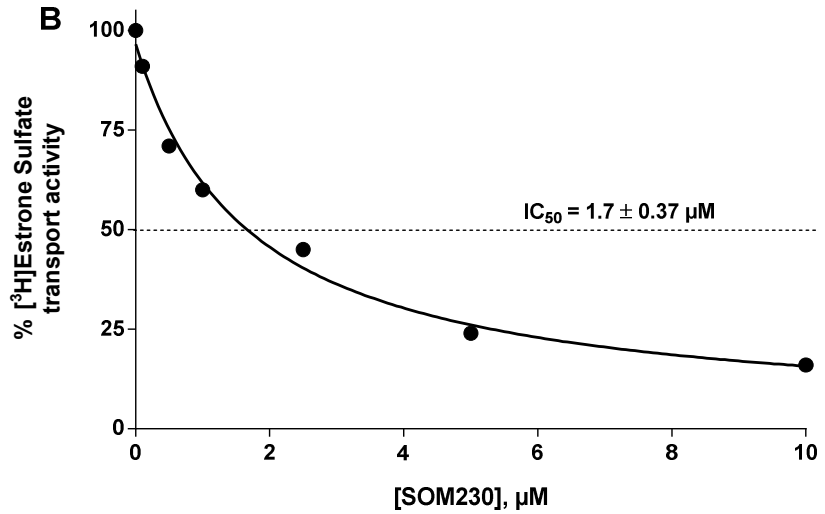
Study Title: Assessment of SOM230 as an inhibitor of human organic anion transporters 1 and 3

Assessment of SOM230 as an inhibitor of OAT1



HEK293 cells stably expressing OAT1 (solid bars), or control untransfected HEK293 cells (hatched bars) were incubated with [^{3}H]cidofovir (1.6 µM) in the presence or absence of probenecid (100 µM; positive control inhibitor) or SOM230. (n = three separate samples). The IC_{50} of OAT1 inhibition by SOM230 was estimated from the % transport activity plot by visual inspection as shown in Panel B

Assessment of SOM230 as an inhibitor of OAT3



HEK293 cells stably expressing OAT3 (solid bars), or control untransfected HEK293 cells (hatched bars) were incubated with [^{3}H]E_3S (0.75 µM) in the presence or absence of probenecid (100 µM; positive control inhibitor) or SOM230. (n = three separate samples). Non-linear regression analysis of the % transport activity relative to control (no inhibitor) is shown in Panel B. The IC_{50} value was estimated using equation $J = \frac{J_{app} \times [S]}{K_{app} + [I]} + C$

Additional information:

The IC_{50} values for SOM230 inhibition of OAT1 and OAT3 activities were: about 10 µM and 1.7 ± 0.37 µM, respectively. Although SOM230 showed the inhibitory effect on the activity of OAT1 and OAT3 in *in vitro* system, it is unlikely to be clinical relevant since the therapeutic levels (Cmax.ss <0.1 µM for Cushing's disease and <0.025 µM for acromegaly) were much lower than the IC_{50} values.