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2.6.4　薬物動態試験の概要文

2.6.4.1　まとめ

フィネレノンの動物及びヒトにおける薬物動態を *in vitro* 及び *in vivo* 試験で評価した。以下に主要な試験成績を要約する（臨床薬理試験については 2.7.2 を参照のこと）。

フィネレノンの絶対的バイオアベイラビリティは、ラットでは 0.3～3mg/kg の用量範囲で約 83%～120%と高く、イヌでは 0.03～0.3mg/kg の用量範囲で約 57%～60%、3mg/kg の用量では約 100%と中程度又は高かった。

フィネレノンの血漿クリアランスはマウス〔約 0.0062L/(h·kg)〕及びラット〔約 0.011～0.014L/(h·kg)〕で極めて低く、イヌ〔約 0.16L/(h·kg)〕及びサル〔0.39L/(h·kg)〕では低かった。分布容積はマウス（約 0.10L/kg）及びラット（約 0.11～0.14L/kg）で小さく、イヌ（約 0.39L/kg）及びサル（約 0.25L/kg）では中程度であった。

フィネレノンを単回静脈内投与したときの血漿中未変化体の終末相における消失半減期は、マウスで約 12 時間、ラットで約 8.1～8.6 時間であった。一方、イヌでの終末相における消失半減期は約 1.7 時間、サルでは約 1.3 時間と短かった。

フィネレノンの血漿タンパク結合には著しい種差が認められた。すなわち、臨床濃度範囲においてフィネレノンの血漿タンパク結合率は、げっ歯類（ラット及びマウス）及びウサギでは高かったが、ほとんどの非げっ歯類（サル、イヌ及びヒト）では中程度であった。臨床濃度範囲における非結合型分率（f_u）は、約 0.047%（ラット）～約 8.3%（ヒト）の範囲であった。ヒト血漿における主要な結合タンパクは、血清アルブミンであった。フィネレノンのα1-酸性糖タンパク、低密度リポタンパク質（LDL）、α-グロブリン及びγ-グロブリンに対する結合率は低かった。フィネレノンは、臨床濃度範囲においてラット及びイヌの全血中では主に血漿に分布した〔血液中濃度／血漿中濃度比（C_b/C_p）がそれぞれ約 0.55 及び約 0.72〕。一方、ヒトでは血液と血漿にほぼ均等に分布した（C_b/C_p：約 0.94）。

ラットに[^{14}C]フィネレノンを単回静脈内又は経口投与したとき、放射能濃度は血液及び血流量が多い臓器・組織（肺、肝臓及び腎臓）並びに間質腔で高かった。脳内放射能濃度は血液中濃度の 2%未満であり、これは採取した脳試料中の残存血液量にほぼ相当する。[^{14}C]フィネレノン及び／又は放射性標識代謝物の有色組織に対する親和性は低かった。妊娠ラットにおいて、血液又は組織中放射能濃度－時間曲線下面積〔AUC(0-24)〕の胎児／母体血液比及び胎児血液／母体血液比はそれぞれ 0.06 及び 0.09 であった。これは、放射能が血液胎盤関門を中程度通過したことを示している。放射能は時間と共にラットの臓器・組織から消失し、投与後 168 時間のラット体内における残存放射能は投与量の 0.1%未満であった。ラットの臓器・組織において放射能の不可逆的な結合や残留は認められなかった。

[^{14}C]フィネレノンを単回経口投与したとき、マウス及びラット血漿中ではフィネレノンが圧倒的な主要成分（総放射能 AUC の 96%超）であり、少量成分としてナフチリジン代謝物 M-1 及びジヒドロジオール代謝物 M-4／水酸化代謝物 M-7 がみられた。対照的に、イヌ及びヒト血漿中では、フィネレノンが総放射能 AUC に占める割合は少なかった（イヌ：約 28%、ヒト：7.1%）。イヌ血漿中では、ヒドロキシメチルナフチリジン代謝物 M-2 が最も多い代謝物（総放射能 AUC の 36%）であり、次いで M-1（総放射能 AUC の 8.1%）及び M-4／M-7（総放射能 AUC の約 11%）、更に少量のナフチリジンカルボン酸代謝物 M-3（総放射能 AUC の 2%未満）が認められた。ヒト血漿中では、M-1、M-2 及び M-3 が主要成分であり、総放射能 AUC に占める割合はそれぞれ約

49%、約 22%及び 9%であった。ヒト血漿中におけるジヒドロジオール代謝物 M-4 及び M-5 の曝露量はわずかに過ぎなかった（それぞれ総放射能 AUC の 3%未満）。

[^{14}C]フィネレノンを動物及びヒトに単回経口投与したとき、尿中に排泄された未変化体は少量（投与量の 1.5%未満）に過ぎなかった。糞中に排泄された未変化体は、ラットで投与量の約 7.9%、イヌで約 2.9%、ヒトで約 0.2%であった。すべての動物種で、尿及び糞中に排泄された放射能の大部分は代謝物 M-2、M-3、M-4 及び M-5 であった。ラット及びヒトではナフチリジンカルボン酸代謝物 M-3 が排泄された放射能の主成分（それぞれ投与量の約 27%及び約 48%）であったが、イヌではヒドロキシメチルナフチリジン代謝物 M-2 が排泄された放射能の主成分（投与量の約 43%）であった。

ヒト血漿中の主成分である代謝物 M-1、M-2 及び M-3 は軸性キラリティを示し、それぞれアトロプ異性体 M-1a、M-1b、M-2a、M-2b、M-3a 及び M-3b から成ることが明らかとなった。[^{14}C]フィネレノン又はフィネレノンをそれぞれ単回又は反復投与後のラット、イヌ及びヒトの血漿及び／又は尿試料を分析した結果、いずれの動物種においても、各代謝物について主に一方のアトロプ異性体（「a」を付した一連の異性体であり、異性体存在比はいずれも 80%超）が認められた。*In vivo* 試験での異性体存在比は、肝ミクロソームを用いた *in vitro* 試験での異性体存在比をよく反映していた。これらの異性体存在比とヒトでのマスバランス試験及び腎機能障害を有する患者での試験で得られた代謝物の曝露量に基づくと、代謝物 M-1a、M-1b、M-2a 及び M-3a がヒト血漿中での主代謝物（薬物由来成分の総 AUC の 10%超）であった。

ヒト血漿中での主代謝物である M-1a、M-1b、M-2a 及び M-3a のタンパク結合率には、マウス、ラット、イヌ、ウサギ及びヒトの間で種差が認められた（非結合型分率は M-1a：約 5.8%～15%、M-1b：約 1.3%～12%、M-2a：約 17%～58%、M-3a：約 68%～82%）。主代謝物におけるタンパク結合の種差は、フィネレノンと比べて小さかった。

In vivo でフィネレノン（*S*－エナンチオマー）が薬理学的に不活性なエナンチオマー（BAY 94-8863：*R*－エナンチオマー）に反転しラセミ化が生じる可能性について、ヒト血漿中において検討した結果、フィネレノンのキラル反転／ラセミ化は生じないことが明らかとなった。

In vitro で[^{14}C]フィネレノンを動物及びヒトの肝ミクロソーム及び肝細胞とインキュベートしたとき、雌ラットの肝ミクロソームでの代謝物の産生がわずかであったことを除き、代謝物の産生量は多かった。*In vivo* での結果と一致して、2 つの重要な代謝経路が明らかとなった。すなわち、フィネレノンのジヒドロピリジン部分の酸化によりナフチリジン代謝物 M-1 が産生される経路（続いて水酸化を受けて M-2 が産生）と、恐らくエポキシド中間体が加水分解を受けてジヒドロジオール代謝物 M-4 が産生される経路である。代謝経路には明らかな種差は認められなかった。

[^{14}C]フィネレノンを単回経口投与したとき、ラットでは放射能は主に胆汁／糞を介する経路（投与量の約 76%）で排泄されたが、イヌでは放射能は胆汁／糞を介する経路（投与量の 42%）及び尿を介する経路（投与量の約 53%）にほぼ均等に排泄された。ヒトに[^{14}C]フィネレノンを単回経口投与したとき、放射能は主に尿（投与量の約 80%）を介して排泄された。授乳ラットに[^{14}C]フィネレノンを単回静脈内投与したとき、投与量の約 20%が乳汁中に分泌された。

フィネレノンはヒト結腸腺癌（Caco-2）細胞における膜透過性が高かった。*In vitro* 試験に基づくと、フィネレノンは P-糖タンパク質（P-gp）の基質であった。一方、フィネレノンは乳癌耐性タンパク（BCRP）、有機カチオントランスポーター（OCT）1、有機アニオン輸送ポリペプチド（OATP）1B1 及び OATP1B3 の基質ではなかった。

フィネレノンの酸化的代謝は主にチトクローム P450（CYP）3A4 により触媒され、CYP2C8 の寄与もわずかに認められた。

フィネレノンはヒトのウリジン二リン酸グルクロン酸転移酵素（UGT）1A1、1A4、1A6、1A9、2B4 及び 2B7 の活性に対して影響を及ぼさなかった。また、ヒト CYP 分子種 1A2、2A6、2B6、2C9、2C19、2D6 及び 2E1 に対しても意味のある阻害作用を示さなかった〔50%阻害濃度（IC_{50}）≧29 μM〕。フィネレノンは CYP2C8〔阻害定数（K_i）：1.9μM〕及び CYP1A1（IC_{50}：6.7μM）に対して競合的阻害作用を示した。また、CYP3A4 に対しては可逆的阻害（IC_{50}：19/12μM）と不可逆的阻害〔最大不活性化速度定数（k_{inact}）：0.012min^{-1}、最大不活性化速度の 50%の速度をもたらす阻害薬の濃度（K_I）：10.3μM〕が認められた。ヒト血漿中での主代謝物である M-1a、M-1b、M-2a 及び M-3a は、いずれも主要な CYP 分子種に対して意味のある阻害作用を示さなかった。

フィネレノンは *in vitro* で P-gp 及び BCRP を阻害し、P-gp に対する IC_{50} は 47／121μM、BCRP に対する IC_{50} は 17.4／18.1μM であった。一方、フィネレノンは、胆汁酸塩排出ポンプ（BSEP）、多剤排出トランスポーター（MATE）1、MATE2K、有機アニオントランスポーター（OAT）1、OAT3、OCT1 及び OCT2 をいずれも阻害しなかった。

OATP1B1 及び OATP1B3 とのプレインキュベーション試験の結果、フィネレノンは OATP1B1 のみを阻害し（IC_{50}：3.2μM）、OATP1B3 に対しては影響を及ぼさなかった。

代謝物 M-1a、M-1b、M-2a 及び M-3a は、排出トランスポーターである BCRP、BSEP、MATE1 及び MATE2K 並びに取込みトランスポーターである OAT1、OAT3、OCT1 及び OCT2 をいずれも阻害しなかった。更に、これらの代謝物は P-gp を阻害しないか（M-2a 及び M-3a）、若しくは意味のある阻害作用を示さなかった（M-1a 及び M-1b の IC_{50}：それぞれ 70 及び 31μM）。しかし、M-1a 及び M-1b はいずれも OATP を阻害し、OATP1B1 に対する IC_{50} は 3.8μM（M-1a）及び 3.9μM（M-1b）、OATP1B3 に対する IC_{50} は 7.6μM（M-1a）及び 7.3μM（M-1b）であった。M-2a は OATP1B1 及び OATP1B3 のいずれも阻害しなかった。M-3a は OATP1B3 を阻害（IC_{50}：3.4μM）したが、OATP1B1 に対しては阻害作用を示さなかった。

ヒト肝細胞を用いた *in vitro* 試験において、フィネレノン及びそのヒト血漿中主代謝物 M-1a、M-1b 及び M-2a は CYP3A4 誘導作用を示した。

薬物動態試験成績の要約を概要表 2.6.5.1 Table 1-1 に示す。

2.6.4.2　　分析法

フィネレノン（BAY 94-8862）又は[^{14}C]フィネレノン、その代謝物についてはアトロプ異性体 M-1a（BAY 1117267）、M-1b（BAY 1117266）、M-2a（BAY 1117268）、M-2b（BAY 1117270）、M-3a（BAY 1117271）及び M-3b（BAY 1117272）又は放射性標識した M-1a、M-1b、M-2a 及び M-3a を用いて *in vivo* 及び *in vitro* 試験を実施した。放射性標識体を用いた *in vivo* 試験では、総放射能、未変化体及びその放射性標識代謝物を、[^{14}C]フィネレノン当量（μg-eq）として示した。

In vivo 試験では次の投与製剤（媒体）を用いた。

- マウス、ラット、イヌ及びサルにおけるフィネレノンの未変化体及び標識体由来放射能の薬物動態試験：エタノール 10%、ポリエチレングリコール（PEG）400 又はソルトール HS50 40%、脱塩水 50%（v/v/v）
- ラット及びイヌにおけるトキシコキネティクス試験：エタノール 10%、ソルトール HS15 40%、水道水 50%（v/v/v）（ラット）、PEG400 100%（イヌ）

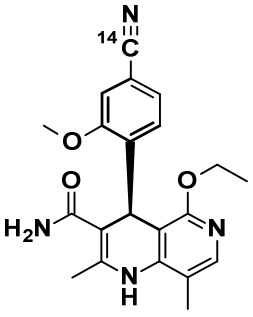
2.6.4.2.1　　フィネレノン及び代謝物の同位体標識

参照項目：4.2.2.1.1　PH-35584
4.2.2.1.2　PH-36288
4.2.2.5.1　A49457
4.2.2.1.4　PH-35402
4.2.2.1.5　A52248
4.2.2.1.6　PH-37636
4.2.2.1.7　PH-37324

マスバランス、タンパク結合、血球／血漿分配などの試験及び液体クロマトグラフィー／タンデム質量分析（LC-MS/MS）による生体試料中薬物濃度分析法に使用するために、常法に従い標識体の合成を実施した。

[^{14}C]フィネレノン：フィネレノン分子のシアノ基を ^{14}C で標識した（図 2.6.4.2- 1）。これに非標識フィネレノンを混合し、比放射能が 3.09MBq/mg 及び 3.13MBq/mg の 2 バッチを得た（4.2.2.1.1 PH-35584 及び 4.2.2.1.2 PH-36288）。放射化学的純度は＞98.1%であった。

図 2.6.4.2- 1　[^{14}C]フィネレノンの構造



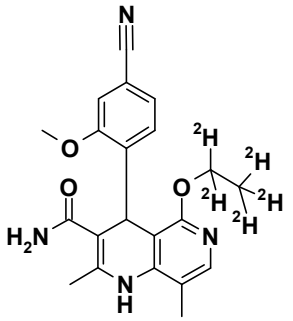
[^{14}C]finerenone
([^{14}C]BAY 94-8862)

Source: 4.2.2.5.1 A49457

ラットに[^{14}C]フィネレノンを経口投与したとき、投与後 24 時間までの呼気中放射能が定量下限（LLOQ）未満であったことから、^{14}C 標識位置は代謝的に安定であることが示された（4.2.2.5.1 A49457）。

[$^{2}H_5$]BAY 85-1980（生体試料中薬物濃度分析における内部標準として使用）：フィネレノンのラセミ体である BAY 85-1980 分子のエチルエーテル基を重水素で標識した（図 2.6.4.2- 2）。標識率は＞98.9%であった（4.2.2.1.4 PH-35402）。

図 2.6.4.2- 2　[$^{2}H_5$]BAY 85-1980 の構造

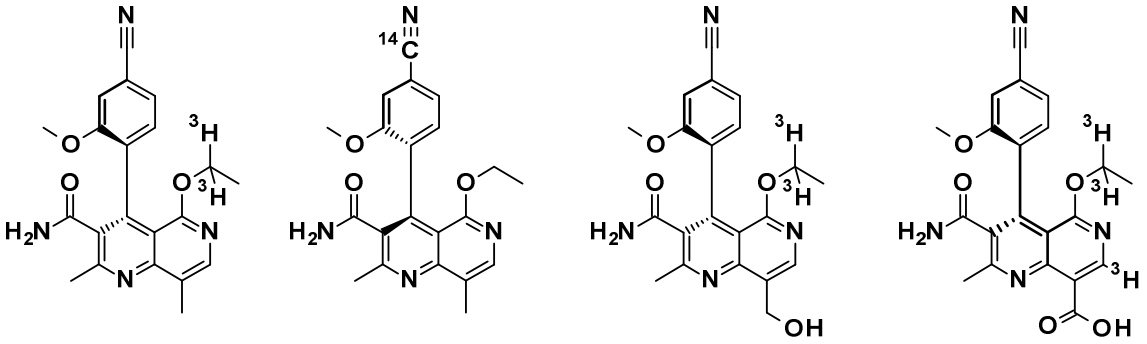


[$^{2}H_5$]BAY 85-1980

Source: 4.2.2.1.4 PH-35402

代謝物の[^{3}H]又は[^{14}C]標識アトロプ異性体：代謝物 M-1a、M-2a 及び M-3a は、イリジウムを触媒として用いた水素／トリチウム交換により、代謝物分子のエチルエーテル基、加えて M-3a の場合には隣接するピリジン環を部分的にトリチウム標識した（図 2.6.4.2- 3）。得られた標識体の比放射能は、4.76GBq/mg（[^{3}H]M-1a）、2.47GBq/mg（[^{3}H]M-2a）及び 4.72GBq/mg（[^{3}H]M-3a）であった（4.2.2.1.5 A52248）。放射化学的純度は＞99.0%であった。また、[^{14}C]M-1b は、[^{14}C]フィネレノンの酸化により合成し、続いてキラル高速液体クロマトグラフィー（HPLC）で分離した。比放射能は 3.32MBq/mg、放射化学的純度は＞97.9%であった（4.2.2.1.6 PH-37636）。

図 2.6.4.2- 3　代謝物の[^{3}H]又は[^{14}C]標識アトロプ異性体の構造

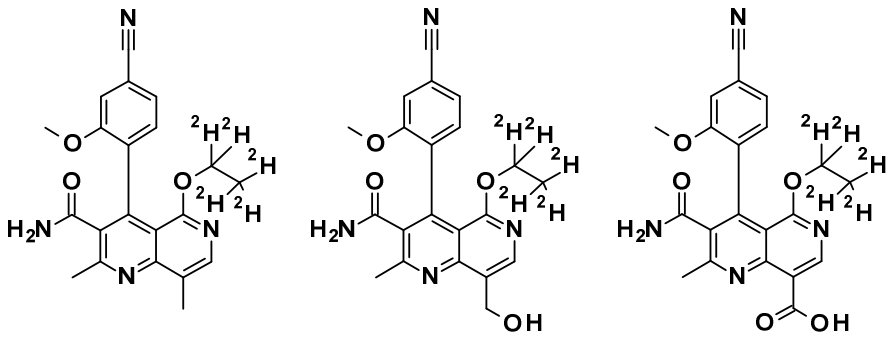


[^{3}H]M-1a ([^{3}H]BAY 1117267)　**[^{14}C]M-1b ([^{14}C]BAY 1117266)**　**[^{3}H]M-2a ([^{3}H]BAY 1117268)**　**[^{3}H]M-3a ([^{3}H]BAY 1117271)**

Source: 4.2.2.1.5 A52248 and 4.2.2.1.6 PH-37636

[$^2H_5$]M-1（[$^2H_5$]BAY 1040818）、[$^2H_5$]M-2（[$^2H_5$]BAY 1088089）及び[$^2H_5$]M-3（[$^2H_5$]BAY 1088090）（生体試料中薬物濃度分析における内部標準として使用）：3 種の代謝物分子のいずれもエチルエーテル基を重水素で標識した（図 2.6.4.2- 4）。標識率はすべての標識代謝物で＞99％であった（4.2.2.1.7 PH-37324）。

図 2.6.4.2- 4　[$^2H_5$]標識代謝物の構造



Source: 4.2.2.1.7 PH-37324

2.6.4.2.2　放射能の測定

体液、臓器・組織及び排泄物試料を適切に前処理した後、液体シンチレーション計数（LSC）法により放射能濃度を測定した。定量的全身オートラジオグラフィー（QWBA）試験では、蛍光イメージング法（ラジオルミノグラフィー）を用いて組織内放射能濃度を測定した。両分析法では、フィネレノンとそれに由来する放射性代謝物を含有する総放射能を測定している。

2.6.4.2.3　血漿及び尿中フィネレノン及び代謝物の測定

参照項目：
4.2.2.1.13　PH-40958
4.2.2.1.12　PH-41142
4.2.2.1.8　R-9602
4.2.2.1.9　R-9546
4.2.2.1.11　R-12055
4.2.2.1.10　R-11117

非臨床及び臨床開発過程において、種々の動物種（マウス、ラット、ウサギ、イヌ、サル及びヒト）の血漿中におけるフィネレノンの未変化体並びに主代謝物である M-1（BAY 1040818）、M-2（BAY 1088089）及び M-3（BAY 1088090）を同時測定するために、個別の試験における必要性に応じて、LC-MS/MS を用いた種々のアキラルな測定法を確立し、バリデーションを実施した。ヒト尿中におけるフィネレノン及びその代謝物は、尿試料をヒト血漿で 10 倍希釈した後にヒト血漿用の LC-MS/MS 分析法を用いて測定した。分析法バリデーション及び実試料の分析は、生体試料中薬物濃度分析法のバリデーションに関する米国食品医薬品局（FDA）及び欧州医薬品庁（EMA）のガイドライン[1、2、3)]を遵守して行った。

重要な非臨床安全性試験及び臨床試験に用いた生体試料中薬物濃度分析法についてはフルバリデーションを実施した（4.2.2.1.13 PH-40958、4.2.2.1.12 PH-41142、4.2.2.1.8 R-9602、4.2.2.1.9 R-9546、4.2.2.1.11 R-12055 及び 4.2.2.1.10 R-11117）。非臨床安全性試験で得られた実試料の分析は、医薬品の安全性に関する非臨床試験の実施の基準（GLP）を遵守して行っ

た。すべての臨床試験で得られた実試料の分析は、医薬品の臨床試験に関する基準（GCP）及びGLP に従って行った。

除タンパクを含む試料の前処理操作を行った後、LC-MS/MS を用いて分離分析を実施した。定量を最適化するために、安定同位体で標識したフィネレノン及びその代謝物を内標準物質として用いた（2.6.4.2.1）。血漿中における未変化体の LLOQ は、実試料の予測血漿中濃度を考慮して、ヒトを除くすべての動物種では 0.50 又は 100μg/L とし、ヒトでは 0.10μg/L とした（表 2.6.4.2- 1）。代謝物の LLOQ は、すべての動物種の血漿中で 0.50 又は 1.0μg/L とした（表 2.6.4.2- 2）。すべての動物種の血漿中において、いずれの分析対象物質についても測定精度は 15%以内（LLOQ では 20%以内）、真度は 85%～115%（LLOQ では 80%～120%）の範囲内であった。

フィネレノンはヒト血漿中において、-15℃以下で少なくとも 22 ヵ月間安定であった。毒性試験で用いた動物種であるラット、イヌ、マウス及びウサギの血漿中では-15℃以下で少なくとも 14 ヵ月間、サル血漿中では-15℃以下で少なくとも 2 ヵ月間安定であった（表 2.6.4.2- 3）。代謝物は、ヒト血漿中では-15℃以下で少なくとも 12 ヵ月間、そのほかの動物種の血漿中では少なくとも 14 ヵ月間安定であった（表 2.6.4.2- 4）。更に、そのほかのマトリックス（例、標準原液及び標準溶液）中での分析対象物質の安定性、分析操作中での試料取り扱いの各段階を含む種々の保存条件（例、温度及び遮光）での安定性及び実試料に適した保存期間の安定性についても検討した。

表 2.6.4.2- 1　フィネレノンの分析法バリデーション

Species	Method No.	Analyte	Working range [µg/L]	Precision[a] [%]	Accuracy[a] [%]
Human (plasma)	MW1398	Finerenone	0.10 - 200	2.8 - 9.2	88.4 - 98.9
Human (plasma)	MW1921	Finerenone	0.10 - 200	0.76 - 5.8	100.3 - 104.4
Human (plasma)	MW2007	Finerenone	0.10 - 200	3.5 - 6.0	100.9 - 104.5
Human (plasma)	MW1452	Finerenone	0.10 - 500	5.2 - 18.6	96.7 - 108.0
Human (plasma)	SBQ-13062	Finerenone	0.10 - 200	2.5 - 9.4	96.8 - 104.7
Human (plasma)	SBQ-14068	Finerenone	0.10 - 500	0.8 - 8.7	99.0 - 104.0
Human (urine)	MW1398	Finerenone	1.0 - 2000	1.0 - 5.4	96.8 - 100.8
Human (urine)	MW1452	Finerenone	1.0 - 5000	1.7 - 8.2	97.8 - 108.5
Human (urine)	SBQ-14069	Finerenone	1.0 - 5000	3.7 - 15.7	89.3 - 108.0
Rat (plasma)	MW1353	Finerenone	0.50 - 1000	1.6 - 9.4	89.1 - 112.7
Rat (plasma)	MW1449	Finerenone	0.50 - 1000	3.1 - 8.6	93.6 - 99.4
Rat (plasma)	MW1358	Finerenone	100 - 100000	2.0 - 7.4	96.0 - 103.4
Rat (plasma)	MW1923	Finerenone	100 - 100000	1.0 - 7.3	92.2 - 102.4
Dog (plasma)	MW1353	Finerenone	0.50 - 1000	0.6 - 9.4	95.4 - 98.8
Dog (plasma)	MW1449	Finerenone	0.50 - 1000	2.4 - 9.8	86.7 - 96.3
Dog (plasma)	MW1358	Finerenone	100 - 100000	0.4 - 4.4	96.5 - 103.7
Mouse (plasma)	MW1353	Finerenone	0.50 - 1000	0.9 - 4.0	100.3 - 105.0
Mouse (plasma)	MW1449	Finerenone	0.50 - 1000	1.4 - 7.6	97.7 - 105.9
Mouse (plasma)	MW1358	Finerenone	100 - 100000	2.9 - 6.0	97.0 - 102.2
Rabbit (plasma)	MW1449	Finerenone	0.50 - 1000	2.3 - 9.0	95.4 - 104.8
Monkey (plasma)	MW1353	Finerenone	0.50 - 1000	0.7 - 3.9	98.8 - 102.5

Source: 4.2.2.1.13 PH-40958; 4.2.2.1.8 R-9602; 4.2.2.1.9 R-9546; 4.2.2.1.10 R-11117; 4.2.2.1.12 PH-41142
a = LLOQ-QC, low-QC, mid-QC, high-QC and/or ULOQ

表 2.6.4.2- 2 代謝物 M-1（BAY 1040818）、M-2（BAY 1088089）及び M-3（BAY 1088090）の分析法バリデーション

Species	Method No.	Analyte	Working range [µg/L]	Precision[a] [%]	Accuracy[a] [%]
Human (plasma)	MW1452	M-1	0.50 - 500	3.2 - 11.9	91.0 - 99.5
Human (plasma)	MW1452	M-2	0.50 - 500	6.9 - 17.0	95.4 – 103.5
Human (plasma)	MW1452	M-3	0.50 - 500	3.7 - 9.3	96.7 - 99.3
Human (plasma)	SBQ-14068	M-1	0.50 - 500	3.6 - 17.3	96.0 - 100.6
Human (plasma)	SBQ-14068	M-2	0.50 - 500	1.3 - 7.1	101.3 - 103.6
Human (plasma)	SBQ-14068	M-3	0.50 - 500	1.7 - 6.6	96.0 - 100.0
Human (urine)	MW1452	M-1	5.0 - 5000	2.3 - 7.6	98.9 - 103.0
Human (urine)	MW1452	M-2	5.0 - 5000	3.8 - 5.5	99.0 - 101.6
Human (urine)	MW1452	M-3	5.0 - 5000	3.2 - 4.3	98.9 – 104.3
Human (urine)	SBQ-14069	M-1	5.0 - 5000	4.5 - 13.1	98.6 - 104.0
Human (urine)	SBQ-14069	M-2	5.0 - 5000	4.2 - 7.8	98.7 - 105.6
Human (urine)	SBQ-14069	M-3	5.0 - 5000	2.4 - 7.0	98.2 - 102.6
Rat (plasma)	MW1449	M-1	0.50 - 1000	3.5 - 13.1	99.4 - 104.7
Rat (plasma)	MW1449	M-2	0.50 - 1000	4.3 - 8.1	97.1 - 109.5
Rat (plasma)	MW1449	M-3	0.50 - 1000	3.3 - 7.6	95.0 - 101.1
Dog (plasma)	MW1449	M-1	0.50 - 1000	3.2 - 18.7	86.4 - 107.0
Dog (plasma)	MW1449	M-2	0.50 - 1000	3.0 - 3.7	87.8 - 103.4
Dog (plasma)	MW1449	M-3	0.50 - 1000	2.6 - 5.7	91.7 - 99.0
Mouse (plasma)	MW1449	M-1	1.0 - 1000	1.7 - 7.9	89.5 - 103.7
Mouse (plasma)	MW1449	M-2	0.50 - 1000	1.3 - 12.8	96.8 - 103.2
Mouse (plasma)	MW1449	M-3	0.50 - 1000	1.2 - 4.3	97.7 - 100.2
Rabbit (plasma)	MW1449	M-1	0.50 - 1000	2.5 - 16.2	99.6 - 115.5
Rabbit (plasma)	MW1449	M-2	0.50 - 1000	3.5 - 12.8	94.4 - 105.5
Rabbit (plasma)	MW1449	M-3	0.50 - 1000	0.5 - 4.2	97.4 - 101.4

Source: 4.2.2.1.9 R-9546; 4.2.2.1.10 R-11117; 4.2.2.1.13 PH-40958; 4.2.2.1.12 PH-41142

a = LLOQ-QC, low-QC, mid-QC, high-QC and/or ULOQ

表 2.6.4.2- 3 血漿中におけるフィネレノンの安定性

Stability type	Species	Temperature	Period	Stable
Freezer	Human	≤ -15°C	> 22 months	Yes
Freezer	Wistar rat, Beagle dog, CD-1 mouse, Himalayan rabbit	≤ -15°C	> 14 months	Yes
	Cynomolgus monkey	≤ -15°C	> 2 months	Yes
Physiological incubation	CD-1 mouse, Wistar rat, Beagle dog, Himalayan rabbit, Cynomolgus monkey, human	37°C	> 2 h	Yes

Source: 4.2.2.1.13 PH-40958; 4.2.2.1.12 PH-41142

表 2.6.4.2- 4　血漿中における代謝物 M-1（BAY 1040818）、M-2（BAY 1088089）及び M-3（BAY 1088090）の安定性

Stability type	Species	Temperature	Period	Stable
Freezer	Human	≤ -15°C	> 12 months	Yes
Freezer	Wistar rat, Beagle dog, CD-1 mouse, Himalayan rabbit	≤ -15°C	> 14 months	Yes
Physiological incubation	CD-1 mouse, Wistar rat, Beagle dog, Himalayan rabbit, human	37°C	> 2 h	Yes

Source: 4.2.2.1.13 PH-40958; 4.2.2.1.12 PH-41142

2.6.4.2.4　代謝物プロファイルの検討

参照項目：4.2.2.4.11　PH-39577
4.2.2.4.1　PH-41146

代謝物プロファイルは逆相カラムを接続した HPLC を用いて検討した。0.05%ギ酸、0.1%トリフルオロ酢酸又は 25mM ギ酸アンモニウム（pH4）／アセトニトリルのグラジエントあるいは 0.2%リン酸二水素カリウム水溶液（pH2）／アセトニトリルのグラジエントにより溶出し、オフラインで放射能を検出した。代謝物 M-4 及び M-5 は生体試料を固相抽出法により前処理した後、分取 HPLC を用いて単離した（4.2.2.4.11 PH-39577）。構造解析には液体クロマトグラフィー／高分解能質量分析（LC-HRMS）、LC-MS/MS、核磁気共鳴（NMR）などの手法を用いた（4.2.2.4.1 PH-41146）。フィネレノン並びに代謝物 M-1a、M-1b、M-2a、M-2b、M-3a 及び M-3b の化学構造は、化学的及び生化学的合成法で得られた標準品との比較により確認した。

2.6.4.2.5　薬物動態データの解析

薬物濃度－時間データの薬物動態評価は、ToxKin®プログラム（Entimo 社、ドイツ）あるいは KINCALC プログラム（Bayer 社、ドイツ）を用いたノンコンパートメント（モーメント）解析により行った。この方法で得られた薬物動態パラメータは、非臨床薬物動態の評価及びヒト薬物動態との比較を行う上で適切と考えられる。

なお、フィネレノンの分子量は 378.42 をモル及び重量単位の相互換算に用いた（378.42μg/L＝1μM）。また、代謝物 M-1、M-2 及び M-3 については、分子量をそれぞれ 376.41（376.41μg/L＝1μM）、392.41（392.41μg/L＝1μM）及び 406.39（406.39μg/L＝1μM）として換算した。

薬物動態パラメータ及び濃度値は幾何平均及び標準偏差（S.D.）（1s 範囲：$\overline{X}_g/s_g$；$\overline{X}_g \cdot s_g$）として示した。一部の試験では濃度の幾何平均データから薬物動態パラメータを算出した。一方、血漿タンパク結合のデータ、排泄率及び回収率は算術平均及び標準偏差として示した。

2.6.4.3 吸収

2.6.4.3.1 単回投与後の薬物動態

参照項目： 4.2.2.2.1 A49288
4.2.2.2.2 A49516
4.2.2.5.1 A49457
4.2.2.2.3 A49278
4.2.2.5.2 PH-37447
4.2.2.2.4 A49292

マウス、ラット、イヌ及びサルにフィネレノン又は[^{14}C]フィネレノンを単回投与したときの薬物動態試験の概要を表 2.6.4.3- 1～表 2.6.4.3- 4 に、試験成績を表 2.6.4.3- 5～表 2.6.4.3- 7 及び図 2.6.4.3- 1 に示す。

表 2.6.4.3- 1 マウスにおける単回投与薬物動態試験の概要

Study type	Single dose pharmacokinetics, *in vivo* study	
Bayer reference	4.2.2.2.1 A49288	
Test system	Mice, 3 males/time point, strain: CD-1	
Dosage	Finerenone[a]:	0.3 mg/kg (iv)
Vehicle, volume & route of admin.	iv administration:	10% ethanol, 40% PEG 400, 50% demin. water, v/v/v, 10 mL/kg, bolus injection
Assay, matrix	LC-MS/MS, plasma samples	

a = batch No. BFS 3779-5-1

表 2.6.4.3- 2 ラットにおける単回投与薬物動態試験の概要

Study type	Single dose pharmacokinetics, *in vivo* study	
Bayer reference	4.2.2.2.2 A49516; 4.2.2.5.1 A49457	
Test system	Intact rats: 3 males/time point, strain: Wistar Bile duct-cannulated rats: 4-5 males/dose group, strain: Wistar	
Dosage	[^{14}C]finerenone[a]:	1 mg/kg (iv) and 1 mg/kg (po)
	Finerenone[b]:	0.3 mg/kg (iv) and 0.3, 3 mg/kg (po)
Vehicle, volume & route of admin.	iv administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 5 mL/kg, bolus injection
	po administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 5 mL/kg, gavage
Assay, matrix	LSC, LC-MS/MS, plasma samples, urine, bile, feces	

a = specific activity: 3.09 MBq/mg

b = batch No. BXR42XB

表 2.6.4.3- 3 イヌにおける単回投与薬物動態試験の概要

Study type	Single dose pharmacokinetics, *in vivo* study	
Bayer reference	4.2.2.2.3 A49278; 4.2.2.5.2 PH-37447	
Test system	Dogs, 3-4 females/dose group, strain: Beagle	
Dosage	[^{14}C]finerenone[a]:	3 mg/kg (po)
	Finerenone[b]:	0.3 (iv) and 0.03, 0.3, 3 mg/kg (po)
Vehicle, volume & route of admin.	iv administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 1 mL/kg, infusion [T = 0.25 h]
	po administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 1 mL/kg, gavage
Assay, matrix	LSC, LC-MS/MS, plasma samples, urine, feces	

a = specific activity: 1.545 MBq/mg

b = batch No. BXR42XB

表 2.6.4.3- 4 サルにおける単回投与薬物動態試験の概要

Study type	Single dose pharmacokinetics, *in vivo* study	
Bayer reference	4.2.2.2.4 A49292	
Test system	Monkeys, 3 females/dose group, strain: Cynomolgus	
Dosage	Finerenone[a]:	1 mg/kg (iv)
Vehicle, volume & route of admin.	iv administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 1 mL/kg, infusion [T = 0.25 h]
Assay, matrix	LC-MS/MS, plasma samples	

a = batch No. BXR42XB

表 2.6.4.3- 5 [^{14}C]フィネレノン単回投与後の放射能の薬物動態パラメータ

Species		**Rat**	**Rat**	**Dog**
Gender		**Male**	**Male**	**Female**
Dose	**[mg/kg]**	**1**	**1**	**3**
Route		**iv**	**po**	**po**
AUC	[µg-eq·h/L]	88620	73498	68400
AUC_{norm}	[kg·h/L]	88.6	73.5	22.8
$C_{eq,max}$	[µg-eq/L]	17428	9015	6590
$C_{eq,max,norm}$	[kg/L]	17.4	9.02	2.20
t_{max}	[h]	0.0333	0.750	0.875
$t_{1/2}$	[h]	19.3	8.1	167
Interval[a]	[h]	72-168	4-72	144-336
$t_{1/2,app}$	[h]	7.15	n.c.[b]	7.13
Interval[a]	[h]	2-48	n.c.[b]	2-32

Source: 4.2.2.2.2 A49516; 4.2.2.5.2 PH-37447

a = used for regression to determine half-life

b = not calculated

表 2.6.4.3- 6 フィネレノン単回静脈内投与後の未変化体の薬物動態パラメータ

Species		**Mouse**	**Rat**	**Rat**	**Dog**	**Monkey**
Gender		**Male**	**Male**	**Male**	**Female**	**Female**
Dose	**[mg/kg]**	**0.3**	**0.3**	**1[b]**	**0.3**	**1**
AUC	[µg·h/L]	48527	28106	72200	1908	2565
AUC_{norm}	[kg·h/L]	162	93.7	72.2	6.36	2.57
C_{max}	[µg/L]	4349	5502	14725	730	3998
$C_{max,norm}$	[kg/L]	14.5	18.3	14.7	2.43	4.00
t_{max}	[h]	0.0833	0.0333	0.0333	0.250	0.250
CL	[L/(h·kg)]	0.00618	0.0107	0.0139	0.157	0.390
V_{ss}	[L/kg]	0.0996	0.112	0.135	0.388	0.247
$t_{1/2}$	[h]	11.7	8.60	8.13	1.68	1.31
Interval[a]	[h]	0.5-72	2-72	2-72	0.333-10	3-10

Source: 4.2.2.2.1 A49288; 4.2.2.2.2 A49516; 4.2.2.2.3 A49278; 4.2.2.2.4 A49292

a = used for regression to determine half-life

b = [^{14}C]finerenone was administered

表 2.6.4.3- 7 フィネレノン単回経口投与後の未変化体の薬物動態パラメータ

Species		**Rat**	**Rat**	**Rat**	**Dog**	**Dog**	**Dog**	**Dog**
Gender		**Male**	**Male**	**Male**	**Female**	**Female**	**Female**	**Female**
Dose	**[mg/kg]**	**0.3**	**1[c]**	**3**	**0.03**	**0.3**	**3**	**3[c]**
AUC	[µg·h/L]	25473	59998	260257	108	1137	18503	19100
AUC_{norm}	[kg·h/L]	84.9	60.0	86.8	3.59	3.79	6.17	6.36
C_{max}	[µg/L]	1870	7465	24471	29.6	303	4033	5020
$C_{max,norm}$	[kg/L]	6.23	7.47	8.16	0.986	1.01	1.34	1.67
t_{max}	[h]	2.00	0.750	0.750	2.00	0.909	0.630	0.500
$t_{1/2}$	[h]	9.12	7.79	9.14	1.47	1.76	2.35	2.44
Interval[a]	[h]	3-72	2-72	8-72	2-10	2-10	0.75-32	2-32
F	[%]	90.6[b]	83.1[b]	120[d]	56.5[d]	59.6[b]	97.0[d]	100[d]

Source: 4.2.2.2.2 A49516; 4.2.2.2.3 A49278; 4.2.2.5.2 PH-37447

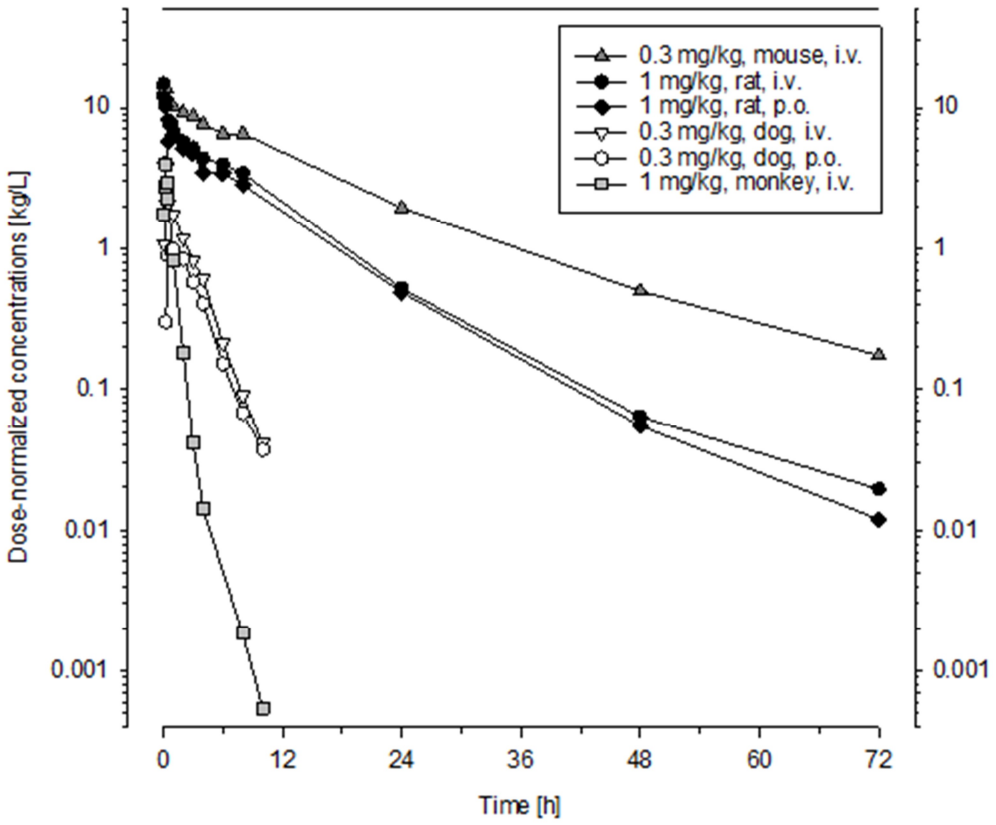
a = used for regression to determine half-life

b = related to the corresponding AUC_{norm}

c = [^{14}C]finerenone was administered

d = bioavailability calculated with the AUC_{norm} iv of 1 mg/kg for rats and the AUC_{norm} iv of 0.3 mg/kg for dogs

図 2.6.4.3- 1　CD-1 マウス、Wistar ラット、ビーグル犬及びカニクイザルにフィネレノンを単回経口投与及び静脈内投与後の用量補正した血漿中未変化体濃度



Source: 4.2.2.2.1 A49288; 4.2.2.2.2 A49516; 4.2.2.2.3 A49278; 4.2.2.2.4 A49292

雄ラットにフィネレノンを単回静脈内投与（0.3 及び 1mg/kg）及び単回経口投与（0.3～3mg/kg）したとき、未変化体の薬物動態は検討した用量範囲でほぼ線形であった。イヌにフィネレノンを単回経口投与（0.03～3mg/kg）したとき、未変化体の AUC 及び最高血漿中濃度（C_{max}）は 0.3mg/kg までの用量範囲で用量比例性を示した。0.3～3mg/kg の用量範囲では、AUC 及び C_{max} は用量比例性を上回って増加した（表 2.6.4.3- 6 及び表 2.6.4.3- 7）。

無処置ラット及び胆管カニュレーションを施した（BDC）ラットに[^{14}C]フィネレノンを単回経口投与及び静脈内投与したマスバランス試験の結果に基づくと、消化管からの放射能の吸収率は高い又は完全であった（2.6.4.6.1）。ラットにおいて、フィネレノンの絶対的バイオアベイラビリティは高く、0.3～3mg/kg の用量範囲で約 83%～120%であった。イヌでは、フィネレノンのバイオアベイラビリティは 0.03～3mg/kg の用量範囲で約 57%～100%であった。なお、イヌで約 100%の高いバイオアベイラビリティを示したのは、AUC が明らかに用量比例性を上回った 3mg/kg 経口投与時であった（表 2.6.4.3- 7）。

フィネレノンの血漿クリアランスはマウス〔約 0.0062L/(h·kg)〕及びラット〔約 0.011～0.014L/(h·kg)〕で極めて低く、イヌ〔約 0.16L/(h·kg)〕及びサル〔0.39L/(h·kg)〕では低かった。分布容積はマウス（約 0.10L/kg）及びラット（約 0.11～0.14L/kg）で小さく、イヌ（約 0.39L/kg）及びサル（約 0.25L/kg）では中程度であった（表 2.6.4.3- 6）。

マウスにフィネレノンを単回静脈内投与したときの血漿中未変化体濃度の終末相における消失半減期は長く、約 12 時間（投与後 72 時間までの時間範囲で算出）であった。また、ラットにフィネレノンを単回静脈内及び経口投与したときの消失半減期も長く、それぞれ約 8.1～8.6 時間及び約 7.8～9.1 時間（投与後 72 時間までの時間範囲）であった。対照的に、イヌ及びサルでは消失半減期は短く、イヌにフィネレノンを単回静脈内投与及び経口投与したときの終末相における消失半減期はそれぞれ約 1.7 時間及び約 1.5～2.4 時間（投与後 10 又は 32 時間までの時間範囲）、サルに単回静脈内投与したときの終末相における消失半減期は約 1.3 時間（投与後 10 時間までの時間範囲）であった（表 2.6.4.3- 6 及び表 2.6.4.3- 7）。

ラットに[^{14}C]フィネレノンを単回静脈内及び経口投与したときの血漿中放射能の消失半減期は、未変化体の場合と同等の時間範囲（投与後 48 又は 72 時間まで）で算出したとき、約 7～8 時間であり未変化体と同様であった。一方、単回静脈内投与したときの血漿中放射能濃度が最高フィネレノン当量濃度（$C_{eq,max}$）の 0.2%未満である終末相（投与後 72～168 時間までの時間範囲）においては、放射能は約 20 時間の消失半減期で消失した。イヌに[^{14}C]フィネレノンを単回経口投与したとき、血漿中放射能濃度が $C_{eq,max}$ の 0.5%未満である終末相（投与後 144～336 時間までの時間範囲）において、放射能は 167 時間の消失半減期で消失した（表 2.6.4.3- 5）。

2.6.4.3.2　反復投与後の薬物動態

参照項目：
4.2.3.2.6　PH-36275
4.2.3.2.10　PH-36393
4.2.3.2.9　PH-37792
4.2.3.2.8　PH-36695
4.2.3.2.11　PH-36687
4.2.3.2.12　PH-37743

フィネレノンを反復経口投与後の薬物動態は、GLP 基準に従って実施された毒性試験の一環として得られた曝露量に基づき限定的な評価を行った（2.6.6）。

ラット及びイヌにフィネレノンを反復投与したときのトキシコキネティクス試験の概要を表 2.6.4.3- 8 に、試験成績を表 2.6.4.3- 9 及び表 2.6.4.3- 10 に示す。

表 2.6.4.3- 8　主要なトキシコキネティクス試験の概要

Study type	Toxicokinetics		
Bayer reference	4.2.3.2.6 PH-36275; 4.2.3.2.10 PH-36393; 4.2.3.2.9 PH-37792; 4.2.3.2.8 PH-36695; 4.2.3.2.11 PH-36687; 4.2.3.2.12 PH-37743		
Test system	Wistar rats:	3 females and males / time point	
	Beagle dogs:	3 females and males / dose group (4 weeks study)	
		4 females and males / dose group (13 and 39 weeks study)	
Dosage	Finerenone:	Rat	3, 10, 30 mg/kg/d over 4 weeks
		Rat	3, 10, 30 mg/kg/d over 13 weeks
		Rat (F)	0.5, 1.5, 5 mg/kg/d over 26 weeks
		Rat (M)	1.5, 5, 15 mg/kg/d over 26 weeks
		Dog	1.5, 5, 15 mg/kg/d over 4 weeks
		Dog	1, 3, 10 mg/kg/d over 13 weeks
		Dog	0.5, 1.5, 5 mg/kg/d over 39 weeks
Vehicle	Rat:	10% Ethanol, 40% Solutol HS15, 50% tap water, v/v/v	
	Dog:	100% PEG 400	
Assay, matrix	LC-MS/MS, plasma samples		

表 2.6.4.3- 9 ラットにフィネレノンを反復経口投与後の未変化体の薬物動態パラメータ

Daily dose [mg/kg/d]	Gender	Date Day	C_{max} [µg/L]	AUC(0-24) [µg·h/L]	$AUC(0\text{-}24)_{norm}$ [kg·h/L]	$C(24)/C_{max}$ [%]	R_AC_{max} [%]	R_AAUC [%]
Rat study (4 weeks) T6078272, 4.2.3.2.6 PH-36275								
3	F	29	59273	1190202	397	71.8	306	288
10	F	29	104374	2060230	206	64.0	191	178
30	F	29	135460	2524171	84.1	56.9	115	104
3	M	29	18975	315146	105	37.8	156	178
10	M	29	57398	993599	99.4	40.8	141	169
30	M	29	116639	1842506	61.4	27.8	129	126
Daily dose [mg/kg/d]	**Gender**	**Date Day**	**C_{max} [µg/L]**	**AUC(0-24) [µg·h/L]**	**$AUC(0\text{-}24)_{norm}$ [kg·h/L]**	**$C(24)/C_{max}$ [%]**	**R_AC_{max} [%]**	**R_AAUC [%]**
Rat study (13 weeks) T0081579, 4.2.3.2.8 PH-36695								
3	F	90	57285	1211627	404	76.2	323	327
10	F	90	123245	2211234	221	46.0	174	214
30	F	90	155810	2680696	89.4	44.1	102	126
3	M	90	25813	419184	140	36.9	282	253
10	M	90	80808	1375110	138	40.1	248	236
30	M	90	115355	1821813	60.7	26.9	126	122
Daily dose [mg/kg/d]	**Gender**	**Date Day**	**C_{max} [µg/L]**	**AUC(0-24) [µg·h/L]**	**$AUC(0\text{-}24)_{norm}$ [kg·h/L]**	**$C(24)/C_{max}$ [%]**	**R_AC_{max} [%]**	**R_AAUC [%]**
Rat study (26 weeks) T9082784, 4.2.3.2.9 PH-37792								
0.5	F	164	17000	349000	699	73.2	525.1	601.0
1.5	F	164	46500	992000	661	80.7	257.5	332.0
5	F	164	101000	1990000	398	74.2	311.4	351.9
1.5	M	164	7610	118000	78.5	35.2	185.9	137.2
5	M	164	42500	704000	141	32.2	241.6	337.1
15	M	164	107000	1980000	132	48.7	211.1	197.5

Source: 4.2.3.2.6 PH-36275; 4.2.3.2.8 PH-36695; 4.2.3.2.9 PH-37792

表 2.6.4.3- 10 イヌにフィネレノン反復経口投与後の未変化体の薬物動態パラメータ

Daily dose [mg/kg/d]	Gender	Date Day	C_{max} [µg/L]	AUC(0-24) [µg·h/L]	$AUC(0\text{-}24)_{norm}$ [kg·h/L]	$C(24)/C_{max}$ [%]	R_AC_{max} [%]	R_AAUC [%]
Dog study (4 weeks) T6079677, 4.2.3.2.10 PH-36393								
1.5	M / F	25	1265	3868	2.58	0.154	89.9	117
5	M / F	25	4637	19108	3.82	0.134	115	183
15	M / F	25	22144	164713	11.0	2.58	106	167
Daily dose [mg/kg/d]	**Gender**	**Date Day**	**C_{max} [µg/L]**	**AUC(0-24) [µg·h/L]**	**$AUC(0\text{-}24)_{norm}$ [kg·h/L]**	**$C(24)/C_{max}$ [%]**	**R_AC_{max} [%]**	**R_AAUC [%]**
Dog study (13 weeks) T6081467, 4.2.3.2.11 PH-36687								
1	M / F	87	1100	4562	4.56	0.305	131	n.c.[a]
3	M / F	87	3409	17591	5.86	0.476	103	194
10	M / F	87	15847	87738	8.77	0.969	116	170
Daily dose [mg/kg/d]	**Gender**	**Date Week**	**C_{max} [µg/L]**	**AUC(0-24) [µg·h/L]**	**$AUC(0\text{-}24)_{norm}$ [kg·h/L]**	**$C(24)/C_{max}$ [%]**	**R_AC_{max} [%]**	**R_AAUC [%]**
Dog study (39 weeks) T2083353, 4.2.3.2.12 PH-37743								
0.5	M / F	39	560	2110	4.22	0.1	107.7	137.3
1.5	M / F	39	2180	9910	6.61	0.2	104.7	170.0
5	M / F	39	8350	59500	11.9	1.9	123.0	199.1

Source: 4.2.3.2.10 PH-36393; 4.2.3.2.11 PH-36687; 4.2.3.2.12 PH-37743

a = not calculated

雌雄ラットにフィネレノンを 1 日 1 回 4、13 及び 26 週間反復経口投与（雌：0.5～30mg/kg、雄：1.5～30mg/kg）したとき、雌ラットにおいて AUC(0-24)及び C_{max} で評価した曝露量は雄よりも最大で約 8.4 倍高かった。これは、雌ラットの肝 CYP 酵素系の活性が概して雄よりも低いこと[4, 5]に起因するものと考えられる。反復投与後の雌ラットでの曝露量は、0.5～1.5mg/kg の用量間で用量に比例して増加したが、1.5～30mg/kg の範囲では用量比例性を下回って増加した。一方、雄ラットの曝露量は、1.5～3.0mg/kg の間では用量比例性を上回って増加したが、3.0～15mg/kg の範囲では用量に比例して増加し、15～30mg/kg の用量範囲では用量比例性を下回って増加した。フィネレノンを 1 日 1 回、最長 26 週間まで反復経口投与したとき、最高用量の 30mg/kg では反復投与による蓄積性は認められなかったが、30mg/kg 未満の用量の反復投与では AUC(0-24)及び C_{max} の増加が認められた（表 2.6.4.3- 9）。

イヌにフィネレノンを 1 日 1 回 4、13 及び 39 週間反復経口投与（0.5～15mg/kg）したとき、いずれの用量においても全身曝露量に性差は認められなかった。曝露量は用量比例性を軽度～中程度に上回って増加した。反復投与後の C_{max} はいずれの用量においても初回投与時から変化しなかったが、AUC(0-24)は各反復投与試験の中～高用量において反復投与により中程度に増加した（表 2.6.4.3- 10）。

以上のように、ラット及びイヌを用いた亜急性、亜慢性及び慢性毒性試験におけるフィネレノンのトキシコキネティクスは類似していた。

なお、ラット反復投与毒性試験で最高用量（30mg/kg）のフィネレノンを投与したときのフィネレノン及び代謝物 M-1、M-2 及び M-3 の定常状態における薬物動態を再現し、フィネレノン反復経口投与後の M-1、M-2 及び M-3 のアトロプ異性体の存在比を算出するため、フィネレノンの反復投与薬物動態試験を別途実施した。結果は 2.6.4.8.6.1 に要約する。

2.6.4.4 分布

2.6.4.4.1 血漿タンパク結合及び血球／血漿分配

参照項目： 4.2.2.3.1 A44959
4.2.2.3.2 A50448
4.2.2.3.3 PH-38806

フィネレノンのタンパク結合試験の概要を表 2.6.4.4- 1 に、試験成績を表 2.6.4.4- 2 に示す。

表 2.6.4.4- 1 フィネレノンのタンパク結合試験の概要

Study type	*In vitro* assay, ultrafiltration
Bayer reference	4.2.2.3.1 A44959; 4.2.2.3.2 A50448; 4.2.2.3.3 PH-38806
Test compound	[^{14}C]finerenone[a] (monkey, dog, human, rabbit plasma) Finerenone[b] (mouse, rat plasma) [^{14}C]finerenone[c] (human liver microsomes)

a = specific activity: 3.09 MBq/mg

b = batch No. BXR42XB

c = batch SXD 1876-3X-09A, specific activity: 3.20 MBq/mg

表 2.6.4.4- 2 種々の動物血漿及びヒトタンパクに対するフィネレノンのタンパク結合

Species (gender) of plasma or human proteins	**Concentration [µg/L]**	**f_u [%][a]**
CD-1 mouse (M)	440 to 3150	0.0772
	66500	0.120
Wistar rat (M)	515 to 5270	0.0465
	100000	0.0682
Cynomolgus monkey (F)	95.5 to 4396	2.55
	85069	4.20
Beagle dog (F)	99.0 to 4394	5.49
	83087	6.09
Human (M)	94.5 to 4289	8.33
	87549	12.6
Rabbit (F)	529 to 10135	0.183
Human serum albumin	5287	16.5
α1-acid glycoprotein	4934	59.3
α-globulins	4988	58.9
γ-globulins	4948	84.4
LDL	4984	59.8
William's Medium 10% FCS[b]	105	56.2
William's Medium 10% FCS[b]	10420	60.4
Human liver microsomes (0.05 mg/mL)	357 to 7261	86.8
Human liver microsomes (0.1 mg/mL)	369 to 7293	81.0
Human liver microsomes (0.5 mg/mL)	379 to 7362	60.6

Source: M4.2.2.3.1 A44959; M4.2.2.3.2 A50448; M4.2.2.3.3 PH-38806

a = fraction of free (unbound) drug in plasma or protein solution

b = William’s medium containing 10% fetal calf serum

フィネレノンの血漿タンパク結合率は、臨床濃度範囲において、げっ歯類（ラット及びマウス）及びウサギで高かったが、ほとんどの非げっ歯類（サル、イヌ及びヒト）では中程度であり、種

差が認められた。非結合型分率は、臨床濃度範囲において、約 0.047%（ラット）～約 8.3%（ヒト）の範囲であった。臨床濃度を超える最高濃度（66500～100000μg/L）では、いずれの動物種においても血漿タンパク結合の飽和が認められ、非結合型分率のわずかな増加がみられた（表 2.6.4.4- 2）。

フィネレノンのヒト血漿における主要な結合タンパクは、血清アルブミンであった。α1-酸性糖タンパク、LDL、α-グロブリン及びγ-グロブリンに対する結合率は低かった（表 2.6.4.4-2）。

ラット、イヌ及びヒトにおける[^{14}C]フィネレノンの血球／血漿分配を *in vitro* で検討した試験成績を表 2.6.4.4- 3 に示す。

表 2.6.4.4- 3　種々の動物における血液－血漿中濃度比

Species (gender)	Concentration [µg/L]	C_b/C_p
Wistar rat (M)	103 to 5115	0.549
Wistar rat (M)	102040	0.601
Beagle dog (F)	107 to 5105	0.723
Beagle dog (F)	104423	0.779
Human (M)	119 to 6587	0.935
Human (M)	126870	1.09

Source: 4.2.2.3.1 A44959

フィネレノンは、約 5000μg/L までの臨床濃度範囲において、ラット及びイヌの全血中では主に血漿に分布した（C_b/C_pがそれぞれ約 0.55 及び約 0.72）。一方、ヒトの全血中では、この臨床濃度範囲において、血液と血漿にほぼ均等に分布した（C_b/C_pが約 0.94）。検討濃度を約 100000μg/L まで増加させたとき、すべての動物種でわずかに血球への分布が増加した（表 2.6.4.4-3）。

2.6.4.4.2　臓器・組織分布

2.6.4.4.2.1　アルビノ及び有色ラット

参照項目： 4.2.2.3.4　A47052

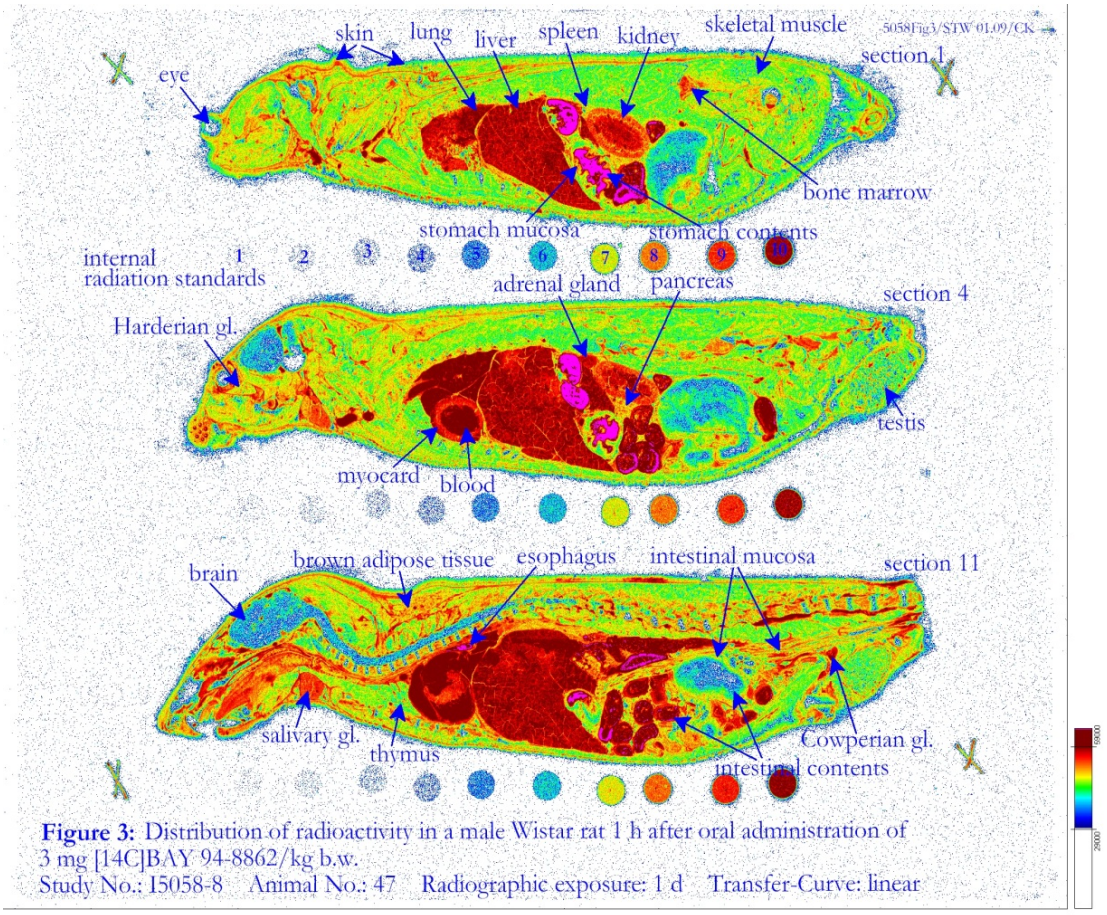
雌雄アルビノラット及び雄有色ラットに[^{14}C]フィネレノンを単回経口投与及び静脈内投与（雄アルビノラットのみ）し、臓器・組織への放射能分布及び消失を QWBA により検討した。試験の概要を表 2.6.4.4- 4 に、試験成績を図 2.6.4.4- 1 及び表 2.6.4.4- 5 に示す。

表 2.6.4.4- 4　ラットにおける定性的及び定量的臓器・組織分布試験の概要

Study type	Quantitative and qualitative, whole-body autoradiography		
Bayer reference	4.2.2.3.4 A47052		
Study design	Rats, 1 animal/time point		
Admin. route	Dosage [^{14}C]finerenone[a]	Species / gender	Sacrifice time
po	3 mg/kg	Wistar rat, male	1, 2, 4, 8, 24, 72, 168 h
po	3 mg/kg	Wistar rat, female	2, 24 h
po	3 mg/kg	Long Evans rat, male	24, 72, 168, 336 h
iv	1 mg/kg	Wistar rat, male	5 min, 2 h
Vehicle, volume & route of admin.	iv administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 5 mL/kg, bolus injection	
	po administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v, 5 mL/kg, gavage	
Assay	Radioluminography		

a = specific activity: 3.09 MBq/mg

図 2.6.4.4- 1　雄アルビノラットに[^{14}C]フィネレノンを 3mg/kg の用量で単回経口投与後 1 時間における放射能の臓器・組織分布



Source: 4.2.2.3.4 A47052

全身オートラジオグラフィーでの定性的評価では、アルビノラットにおける[^{14}C]フィネレノンの放射能の分布パターンは投与経路間及び雌雄間で実質的に同様であった（4.2.2.3.4 A47052）。

また、トキシコキネティクス試験で得られた結果と矛盾なく、雌ラットにおける放射能濃度は、雄に比べて高かった（2.6.5.5 Table 5-1 及び Table 5-4）。ほとんどの臓器・組織において、放射能は投与後 1 時間（最高濃度到達時間：t_{max}）で最高放射能濃度（$C_{eq,max}$）に到達した。雄ラットでは、$C_{eq,max}$ が最も高かったのは血液、次いで肺、肝臓、腎乳頭、副腎髄質の順であった（表 2.6.4.4- 5）。また、動物の全身にわたって高い放射能濃度が間質腔でみられた（図 2.6.4.4- 1）。そのほかのすべての臓器・組織では $C_{eq,max}$ が明らかに低かった（表 2.6.4.4- 5）。

定性的な評価で曝露量が最も高かったのは胆管及び消化管内容物であったが、これは、胆汁／糞中への放射能の排泄を示している。AUC(0-24)は血液及び血流量が多い臓器・組織（肺、肝臓、腎乳頭、副腎髄質など）で高かった（表 2.6.4.4- 5）。脳の AUC 及び放射能濃度は血液のそれぞれ 2%未満であり、これは脳試料中の残存血液量を反映している。

表 2.6.4.4- 5 雄アルビノラットに[^{14}C]フィネレノンを 3mg/kg の用量で単回経口投与後の臓器・組織内放射能の薬物動態パラメータ

Organs / tissues	$C_{eq,max}$ [µg-eq/L]	t_{max} [h]	AUC(0-24) [µg-eq·h/L]	$t_{1/2}$ [h]	Regression range [h]
Adipose tissue, brown	2137	2	14553	4.41	4-24
Adipose tissue, white	685	4	6087	4.78	4-24
Adrenal cortex	5100	1	33925	65.6[a]	72-168
Adrenal glands (average)	5107	1	34124	65.4[a]	72-168
Adrenal medulla	5356	1	36671	73.4[a]	72-168
Blood (heart)	**9919**	**1**	**73245**	**85.0[a]**	**72-168**
Bone marrow	3124	1	21069	6.13	4-24
Brain	191	1	1283	5.26	4-24
Cardiac muscle	4409	1	29815	75.8[a]	72-168
Eye wall	3155	4	24716	5.06	4-24
Harderian gland	1686	4	13225	62.7[a]	72-168
Kidney cortex	2769	1	19920	72.5[a]	72-168
Kidney, inner medulla	5050	1	35918	85.5[a]	72-168
Kidney, outer medulla	2406	1	20296	54.8[a]	72-168
Kidney papilla	5841	1	39976	5.13	4-24
Kidneys (average)	3782	1	27209	69.4[a]	72-168
Liver	6110	1	52626	62.0[a]	72-168
Lung	8729	1	57922	91.8[a]	72-168
Pancreas	1618	1	12154	5.08	4-24
Prostate	1431	1	10266	5.24	4-24
Seminal vesicles	455	4	4370	5.16	4-24
Skeletal muscle	772	1	6180	4.90	4-24
Skin, dorsal	1728	4	15064	66.0[a]	72-168
Spleen	1191	1	10274	4.96	4-24
Submandibular gland	2851	1	22065	4.55	4-24
Testes	1766	4	14636	5.18	4-24
Thymus	783	4	6314	5.15	4-24
Thyroid	4279	1	23501	5.13	4-24

Source: 4.2.2.3.4 A47052

a = rough estimate based on only two measurable time points above LLOQ

放射能は時間と共に臓器・組織から消失した。主要な消失相における半減期は 4～6 時間であった。その結果として、多くの臓器・組織では、放射能濃度が投与後 72～168 時間で LLOQ 未満となった。それ以外の臓器・組織（副腎、肝臓、皮膚、血液、腎臓及び肺を含む）では放射能の終末相における消失半減期は、それぞれの臓器・組織における最高濃度の 0.1%～1.5%に相当する極めて低い濃度範囲での残存放射能の消失を表すものであり、概算（2 時点のデータを用

いて算出）のみ可能であった。終末相消失半減期の概算値は約 55～92 時間であった（表 2.6.4.4- 5）。有色ラットでは、眼球壁における消失半減期が長かった（122 時間）（2.6.5.5 Table 5-5）。経口投与後 168 時間において、アルビノ及び有色ラット体内（消化管を除く）に残存する放射能は投与量の 0.1%未満であった（4.2.2.3.4 A47052）。有色ラットにおいても、フィネレノン及び／又は放射性標識代謝物の分布パターンは同様であり、眼球壁や皮膚有色部などのメラニン含有組織に対する顕著な特異的親和性は認められなかった（2.6.5.5 Table 5-5）。

以上のことから、ラットの臓器・組織において[^{14}C]フィネレノン及び／又は代謝物の不可逆的な結合や残留は認められなかった。

2.6.4.4.2.2　妊娠ラット（胎盤通過性）

参照項目： 4.2.2.3.5　PH-38642

妊娠アルビノラット（妊娠 18 日）に[^{14}C]フィネレノン 3mg/kg を単回経口投与し、母体及び胎児の臓器・組織への放射能分布及び消失を QWBA により検討した。試験の概要を表 2.6.4.4- 6 に、試験成績を図 2.6.4.4- 2 及び表 2.6.4.4- 7 に示す。

表 2.6.4.4- 6　妊娠ラットにおける定性的及び定量的臓器・組織分布試験の概要

Study type	Quantitative and qualitative, whole-body autoradiography		
Bayer reference	4.2.2.3.5 PH-38642		
Study design	Rats, 1 animal/time point		
Admin. route	Dosage [^{14}C]finerenone[a]	Species / gender	Sacrifice time
po	3 mg/kg	Wistar rat, female pregnant	2, 4, 8, 24, 48 h
Vehicle, volume & route of admin.	po administration:	10% Ethanol, 40% PEG 400, 50% demin. Water, v/v/v, 5 mL/kg, gavage	
Assay	Radioluminography		

a = specific activity: 3.09 MBq/mg

[^{14}C]フィネレノン由来の放射能は、ラットの血液胎盤関門を中程度に通過した（図 2.6.4.4- 2）。AUC(0-24)の胎児／母体血液比及び胎児血液／母体血液比は、それぞれ 0.06 及び 0.09 であった（表 2.6.4.4- 7 及び 4.2.2.3.5 PH-38642）。

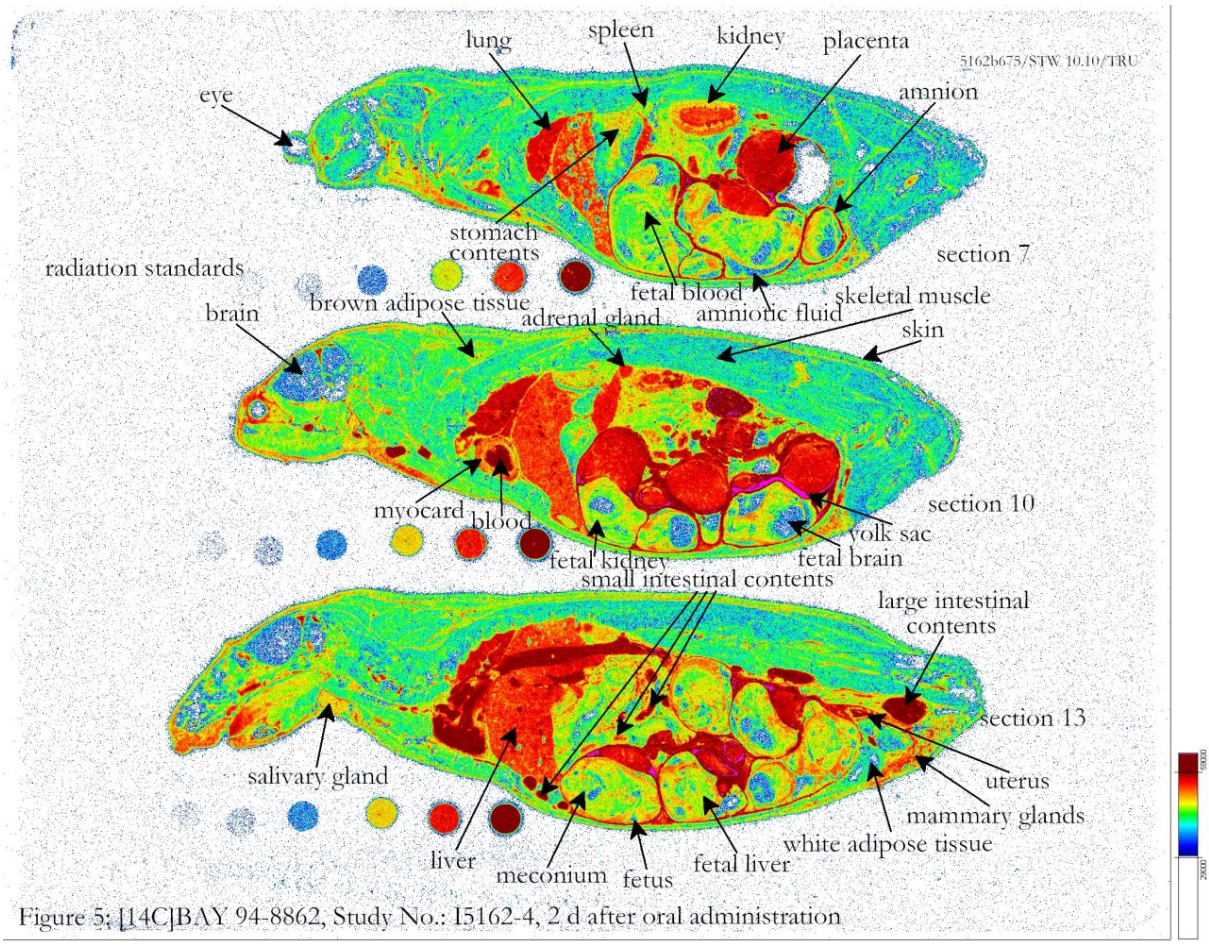
母体において、血液及び胎盤を含むほとんどの臓器・組織で放射能濃度は投与後 4 時間で $C_{eq,max}$ に達した。一方、羊水を含むほとんどの胎児の臓器・組織では、時間と共に濃度の増加が認められ、$C_{eq,max}$ は最終測定時点（投与後 48 時間）であり、$C_{eq,max}$ に到達する時間は明らかに母体よりも遅かった。$C_{eq,max}$ が最も高かったのは母体血液及び胎盤であり、次いで肺、羊膜、腎髄質内層、子宮及び肝臓の順であった。胎児の臓器・組織における $C_{eq,max}$ は、脳及び骨格筋を除き母体に比べて明らかに低かった（表 2.6.4.4- 7）。

母体では多くの臓器で投与後 8～48 時間の間に放射能濃度がプラトーとなり、胎児ではほぼすべての臓器で濃度が投与後 24～48 時間の間で増加したことから、AUC に基づく曝露量の評価では AUC(0-24)を用いた。AUC(0-24)が最も高かったのは母体血液であり、肺、羊膜、胎盤、子宮及び腎髄質内層の AUC(0-24)も高かった。そのほかのすべての母体の臓器・組織における AUC(0-24)は、血液の 1/2 未満であった（表 2.6.4.4- 7）。

胎児の臓器・組織において、放射能の AUC(0-24)は胎児血液、骨格筋及び皮膚で最も高く、それに続く腎臓及び肝臓の曝露量は明らかに低かった。胎児脳における放射能の AUC(0-24)は、胎児血液の AUC(0-24)の約 10%に相当したことから、胎児における放射能の血液脳関門通過が明らかに示された（表 2.6.4.4- 7）。

母体の多くの臓器・組織及び胎児のすべての臓器・組織において、[^{14}C]フィネレノンを投与後 48 時間までの測定期間内に明確な消失相は認められなかったことから、消失半減期は算出しなかった。投与後 48 時間において、投与量の 2.3%が胎児の体内に残存していた（4.2.2.3.5 PH-38642）。

図 2.6.4.4- 2　妊娠ラットに[^{14}C]フィネレノンを 3mg/kg の用量で単回経口投与後 48 時間における放射能の臓器・組織分布



Source: 4.2.2.3.5 PH-38642

表 2.6.4.4- 7 妊娠ラットに[^{14}C]フィネレノンを 3mg/kg の用量で単回経口投与後の臓器・組織内放射能の薬物動態パラメータ

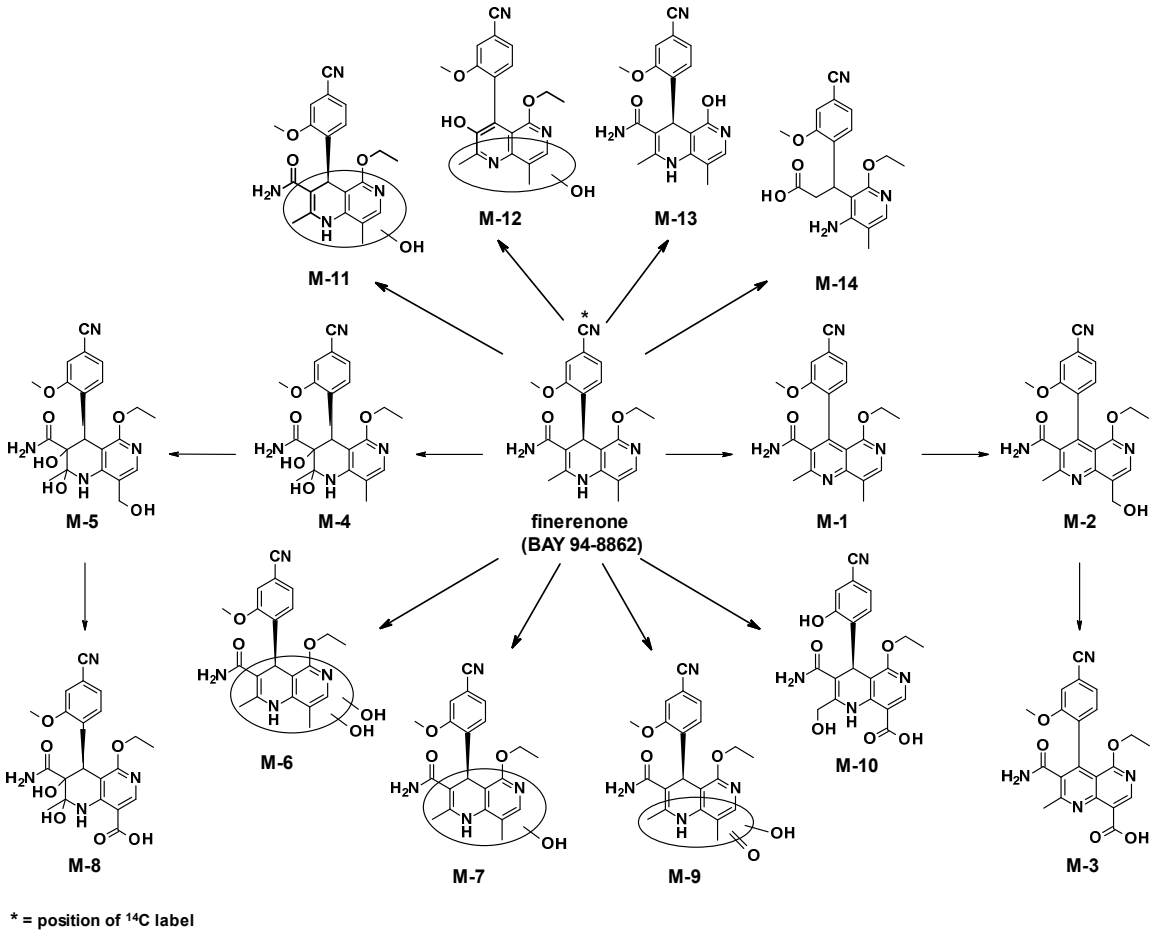
Organs/tissues	$C_{eq,max}$ [µg-eq/L]	t_{max} [h]	AUC(0-24) [µg-eq·h/L]
Adipose tissue, brown	1670	4	29400
Adipose tissue, white	1030	4	10200
Adrenals (average)	5680	4	109000
Amnion	8760	4	172000
Amniotic fluid	549	48	4040
Blood (heart)	**14200**	**4**	**261000**
Brain	193	4	3220
Cardiac muscle	4150	4	74600
Kidney cortex	3000	24	67000
Kidney, inner medulla	7090	4	132000
Kidney, outer medulla	3550	4	74000
Kidneys (average)	4830	4	101000
Liver	6170	4	101000
Lungs	9820	4	196000
Mammary glands	3060	4	61500
Ovaries	5930	4	105000
Placenta	10700	4	164000
Skeletal muscles (dorsal)	607	4	11800
Skin (dorsal)	2360	8	37700
Spleen	1340	4	27000
Submandibular gland	2470	8	45000
Uterus	6679	4	138000
Fetuses (average)	**1030**	**48**	**16400**
Fetal blood	1730	48	24300
Fetal brain	129	48	2320
Fetal kidney	902	48	18000
Fetal liver	1150	48	13300
Fetal lung	718	48	9380
Fetal skeletal muscles	1590	8	23900
Fetal skin	1480	48	23900

Source: 4.2.2.3.5, PH-38642

2.6.4.5　　代謝

ラット、イヌ及びヒトの肝細胞、ヒトを含む複数の動物種の肝ミクロソーム並びにヒト CYP の異種発現系ミクロソームを用いて、*in vitro* におけるフィネレノンの代謝を検討した。また、マウス、ラット、イヌ及びヒトに[^{14}C]フィネレノンを投与したときの、*in vivo* 代謝を検討した。なお、血漿及び尿中の代謝物 M-1、M-2 及び M-3 について、アトロプ異性体の存在比を検討した試験成績は 2.6.4.8.6 に示す。*In vivo* 及び *in vitro* 試験成績より推定される代謝経路を図 2.6.4.5- 1 に示す。

図 2.6.4.5- 1　*In vitro* 及び *in vivo* 試験に基づく[^{14}C]フィネレノンの推定代謝経路



2.6.4.5.1　　*In vitro* 代謝

ヒト及び動物の肝ミクロソーム及び肝細胞におけるフィネレノンの代謝プロファイルを動物種間で比較した。また、ヒトにおけるフィネレノンの代謝に関与する酵素を同定した。フィネレノンが CYP 又は UGT の阻害作用、あるいは CYP 誘導作用を介して薬物相互作用における相互作用薬となる可能性についても *in vitro* で検討した。

2.6.4.5.1.1　動物種間における比較

参照項目： 4.2.2.4.1　PH-41146

フィネレノンの *in vitro* 代謝に関する動物種間における比較検討の概要を表 2.6.4.5- 1 に、試験成績を表 2.6.4.5- 2 及び表 2.6.4.5- 3 に示す。

表 2.6.4.5- 1　フィネレノンの *in vitro* 代謝に関する動物種間における比較検討の概要

Study type	*In vitro* assay, species comparison
Bayer reference	4.2.2.4.1 PH-41146
Test material	Liver microsomal preparations from human, Cynomolgus monkey, Beagle dog, Himalayan rabbit, Wistar rat, CD-1 mouse and NMRI mouse Hepatocytes of Wistar rat, Beagle dog, Cynomolgus monkey and human
Test compound	[^{14}C]finerenone, 1 µM (378 µg/L)

表 2.6.4.5- 2　動物及びヒトの肝ミクロソームにおける[^{14}C]フィネレノン（1µM）の代謝物（%放射能）（タンパク濃度 1mg/mL、インキュベーション 60 分）

Species (gender)/ Metabolite	NMRI mouse (M)	CD-1 mouse (M)	Wistar rat (M)	Wistar rat (F)	Himalayan rabbit (F)	Beagle dog (F)	Cynomolgus monkey (Mix)	Human (Mix)
M-1	18.9	16.4	35.5	4.71	7.97	21.4	0.94	14.2
M-2 (major)[a]/M-6	19.1	28.2	15.0	0.39	19.3	15.6	42.3	35.5
M-3	0.54	2.11	0.60	n.d.[b]	0.90	n.d.[b]	10.8	1.09
M-4	16.7	14.7	19.6	6.11	37.5	17.9	5.16	14.5
M-5	16.9	19.6	7.49	0.94	12.6	5.29	28.6	19.2
M-7	1.73	1.56	2.26	0.88	1.38	2.27	n.d.[b]	0.93
M-8	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	3.47	n.d.[b]
M-14	Trace[c]	Trace[c]	Trace[c]	n.d.[b]	Trace[c]	Trace[c]	Trace[c]	Trace[c]
Finerenone	23.2	11.8	11.5	85.5	11.0	35.3	Trace[c]	6.94
Turnover	76.9	88.2	88.5	14.5	89.0	64.7	~100	93.1

Source: 4.2.2.4.1 PH-41146

a = major component of the peak, based on peak area obtained by LC-MS/MS

b = not detected

c = below LOD of HPLC-LSC, detected by LC-MS/MS

[^{14}C]フィネレノンを 1µM（378µg/L）の濃度で、種々の動物及びヒトの肝ミクロソームとインキュベーションした。産生された代謝物の割合は、雌ラットでは約 15%と低かったが、そのほかの動物種では約 65%～100%の範囲であり高かった（表 2.6.4.5- 2）。産生された代謝物に基づき、2 つの主要な代謝経路が明らかとなった。すなわち、(a)フィネレノンのジヒドロピリジン部分の酸化によりナフチリジン代謝物 M-1 が産生、更なる水酸化によりヒドロキシメチルナフチリジン代謝物 M-2 が産生、続いて酸化を受けてカルボン酸代謝物 M-3 が産生される経路、(b)恐らくエポキシド中間体の産生に続く加水分解によってジヒドロジオール代謝物 M-4 が産生され、更に水酸化されて M-5 が産生される経路である。また、フィネレノンの水酸化代謝物 M-7 についても、ほとんどの動物種で産生された。明らかな種差はみられなかった。

表 2.6.4.5- 3 動物及びヒトの肝細胞における[14C]フィネレノン（1μM）の代謝物（%放射能）（インキュベーション 2 時間）

Species (gender)/ Metabolite	Wistar rat[a] (M)	Beagle dog (F)	Cynomolgus monkey (F)	Human[a]
M-1	31.2/3.71	17.6	6.84	20.3/17.5
M-2 (major)[b]/M-6	13.4/28.7	36.6	32.5	6.80/5.31
M-3	3.00/26.7	n.d.[c]	3.89	n.d.[c]/n.d.[c]
M-4	11.8/7.06	13.6	13.2	13.2/12.1
M-5	5.69/9.86	4.04	13.3	8.68/6.50
M-7	n.d.[c]/0.45	3.16	2.67	1.63/1.69
M-8	1.55/8.31	n.d.[c]	Trace[d]	n.d.[c]/n.d.[c]
M-9	0.88/3.19	2.56	n.d.[c]	n.d.[c]/n.d.[c]
M-10	2.60/1.84	n.d.[c]	1.66	n.d.[c]/n.d.[c]
M-11	n.d.[c]/n.d.[c]	n.d.[c]	3.02	n.d.[c]/n.d.[c]
M-13	n.d.[c]/n.d.[c]	n.d.[c]	6.00	n.d.[c]/n.d.[c]
Finerenone	16.5/trace[d]	18.0	14.7	47.6/55.7
Turnover	83.5/~100	82.0	85.3	52.4/44.3

Source: 4.2.2.4.1 PH-41146

a = two different hepatocyte preparations

b = major component of the peak, based on peak area obtained by LC-MS/MS

c = not detected

d = below LOD of HPLC-LSC, detected by LC-MS/MS

[14C]フィネレノンを 1μM（378μg/L）の濃度で、種々の動物及びヒトの肝細胞とインキュベーションした。産生された代謝物の割合は約 44%～100%の範囲であった（表 2.6.4.5- 3）。肝ミクロソームと一致する代謝経路が認められた。検討した動物種すべてでナフチリジン代謝物の産生経路（M-1、M-2 及び M-3 が産生）が主要でありジヒドロジオール代謝物の産生経路（M-4 及び M-5 が産生）を上回った。ラット及びサルの肝細胞では、ひとつ又は複数の第 I 相代謝反応、又はその多段階反応によって産生された微量代謝物が複数認められた。

2.6.4.5.1.2 CYP 分子種に対するフィネレノンの基質特性

参照項目： 4.2.2.4.2 PH-39534

フィネレノンの代謝に関与する CYP 分子種同定試験の概要を表 2.6.4.5- 4 に、試験成績を 2.6.5.10 Table 10-3～Table 10-6 に示す。

表 2.6.4.5- 4 フィネレノンの代謝に関与する CYP 酵素同定試験の概要

Study type	*In vitro* assay, CYP enzymes involved (phenotyping)
Bayer reference	4.2.2.4.2 PH-39534
Test material	Human liver microsomes and hepatocytes Recombinant CYP isoforms
Test compound	Finerenone, 0.05 – 0.2 µM (18.9 – 75.6 µg/L) or [14C]finerenone, 1 – 151 µM (378 – 57141 µg/L)

[14C]フィネレノンを 19 種類のヒト CYP 分子種の発現系とインキュベーションした結果、5 種類の分子種がフィネレノンの代謝に関与することが明らかとなり、このうち CYP3A4 の代謝能が最も顕著で、CYP1A1、CYP2C8、CYP3A5 及び CYP3A7 の代謝能は極めて低かった。これらの分子種によりナフチリジン代謝物の産生経路（M-1、M-2 及び M-3）及びジヒドロジオール代謝物の産生経路（M-4 及び M-5）の両経路による代謝物が産生された。更に、CYP2C8 により M-7 及び M-11、

CYP2C8 及び CYP3A4 により M-6 及び M-14、CYP1A1 により M-13 が産生された。CYP 分子種発現系を用いて求めた CYP3A4 の固有クリアランスは CYP1A1 及び CYP2C8 のそれぞれ 9 及び 16 倍高かった。CYP3A4 の特異的阻害薬であるエリスロマイシン及びベラパミル、並びに CYP2C8 の特異的阻害薬であるゲムフィブロジルグルクロニドを用いてヒト肝細胞で検討した結果、ヒト肝におけるフィネレノンの代謝に対する CYP3A4 の寄与率は 80～90%であった。残りの寄与は CYP2C8 によるものと考えられ、CYP1A1 の寄与は認められなかった。フィネレノンは、恐らく消化管においても代謝を受け、その代謝には CYP3A4 のみが関与すると考えられる（2.6.5.10 Table 10-3～Table 10-6 及び 4.2.2.4.2 PH-39534）。

2.6.4.5.1.3 UGT 分子種に対するフィネレノンの基質特性

ヒト及び種々の動物の肝細胞を用いた検討（2.6.4.5.1.1）において、未変化体及び第 I 相代謝物のいずれに由来するグルクロン酸抱合体の産生も認められなかった。

2.6.4.5.1.4 CYP 分子種に対するフィネレノンの阻害作用

参照項目： 4.2.2.4.3 PH-37733
4.2.2.4.4 PH-40971
4.2.2.4.5 PH-40973

フィネレノンの CYP 阻害作用に関する検討試験の概要を表 2.6.4.5- 5 に、試験成績を表 2.6.4.5- 6 に示す。

表 2.6.4.5- 5 CYP 分子種に対するフィネレノンの阻害作用検討試験の概要

Study type	*In vitro* assay, CYP inhibition
Bayer reference	4.2.2.4.3 PH-37733; 4.2.2.4.4 PH-40971; 4.2.2.4.5 PH-40973
Test system	Human liver microsomes, recombinant CYP isoforms 1A1 and 2E1
Test compound	Finerenone, 1.0 – 50 µM (378 – 18921 µg/L)

表 2.6.4.5- 6 CYP 分子種に対するフィネレノンの阻害作用

CYP isoform	Probe substrate	IC_{50} (K_i) [µM]
1A1	Granisetron	6.7
1A2	Phenacetin	>50
2A6	Coumarin	>50
2B6	Bupropion	>50
2C8	Amodiaquine	6.8 (1.9)
2C9	Diclofenac	29 (16)
2C19	Mephenytoin	31
2D6	Dextromethorphan	>50
2E1	Chlorzoxazone	>50
3A4	Midazolam	19
3A4	Testosterone	12

Source: 4.2.2.4.3 PH-37733, 4.2.2.4.5 PH-40973

フィネレノンは検討した最高濃度まで CYP1A2、2A6、2B6、2D6 及び 2E1 の酵素活性に影響を及ぼさなかった〔IC_{50}＞50μM（18921μg/L）〕。フィネレノンが阻害作用を示した CYP 分子種は、阻害の強い順に、CYP2C8〔IC_{50}：6.8μM（2573μg/L）、Ki：1.9μM（719μg/L）〕、CYP1A1〔IC_{50}：6.7μM（2535μg/L）〕、CYP3A4〔基質：ミダゾラム IC_{50}：19μM（7190μg/L）、基質：テストステロン IC_{50}：12μM（4541μg/L）〕、CYP2C9〔IC_{50}：29μM（10974μg/L）、Ki：16μM（6055μg/L）〕及び CYP2C19〔IC_{50}：31μM（11731μg/L）〕であった（表 2.6.4.5- 6）。フィ

ネレノンの CYP1A1、CYP2C8 及び CYP3A4 活性に対する阻害作用は、ニコチンアミドアデニンジヌクレオチドリン酸（NADPH）存在下でヒト肝ミクロソーム又は CYP 発現系と 30 分間プレインキュベーションすることによって増強が認められた。そこで、希釈法による評価を実施したところ、CYP3A4 に対する阻害作用には NADPH、濃度及び時間依存性が認められ、不可逆的阻害作用が確認された。一方、CYP2C8 に対しての不可逆的阻害は認められなかった。CYP3A4 に対する不可逆的阻害に関するパラメータは k_{inact}：0.012min^{-1} 及び K_I：10.3μM（3898μg/L）であった（2.6.5.12 Table 12-1）。

2.6.4.5.1.5　UGT 分子種に対するフィネレノンの阻害作用

参照項目： 4.2.2.4.6　A50906

フィネレノンの UGT 阻害作用に関する検討試験の概要を表 2.6.4.5- 7 に、試験成績を表 2.6.4.5- 8 に示す。

表 2.6.4.5- 7　UGT に対するフィネレノンの阻害作用検討試験の概要

Study type	*In vitro* assay, UGT inhibition
Bayer reference	4.2.2.4.6 A50906
Test system	Human liver microsomes
Test compound	Finerenone, 1.0 – 50 µM (378 – 18921 µg/L)

表 2.6.4.5- 8　UGT 分子種に対するフィネレノンの阻害作用

UGT isoform	Substrate	IC_{50} [µM]
1A1	Estradiol	>50
1A4	Trifluoperazine	>50
1A6	α-Naphthol	>50
1A9	Propofol	>50
2B4	1'-Hydroxymidazolam	>50
2B7	3'-Azido-3'-deoxythymidine (AZT)	>50

Source: 4.2.2.4.6 A50906

フィネレノンは検討した最高濃度まで UGT1A1、1A4、1A6、1A9、2B4 及び 2B7 のグルクロン酸抱合活性に影響を及ぼさなかった〔IC_{50}＞50μM（18921μg/L）〕（表 2.6.4.5- 8）。

2.6.4.5.1.6　CYP 分子種に対するフィネレノンの誘導作用

参照項目： 4.2.2.4.7　PH-39130

3 名のドナーに由来するヒト初代培養肝細胞を用いて、CYP 分子種に対するフィネレノンの誘導作用を評価した。フィネレノンの CYP 誘導作用に関する検討試験の概要を表 2.6.4.5- 9 に、試験成績を表 2.6.4.5- 10 に示す。

表 2.6.4.5- 9　CYP 分子種に対するフィネレノンの誘導作用検討試験の概要

Study type	*In vitro* assay, induction of CYP1A2, 2B6, 2C19 and 3A4
Bayer reference	4.2.2.4.7 PH-39130
Test system	Cultured human hepatocytes
Test compound	Finerenone, 41 – 90000 µg/L (0.11 – 238 µM)

表 2.6.4.5- 10 CYP 分子種に対するフィネレノンの誘導作用（mRNA 発現量）

CYP	Result
1A2	Concentration-dependent induction up to 2.3-fold
3A4	Concentration-dependent induction up to 25-fold
2B6	Concentration-dependent induction up to 7.9-fold
2C19	Concentration-dependent induction up to 3.0-fold

Source: 4.2.2.4.7 PH-39130

3 名すべてのドナー由来の培養肝細胞において、フィネレノンは CYP1A2 の mRNA 発現量及び酵素活性レベルのいずれについても、検討した最高濃度〔90000μg/L（238μM）〕まで明確な誘導作用を示さず、最大誘導作用は、mRNA 発現量で 2.3 倍、CYP 活性で 1.2 倍であった。これらのわずかに認められた誘導作用は臨床的に有意なものではないと考えられる（表 2.6.4.5- 10 及び 4.2.2.4.7 PH-39130）。

一方、すべてのドナー由来の肝細胞において、フィネレノンは概して濃度依存的［最高濃度〔90000μg/L（238μM）〕］に CYP3A4 の mRNA 発現を誘導し、その最大誘導作用はドナー1 で 12.5 倍（陽性対照であるリファンピシンの誘導作用の 77%）、ドナー2 で 18.2 倍（同、135%）、ドナー3 で 25.0 倍（同、110%）であった。これは、フィネレノンによってプレグナン X 受容体（PXR）が活性化されることに起因するものである。また、フィネレノンによる CYP2B6 及び CYP2C19 の誘導も認められた（核内受容体間のクロストーク）（表 2.6.4.5- 10 及び 4.2.2.4.7 PH-39130）。対して、CYP3A4 活性レベルに対する誘導作用は認められず、3 名すべてのドナーで濃度依存的な阻害（溶媒対照における活性レベルの 7%～10%）が認められた。これは、フィネレノンが *in vitro* において CYP3A4 に対して可逆的及び不可逆的阻害を示したことによる結果と考えられる（4.2.2.4.7 PH-39130）。

2.6.4.5.2 *In vivo* 代謝

参照項目： 4.2.2.4.8 A52016
4.2.2.4.9 PH-39348
4.2.2.4.10 PH-39368
4.2.2.4.11 PH-39577

雄 CD-1 マウス（4.2.2.4.8 A52016）、雄 Wistar ラット（4.2.2.4.9 PH-39348）、雌ビーグル犬（4.2.2.4.10 PH-39368）並びにヒト（4.2.2.4.11 PH-39577）におけるフィネレノンの *in vivo* 代謝を検討した。

マウスにおけるフィネレノン代謝試験の概要を表 2.6.4.5- 11 に示す。ラット及びイヌにおける試験の概要は 2.6.4.3.1 に要約した。マウス、ラット、イヌ及びヒトにおける *in vivo* 代謝試験の成績を表 2.6.4.5- 12 及び表 2.6.4.5- 13 に示す。

表 2.6.4.5- 11 *In vivo* におけるマウス血漿中代謝物検討試験の概要

Study type	*In vivo* study, single dose biotransformation	
Bayer reference	4.2.2.4.8 A52016	
Test system	Mice:	3 males / time point, strain: CD-1
Dosage	[^{14}C]finerenone[a]:	1 mg/kg
Vehicle, route of admin.	po administration:	10% Ethanol, 40% PEG 400, 50% demin. water, v/v/v
Time points/samples	0.5, 0.75, 1, 2, 4, 8, 24, 32, 48, 72 h / plasma	

a = specific activity: 3.09 MBq/mg, SXD 1876-2-10-A

表 2.6.4.5- 12 [^{14}C]フィネレノンを単回経口投与後の血漿中代謝物

Species	Mouse	Rat[a]	Dog	Human
Gender	Male	Male	Female	Male
Dose	1 mg/kg	1 mg/kg	3 mg/kg	10 mg
Component	[% of total radioactivity AUC]			
Finerenone	96.8	96.4	28.2	7.1
M-1	0.4	1.0	8.1	48.9
M-2	n.d.[b]	n.d.[b]	36.0	21.5
M-3	n.d.[b]	n.d.[b]	1.6	9.0
M-4/M-7	0.9	2.4	11.1	2.4[c]
M-5	n.d.[b]	n.d.[b]	0.6	1.4

Source: 4.2.2.4.8 A52016; 4.2.2.4.9 PH-39348; 4.2.2.4.10 PH-39368; 4.2.2.4.11 PH-39577

a = total radioactivity AUC(0-8)

b = not detected

c = radioactivity solely covered by M-4

[^{14}C]フィネレノンを単回経口投与したとき、マウス及びラット血漿中では未変化体が圧倒的な主要成分であり（総放射能 AUC の 96%超）、少量成分として 3 種の代謝物（M-1、M-4 及び M-7）が認められた。対照的に、イヌ及びヒト血漿中では、フィネレノンが総放射能 AUC に占める割合はそれぞれ約 28%及び 7.1%に過ぎなかった。イヌ血漿中では、ヒドロキシメチルナフチリジン代謝物 M-2 が最も多い代謝物であり（総放射能 AUC の 36%）、次いでナフチリジン代謝物 M-1 及びジヒドロジオール代謝物 M-4／未変化体の水酸化代謝物 M-7（総放射能 AUC のそれぞれ 8.1%及び約 11%）、更に少量のナフチリジンカルボン酸代謝物 M-3（総放射能 AUC の 2%未満）が認められた。ヒト血漿中では、ナフチリジン代謝物が M-1、M-2 及び M-3 の順に多い主要成分であり、総放射能 AUC のそれぞれ約 49%、約 22%及び 9.0%を占めた。ヒト血漿中においてジヒドロジオール代謝物 M-4 及び M-5 は少量に過ぎなかった（それぞれ総放射能 AUC の 3%未満）。イヌ血漿において、構造未知の極性代謝物（総放射能 AUC の約 4%）が投与後長時間にわたって低濃度で認められ、このことはイヌにおいて放射能濃度の半減期が長い原因と考えられた（表 2.6.4.5- 12 及び 4.2.2.4.10 PH-39368）。

表 2.6.4.5- 13 [14C]フィネレノンを単回経口投与後の排泄物中代謝物

Species	Rat	Dog	Human
Dose	1 mg/kg	3 mg/kg	10 mg
Sampling interval	0 – 168 h	0 – 336 h	0 – 240 h
Components		[% of dose]	
Urine	**19.5**	**52.7**	**79.6**
Finerenone	0.640	1.26	0.825
M-1	0.165	0.122	n.d.[c]
M-2	4.98	27.8	13.1
M-3	6.91	4.16	46.3
M-4/M-7	2.36	3.81	3.95[a]
M-5	0.356	2.46	2.72
M-7	n.a.[b]	n.a.[b]	0.376
M-8	n.d.[c]	n.d.[c]	2.44
M-9	n.d.[c]	0.443	n.d.[c]
Feces	**75.7**	**42.0**	**21.2**
Finerenone	7.85	2.86	0.184
M-1	0.953	0.246	0.0506
M-2	8.10	14.7	1.86
M-3	19.9	0.856	1.48
M-4/M-7	4.86	3.44	0.823[a]
M-5	7.30	6.08	9.40
M-7	n.a.[b]	n.a.[b]	1.25
M-8	2.21	0.889	2.61
M-9	n.d.[c]	3.24	1.11
M-10	3.13	n.d.[c]	0.794

Source: 4.2.2.4.9 PH-39348; 4.2.2.4.10 PH-39368; 4.2.2.4.11 PH-39577

a = solely covered by M-4

b = not applicable, co-eluting with M-4

c = not detected

[14C]フィネレノンを単回経口投与したとき、ラットでは放射能は主に胆汁／糞を介する経路（投与量の約 76%）で排泄されたが、イヌでは放射能は胆汁／糞を介する経路（投与量の 42%）及び尿を介する経路（投与量の約 53%）にほぼ均等に排泄された。ヒトでは、放射能は主に尿（投与量の約 80%）を介して排泄された（表 2.6.4.5- 13）。

すべての動物種で、尿中に排泄された未変化体は少量（投与量の 1.5%未満）に過ぎなかった。糞中に排泄された未変化体は、ラットで投与量の約 7.9%、イヌで約 2.9%、ヒトで約 0.2%であった。なお、フィネレノンは *ex vivo* でヒト糞便とインキュベーションしても安定であることが示されており、糞便中に認められた代謝物は消化管内でフィネレノンから変換されたものではないと考えられることは重要な点である。すべての動物種で、排泄された放射能の大部分は代謝物 M-2、M-3、M-4 及び M-5 であった。ラット及びヒトではナフチリジンカルボン酸代謝物 M-3 が排泄された放射能の主成分（それぞれ投与量の約 27%及び約 48%）であったが、イヌではヒドロキシメチルナフチリジン代謝物 M-2 が排泄された放射能の主成分（投与量の約 43%）であった（表 2.6.4.5- 13）。

BDC ラットに[14C]フィネレノンを静脈内投与後 24 時間以内に、投与量の約 7.8%が胆汁を介さずに直接的に糞中に排泄（消化管分泌）され、主にフィネレノン（投与量の約 2.8%）、M-2（投与量の 2.4%）及び M-4/M-7（投与量の 1.5%）が認められた。少量ながらフィネレノンが直接的に腸内に分泌されることが示唆された（2.6.5.9 Table 9-2）。

以上、未変化体として糞中及び尿中に排泄されるフィネレノンが少ないこと及び酸化的経路により産生される代謝物が排泄物中の主成分であったことから、フィネレノンはほぼ完全に吸収され、ほぼ酸化的代謝によってのみ消失することが示された。いずれの動物種においても、フィネレノンの消失に対する寄与は主にナフチリジン代謝物を産生する経路（M-1、M-2 及び M-3 の排泄率の合計はラットで約 41%、イヌで約 48%、ヒトで約 63%）であり、ジヒドロジオール代謝物を産生する経路（M-4、M-5 及び M-8 の排泄率の合計はラットで約 17%、イヌで約 17%、ヒトで約 22%）よりも優勢であった。また、ひとつ又は複数の第 I 相代謝反応によって産生された代謝物 M-7、M-9 及び M-10 も認められた（表 2.6.4.5- 13）。

2.6.4.5.3　血漿中におけるフィネレノンのキラル反転の可能性評価

参照項目： 4.2.2.4.12　PH-39816

In vivo において、ヒトでフィネレノン（*S*-エナンチオマー）が薬理学的に不活性なエナンチオマー（BAY 94-8863：*R*－エナンチオマー；4.2.1.1.4　PH-35690）に反転しラセミ化が生じる可能性を検討するために、臨床試験〔2.7.2.2.1.4 処置群 B（[^{14}C]フィネレノン 10mg を液剤として経口投与したときの代謝、排泄パターン及びマスバランスを検討した試験）〕由来の血漿試料について立体特異的なキラルクロマトグラフィーを用いて分析を行った。フィネレノンを投与した 4 名の健康被験者全例の血漿試料（フィネレノン濃度≧10μg/L）において、キラル反転の程度／ラセミ化の有無を検討した。ここで、血漿中フィネレノン濃度が 100μg/L のとき、その 100 分の 1 濃度の BAY 94-8863（*R*－エナンチオマー）へのキラル反転が検出できるように、BAY 94-8863 の検出限界を 1μg/L に設定した。

その結果、フィネレノンのキラル反転／ラセミ化は、分析したいずれのヒト血漿試料（濃度範囲：11.5～103μg/L）においても認められなかった（4.2.2.4.12 PH-39816）。

2.6.4.6 排泄

2.6.4.6.1 ラット

参照項目： 4.2.2.5.1 A49457

ラットにおける単回投与マスバランス試験の概要を表 2.6.4.3- 2（用いた分析法：LSC）に示した。試験成績を表 2.6.4.6- 1 に示す。

表 2.6.4.6- 1 ラットに[^{14}C]フィネレノンを単回投与したときの放射能の排泄率〔%投与量〕

Route / time [h]	Dose [mg/kg]	Urine	Bile	Feces	GIT	Residues[a]	Recovery
iv / 168	1	21.4	n.a.[b]	74.0	0.0149	0.167	95.8
po / 168	1	19.5	n.a.[b]	75.7	0.0152	0.153	95.5
iv BDC / 24	1	10.9	44.1	7.78	5.80	27.1	97.3
po BDC / 24	1	12.1	52.7	9.27	4.78	17.4	97.6

Source: 4.2.2.5.1 A49457

a = total body excluding gastrointestinal tract

b = not applicable

無処置ラットに[^{14}C]フィネレノンを経口投与したとき、放射能は主に胆汁／糞を介する経路で排泄された。投与後 168 時間までに、糞中には投与量の約 76%が回収され、尿中排泄の寄与も大きく、投与量の約 20%が回収された（表 2.6.4.6- 1）。

BDC ラットに[^{14}C]フィネレノンを経口投与後 24 時間以内に、投与量の約 53%が胆汁中に排泄された。更に、投与量の約 4.8%が消化管に認められ、投与量の約 9.3%が糞中に排泄された。静脈内投与後においても同様に糞中及び消化管に放射能が認められたことから、腸内への直接的な放射能分泌が示された（表 2.6.4.6- 1）。

[^{14}C]フィネレノンを静脈内及び経口投与後 24 時間においては、それぞれ投与量の約 27%及び約 17%がラット体内に残存していた。その後、時間と共に放射能の排泄がみられ、投与後 168 時間までに残存放射能は投与量の 0.2%未満まで減少した（表 2.6.4.6- 1）。

2.6.4.6.2 イヌ

参照項目： 4.2.2.5.2 PH-37447

イヌにおける単回投与マスバランス試験の概要を表 2.6.4.3- 3（用いた分析法：LSC）に示した。試験成績を表 2.6.4.6- 2 に示す。

表 2.6.4.6- 2 イヌに[^{14}C]フィネレノンを単回経口投与したときの放射能の排泄率〔%投与量〕

Route / time [h]	Dose [mg/kg]	Urine	Feces	Cage wash	Recovery
po / 336	3	52.7	42.0	2.42	97.2

Source: 4.2.2.5.2 PH-37447

イヌに [^{14}C]フィネレノンを経口投与したとき、放射能は尿（投与量の約 53%）及び糞中（投与量の 42%）に排泄された（表 2.6.4.6- 2）。

2.6.4.6.3　　ヒト

参照項目： 4.2.2.4.11　PH-39577

4 名の健康男性被験者に[^{14}C]フィネレノンを 10mg（約 2.89MBq）単回経口投与し、薬物動態、代謝及び排泄を検討した。排泄の試験成績を表 2.6.4.6- 3 に示す。

表 2.6.4.6- 3　ヒトに[^{14}C]フィネレノンを単回経口投与したときの放射能の排泄率〔%投与量〕

Route / time [h]	Dose [mg/subject]	Urine	Feces	Recovery
po / 240	10	79.6	21.2	101

Source: 4.2.2.4.11 PH-39577

ヒトにおいて、放射能は主要な排泄経路である尿中に投与量の約 80%が排泄され、糞中には投与量の約 21%が排泄された（表 2.6.4.6- 3）。

2.6.4.6.4　　乳汁排泄

参照項目： 4.2.2.5.4　PH-40956

授乳ラットに[^{14}C]フィネレノンを静脈内投与したとき、中程度の放射能（未変化体及び／又は放射性代謝物）が乳汁中に分泌された。乳汁中に排泄された放射能は、投与後 48 時間までの評価期間において投与量の約 20%と見積もられた（2.6.5.7　Table 7-3）。

2.6.4.7　薬物動態学的薬物相互作用

本項以外の薬物相互作用に関する試験成績は、代謝酵素を介する薬物相互作用については2.6.4.5.1に、トランスポーターを介した薬物相互作用については2.6.4.8に記載する。

2.6.4.7.1　フィネレノンとSGLT2阻害薬との薬物相互作用の可能性

参照項目： 4.2.2.6.1　PH-41050

フィネレノンの対象患者において、フィネレノンと併用される可能性があるナトリウム - グルコース共輸送体（SGLT）2 阻害薬カナグリフロジン、ダパグリフロジン、エンパグリフロジン、エルツグリフロジン、イプラグリフロジン及びトホグリフロジンの代謝に対するフィネレノンの阻害作用をヒト肝細胞を用いた *in vitro* 試験で検討した。試験の概要を表2.6.4.7- 1に示す。

表2.6.4.7- 1　*In vitro*におけるフィネレノンとSGLT2阻害薬との薬物相互作用試験の概要

Study type	*In vitro* assay, drug-drug interaction with SGLT2 inhibitors
Bayer reference	4.2.2.6.1 PH-41050
Test system	Human hepatocytes
Victim (SGLT2 inhibitors)	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Tofogliflozin
Test compound	Finerenone, 5 µM (1892 µg/L)

フィネレノン 5μM の存在下で、SGLT2 阻害薬のヒト肝細胞における代謝クリアランスはいずれも意味のある阻害を受けなかった。エンパグリフロジンについては、肝細胞による代謝物産生が少なかったが、エンパグリフロジンは未変化体の直接排泄、UGT2B7、UGT1A3、UGT1A8、UGT1A9による代謝により消失することから、フィネレノンがエンパグリフロジンの曝露量を増加させる可能性は低いと考えられる。以上より、フィネレノンが相互作用薬として、これら検討したSGLT2 阻害薬の代謝を阻害することによって臨床的に問題となる薬物動態学的薬物相互作用を引き起こす可能性は低いと考えられる（2.6.5.15 Table 15-1）。

2.6.4.8 その他の薬物動態試験

2.6.4.8.1 Caco-2 細胞におけるフィネレノンの膜透過性

参照項目： 4.2.2.7.1 R-12248

Caco-2 細胞の単層培養膜を用いて、*in vitro* におけるフィネレノンの膜透過性を検討した。試験の概要を表 2.6.4.8- 1 に、試験成績を表 2.6.4.8- 2 に示す。

表 2.6.4.8- 1 膜透過性試験の概要

Study type	*In vitro* assay, permeability
Bayer reference	4.2.2.7.1 R-12248
Test system	Caco-2 cells
Test compound	Finerenone: 2, 21, 210 µM (757, 7947, 79468 µg/L)

表 2.6.4.8- 2 Caco-2 細胞におけるフィネレノンの膜透過性

Concentration [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean	Recovery A-B [%]	Recovery B-A [%]
2.0	191	22	439	30	2.3	103	102
21	245[a]	n.c.[b]	368	29	1.5	96.5	92.6
210	322	26	276	50	0.9	107	88.1

Source: 4.2.2.7.1 R-12248

a = n = 2

b = not calculated

フィネレノン 2～210µM の濃度範囲において、Caco-2 細胞の頂端膜（A）から基底膜（B）方向へのみかけの透過係数（P_{app} A-B）は 191nm/s（2µM）から 322nm/s（210µM）と、フィネレノン濃度と共に若干増加した。基底膜から頂端膜方向への P_{app} B-A は 439nm/s（2µM）から 276nm/s（210µM）の範囲であり、これらの値から求めた排出比（efflux ratio）は 2.3（2µM）～0.9（210µM）であり、検討した濃度範囲において飽和性を示した（表 2.6.4.8- 2）。

上記の膜透過性のデータをメトプロロールやプロプラノロールのような膜透過性が高い基準化合物と比較した結果、生物薬剤学分類システム（BCS）に関する FDA ガイダンス[6]に基づくと、フィネレノンは膜透過性が高い化合物であることが明らかとなった（4.2.2.7.1 R-12248）。

2.6.4.8.2 排出トランスポーターに対するフィネレノンの基質特性

参照項目： 4.2.2.7.2 PH-40755
4.2.2.7.4 PH-40764

ヒト P-gp 及び BCRP 遺伝子をトランスフェクトした細胞及び対照細胞を用いて、P-gp 及び BCRP に対するフィネレノンの基質特性を検討した。このとき、P-gp 又は BCRP に対する典型阻害薬の非存在下又は存在下でフィネレノンの輸送を測定した。この輸送試験は、陽性対照として典型基質についても行った。試験の概要を表 2.6.4.8- 3 に、試験成績を 2.6.5.16 Table 16-2 及び Table 16-4 に示す。

表 2.6.4.8- 3 排出トランスポーターに対するフィネレノンの基質特性検討試験の概要

Study type	*In vitro* assay, substrate characteristics for efflux transporters
Bayer reference	4.2.2.7.2 PH-40755, 4.2.2.7.4 PH-40764
Test system	Control cells and transfected LLC-PK1 cells: P-gp; Control cells and transfected MDCKII cells: BCRP
Probe substrates	Dipyridamole (P-gp), topotecan (BCRP)
Reference Inhibitor	Ivermectin (P-gp); Ko143 (BCRP)
Test compound	Finerenone: 0.2 - 100 µM (75.7 – 37842 µg/L)

これらの試験のデータに基づくと、フィネレノンは P-gp の基質と判定され、基質濃度 0.2～100μM の範囲における排出比は 4.2～7.2 であった。「P-gp をトランスフェクトした細胞での排出比／対照細胞での排出比」の比率は 6.6～8.9（基質濃度：2～100μM）であった。また、この排出は強力な P-gp 阻害薬であるイベルメクチン添加により、完全に阻害された（2.6.5.16 Table 16-2、4.2.2.7.2 PH-40755）。一方、BCRP に対するフィネレノンの基質特性は認められなかった（排出比＜2、「BCRP をトランスフェクトした細胞での排出比／対照細胞での排泄比」の比率＜2）（2.6.5.16 Table 16-4、4.2.2.7.4 PH-40764）。

2.6.4.8.3 取込みトランスポーターに対するフィネレノンの基質特性

参照項目： 4.2.2.7.11 R-9495
4.2.2.7.8 R-9574

取込みトランスポーター遺伝子をトランスフェクトした細胞及び対照細胞を用いて、OATP1B1、OATP1B3 及び OCT1 に対するフィネレノンの基質特性を検討した。典型阻害薬の非存在下又は存在下（OCT1 を除く）でフィネレノンの取込みを測定した。この輸送試験は、陽性対照として典型基質についても行った。試験の概要を表 2.6.4.8- 4 に、試験成績を 2.6.5.16 Table 16-8 及び Table 16-11 に示す。

表 2.6.4.8- 4 取込みトランスポーターに対するフィネレノンの基質特性検討試験の概要

Study type	*In vitro* assay, substrate characteristics for uptake transporters
Bayer reference	4.2.2.7.11 R-9495; 4.2.2.7.8 R-9574
Test system	Control cells and transfected HEK cells: OATP1B1, OATP1B3, OCT1
Probe substrate	[^{3}H]estrone-3-sulfate (OATP1B1); [^{3}H]bromosulfophthalein (OATP1B3) ; MPP^{+} [a] (OCT1)
Reference inhibitor	Rifampicin (OATPs)
Test compound	[^{14}C]finerenone: 0.5 – 5 µM (189 – 1892 µg/L for OATPs); finerenone: 0.1 – 0.5 µM (37.8 – 189 µg/L for OCT1)

a = 1-methyl-4-phenylpyridinium

これらの試験の結果、OATP1B1、OATP1B3 及び OCT1 を介したフィネレノンの能動的な取込みは認められなかった（2.6.5.16 Table 16-8 及び Table 16-11）。

2.6.4.8.4 排出トランスポーターに対するフィネレノンの阻害作用

参照項目： 4.2.2.7.3 PH-40886
4.2.2.7.5 PH-40885
4.2.2.7.6 R-11129
4.2.2.7.7 R-11196

排出トランスポーター遺伝子をトランスフェクトした細胞及びサンドイッチ培養ヒト肝細胞を用いて、P-gp、BCRP、BSEP、MATE1 及び MATE2K を介した典型基質の輸送に対するフィネレノンの阻害作用を評価した。試験の概要を表 2.6.4.8- 5 に、試験成績を表 2.6.4.8- 6 に示す。

表 2.6.4.8- 5　排出トランスポーターに対するフィネレノンの阻害作用検討試験の概要

Study type	*In vitro* assay, inhibitory potential towards efflux transporters
Bayer reference	4.2.2.7.3 PH-40886; 4.2.2.7.5 PH-40885; 4.2.2.7.6 R-11129; 4.2.2.7.7 R-11196
Test system	Transfected LLC-PK1 cells: P-gp Transfected MDCKII cells: BCRP Sandwich-Cultured Human Hepatocytes: BSEP Transfected HEK cells: MATE1 and MATE2K
Probe substrates	Digoxin, dipyridamole (P-gp); topotecan, PhIP (BCRP); d8-TCA (BSEP); metformin (MATE1 and MATE2K)
Reference Inhibitors	Ivermectin (P-gp); Ko143 (BCRP); cyclosporin (BSEP); cimetidine (MATE1); pyrimethamine (MATE2K)
Test compound	Finerenone: 0.6 – 600 µM (227 – 227052 µg/L for P-gp), 0.1 – 300 µM (37.8 – 113526 µg/L for BCRP), 0.1 – 100 µM (37.8 – 37842 µg/L for BSEP), 0.5 – 5 µM (189 – 1892 µg/L for MATE1 and MATE2K)

表 2.6.4.8- 6　排出トランスポーターに対するフィネレノンの阻害作用

Transporter	**Probe substrate**	**IC_{50} [µM]**
P-gp	Digoxin	121
P-gp	Dipyridamole	47
BCRP	Topotecan	18.1
BCRP	2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)	17.4
BSEP	d8-taurocholic acid (d8-TCA)	>100
MATE1	Metformin	>5
MATE2K	Metformin	>5

Source: 4.2.2.7.3 PH-40886; 4.2.2.7.5 PH-40885; 4.2.2.7.6 R-11129; 4.2.2.7.7 R-11196

フィネレノンは P-gp〔IC_{50}（2 種類の基質での値）：47 μM（17786 μg/L）及び 121 μM（45789 μg/L）〕及び BCRP〔IC_{50}（同）：17.4 μM（6585 μg/L）及び 18.1 μM（6849 μg/L）〕に対して阻害作用を示した。一方、フィネレノンは、検討した濃度範囲で BSEP（IC_{50}＞100 μM）あるいは MATE1／MATE2K（IC_{50}＞5 μM）のいずれも阻害しなかった（表 2.6.4.8- 6）。

2.6.4.8.5　取込みトランスポーターに対するフィネレノンの阻害作用

参照項目：4.2.2.7.9　PH-40952
4.2.2.7.10　R-9494
4.2.2.7.11　R-9495
4.2.2.7.12　R-9440

取込みトランスポーター遺伝子をトランスフェクトした細胞において、OATP1B1、OATP1B3、OAT1、OAT3、OCT1 及び OCT2 を介した典型基質の取込み輸送に対するフィネレノンの阻害作用を検討した。OATP に対する阻害作用を検討する場合には、フィネレノンと細胞を 1 時間プレインキュベーションした。試験の概要を表 2.6.4.8- 7 に、試験成績を表 2.6.4.8- 8 に示す。

表 2.6.4.8- 7　取込みトランスポーターに対するフィネレノンの阻害作用検討試験の概要

Study type	*In vitro* assay, inhibitory potential towards uptake transporters
Bayer reference	4.2.2.7.9 PH-40952; 4.2.2.7.10 R-9494; 4.2.2.7.11 R-9495; 4.2.2.7.12 R-9440
Test system	Transfected HEK cells: OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2
Probe substrates	Pravastatin (OATPs); PAH (OAT1); furosemide (OAT3); MPP^+ (OCTs)
Reference inhibitors	Rifamycin (OATPs); probenecid (OATs); repaglinide (OCT1); imipramine (OCT2)
Test compound	Finerenone: 0.2 - 10 µM (75.7 – 3784 µg/L for OATPs), 0.3 – 3 µM (114 – 1135 µg/L for OATs, OCT2), 0.5 - 5 µM (189 – 1892 µg/L for OCT1)

表 2.6.4.8- 8　取込みトランスポーターに対するフィネレノンの阻害作用

Transporter	**Probe substrate**	**IC_{50} [µM]**
OATP1B1	Pravastatin	3.2
OATP1B3	Pravastatin	>10
OAT1	p-aminohippuric acid (PAH)	>3
OAT3	Furosemide	>3
OCT1	MPP^+	>5
OCT2	MPP^+	>3

Source: 4.2.2.7.9 PH-40952; 4.2.2.7.10 R-9494; 4.2.2.7.11 R-9495; 4.2.2.7.12 R-9440

フィネレノンは、検討した濃度範囲では OATP1B3、OAT1、OAT3、OCT1 及び OCT2 のいずれに対しても阻害作用を示さなかった。一方、フィネレノンは肝臓における取込みトランスポーターである OATP1B1 を阻害した（IC_{50}：3.2µM）（表 2.6.4.8- 8）。

2.6.4.8.6　ヒト血漿中の主代謝物に関する検討

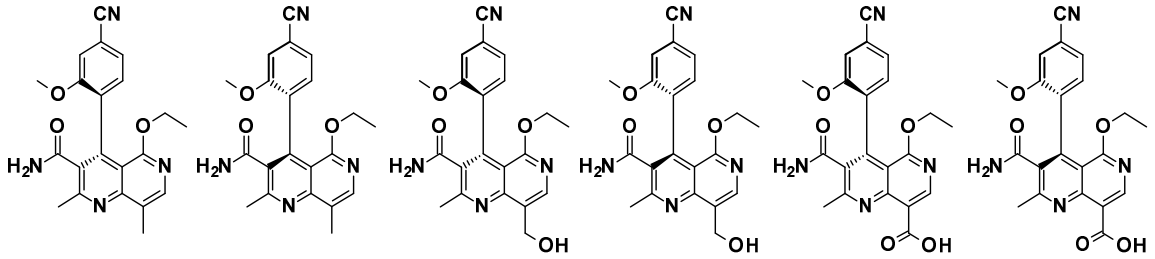
2.6.4.8.6.1　*In vitro* 及び *in vivo* における M-1、M-2 及び M-3 のアトロプ異性体の存在比

参照項目：
4.2.2.4.1　PH-41146
4.2.2.7.16　PH-40365
4.2.2.7.17　PH-40326
4.2.2.7.18　PH-40373
4.2.2.2.5　PH-39791
4.2.2.7.19　PH-40388
4.2.2.4.9　PH-39348
4.2.2.4.10　PH-39368
4.2.2.4.11　PH-39577

ヒト血漿中の主成分である代謝物 M-1、M-2 及び M-3 は軸性キラリティを示し、それぞれ「a」及び「b」を付した対応するアトロプ異性体：M-1a（BAY 1117267）、M-1b（BAY 1117266）、M-2a（BAY 1117268）、M-2b（BAY 1117270）、M-3a（BAY 1117271）及び M-3b（BAY 1117272）から成ることが明らかとなった（図 2.6.4.8- 1）。これらのすべての代謝物は薬理学的に不活性であった（2.6.2.2.1.5）。これらの代謝物についてアトロプ異性体の存在比を、*in vitro* 試験の試料（4.2.2.4.1 PH-41146）、ラット、イヌ及びヒトにおけるマスバランス試験（4.2.2.7.16 PH-40365、4.2.2.7.17 PH-40326 及び 4.2.2.7.18 PH-40373）並びにラット及びヒトにおける反復投与試験（4.2.2.2.5 PH-39791 及び 4.2.2.7.19 PH-40388）から得られた血漿及び／又は尿試料について明らかにした。

In vitro における代謝物のアトロプ異性体存在比を表 2.6.4.8- 9 に、*in vivo* における存在比を表 2.6.4.8- 10（単回投与）及び表 2.6.4.8- 12（反復投与）に示す。更に、これらアトロプ異性体の存在比及び各代謝物の曝露量に基づいて、各代謝物のアトロプ異性体が血漿中総曝露量に占める割合を算出し表 2.6.4.8- 11（単回投与）及び表 2.6.4.8- 13（反復投与）に示す。

図 2.6.4.8- 1　代謝物 M-1、M-2 及び M-3 のアトロプ異性体



マウス、ラット、イヌ及びヒトの肝ミクロソームを用いた *in vitro* 試験の結果、検討したすべての動物種で各代謝物について主に「a」のアトロプ異性体が産生された（表 2.6.4.8- 9 及び 4.2.2.4.1 PH-41146）。「b」のアトロプ異性体の割合は、雌ラットで最も高かった。また、異性体存在比における性差はラットで顕著であった。

表 2.6.4.8- 9　動物及びヒト肝ミクロソーム（プール）におけるフィネレノン（1 又は 2μM：378 又は 757μg/L）の代謝物：アトロプ異性体の存在比〔%〕

Species	Mouse[a]		Rat[a]		Dog[a]	Human[a]
Gender	Male	Female	Male	Female	Female	Mix
M-1a	96.7	91.4	95.5	82.0	92.5	94.6
M-1b	3.3	8.6	4.5	18.0	7.5	5.4
M-2a	97.0	93.8	96.8	86.7	91.9	96.2
M-2b	3.0	6.2	3.2	13.3	8.1	3.8
M-3a	n.a.[b]	96.5	93.7	n.a.[b]	n.a.[b]	n.a.[b]
M-3b	n.a.[b]	3.5	6.3	n.a.[b]	n.a.[b]	n.a.[b]

Source: 4.2.2.4.1 PH-41146

a = LC-MS/MS

b = not applicable

[^{14}C]フィネレノンを単回経口投与後のラット尿（血漿については代謝物濃度が低かったため未分析）、並びにイヌ及びヒトの血漿及び尿において、すべての動物種で各代謝物について主に「a」のアトロプ異性体が認められ（表 2.6.4.8- 10）、*in vitro* 試験成績とよく一致した（4.2.2.7.16 PH-40365、4.2.2.7.17 PH-40326 及び 4.2.2.7.18 PH-40373）。イヌ及びヒトにおいてアトロプ異性体の存在比は、比較が可能な場合には血漿と尿試料の間でほぼ等しかった。「b」のアトロプ異性体の割合が最も高かったのは、ヒト血漿中の M-1b であった（約 21%）。また、各動物種の血漿を用いた生理的条件下における *in vitro* での検討で、各代謝物の一方のアトロプ異性体が他方に反転してラセミ化することはなかった（4.2.2.4.1 PH-41146）。

表 2.6.4.8- 10 動物及びヒトに[^{14}C]フィネレノンを単回経口投与したときの血漿及び尿中における代謝物：アトロプ異性体の存在比〔%〕

Species	Rat		Dog		Human	
Gender	Male		Female		Male	
Matrix	Plasma	Urine[a] 0-72 h	Plasma[b] AUC(0-48)	Urine[a] 0-72 h	Plasma[b] AUC(0-48)	Urine[c] 0-48 h
Dose	10 mg/kg		3 mg/kg		10 mg	
M-1a	n.a.[d]	85.6	91.2	89.3	79.3	n.a.[d]
M-1b	n.a.[d]	14.4	8.8	10.7	20.7	n.a.[d]
M-2a	n.a.[d]	93.2	89.1	81.3	94.6	93.9
M-2b	n.a.[d]	6.8	10.9	18.7	5.4	6.1
M-3a	n.a.[d]	88.2	90.7	83.7	99.1	97.8
M-3b	n.a.[d]	11.8	9.3	16.3	0.9	2.2

Source: 4.2.2.7.16 PH-40365; 4.2.2.7.17 PH-40326; 4.2.2.7.18 PH-40373

a = HPLC-LSC

b = LC-MS/MS

c = LC-HRMS

d = not applicable

フィネレノンを単回経口投与したときの血漿中において、代謝物の各アトロプ異性体が総放射能 AUC に占める割合（%）を表 2.6.4.8- 11 に示す。これは、[^{14}C]フィネレノンをイヌ及びヒトに単回経口投与後、0～48 時間（総放射能 AUC がほぼこの時間範囲に含まれる）における血漿中での各アトロプ異性体の存在比（%）（表 2.6.4.8- 10）を、総放射能 AUC に占める M-1、M-2 及び M-3 それぞれの割合（%）（表 2.6.4.5- 12）に乗じて算出した。その結果、代謝物 M-1a、M-1b 及び M-2a がヒト血漿中における主代謝物（薬物由来成分の総 AUC の 10%超）であることが明らかとなった。

表 2.6.4.8- 11 動物及びヒトに[^{14}C]フィネレノンを単回経口投与したときの血漿中における代謝物（総 AUC に対する%、アトロプ異性体の存在比により補正）

Species	Rat[a]	Dog	Human (study 14502, N=4)
Gender	Male	Female	Male
Dose	1 mg/kg	3 mg/kg	10 mg
Components	[% of total radioactivity AUC]		
Finerenone	96.4	28.2	7.1
M-1a	n.a.[b]	7.4	38.8
M-1b	n.a.[b]	0.7	10.1
M-2a	n.a.[b]	32.1	20.3
M-2b	n.a.[b]	3.9	1.2
M-3a	n.a.[b]	1.5	8.9
M-3b	n.a.[b]	0.1	0.1
M-4/M-7	2.4	11.1	2.4[c]

Source: 4.2.2.4.9 PH-39348; 4.2.2.4.10 PH-39368; 4.2.2.4.11 PH-39577; 4.2.2.7.16 PH-40365; 4.2.2.7.17 PH-40326; 4.2.2.7.18 PH-40373

a = total radioactivity AUC(0-8)

b = not applicable

c = radioactivity solely covered by M-4

フィネレノンを反復経口投与後の雌雄ラット及びヒト（健康被験者）の血漿においても、主に各代謝物の一方の異性体（「a」）が認められた（4.2.2.2.5 PH-39791、4.2.2.7.19 PH-40388）

（表 2.6.4.8- 12）。*In vitro* での結果と矛盾なく、雌ラットの血漿中における「b」の異性体の割合は雄に比べて高かった。更に、ヒト血漿中における「b」異性体の割合は M-1b の約 17%から M-2b の約 5%、M-3b の約 2%の順で減少しており、^{14}C 標識体を単回投与したヒトのマスバランス試験での異性体存在比の結果（表 2.6.4.8- 10）を反映するものであった。

表 2.6.4.8- 12 ラット及びヒトにフィネレノンを反復経口投与したときの血漿中における代謝物：アトロプ異性体の存在比〔%〕

Species	Rat[a] (I5572-9)		Human[a] (study 13785, N=9)
Gender	Male	Female	Male
Dose	30 mg/kg, 7 days		40 mg OD, 10 days
	AUC(0-24) on day 7		AUC(0-24) on day 10
M-1a	96.2	84.4	83.1
M-1b	3.8	15.6	16.9
M-2a	94.9	87.8	95.3
M-2b	5.1	12.2	4.7
M-3a	89.6	89.4	98.0
M-3b	10.4	10.6	2.0

Source: 4.2.2.2.5 PH-39791; 4.2.2.7.19 PH-40388

a = LC-MS/MS

腎機能障害を有する患者にフィネレノンを単回経口投与したときの血漿において、各アトロプ異性体が薬物関連の総 AUC（M-4 及び M-5 は無視する）に占める割合（%）を表 2.6.4.8- 13 に示す。これは、腎機能障害を有する患者におけるフィネレノン及び M-1、M-2 及び M-3 の曝露量（5.3.3.3.1 PH-36810）に、健康被験者に反復経口投与したときのアトロプ異性体の存在比（表 2.6.4.8- 12）を乗じて算出した。その結果、血漿中における薬物由来の総成分をフィネレノン、M-1a、M-1b、M-2a、M-2b、M-3a 及び M-3b が占めると仮定すると、腎機能障害を有する患者では M-3a もまた血漿中の主代謝物（薬物由来成分の総 AUC の 10%超）であることが明らかとなった。

表 2.6.4.8- 13 腎機能障害を有する患者にフィネレノンを単回経口投与したときの血漿中における代謝物（総 AUC に対する%、アトロプ異性体の存在比により補正）

Species	Human [N=8]	Human [N=8 (7)]	Human [N=9]
Study ID	14509	14509	14509
Dose	10 mg	10 mg	10 mg
Impairment	Mild	Moderate	Severe
Components		[% of AUC][a]	
Finerenone	8.5	7.1(7.1)[b]	6.2
M-1a	41.0	45.3 (42.9)[b]	33.7
M-1b	8.3	9.2 (8.7)[b]	6.9
M-2a	24.9	19.7 (19.6)[b]	20.4
M-2b	1.2	1.0 (1.0)[b]	1.0
M-3a	15.6	17.3 (20.3)[b]	31.1
M-3b	0.3	0.4 (0.4)[b]	0.6

Source: 5.3.3.3.1 PH-36810

a = assuming finerenone, M-1a, M-1b, M-2a, M-2b, M-3a and M-3b cover all entities in plasma

b = calculations without data for outlier for finerenone

以上より、ヒトのマスバランス試験（4.2.2.4.11 PH-39577）及び腎機能障害を有する患者を対象とした試験（5.3.3.3.1 PH-36810）における代謝物の曝露量並びに単回及び反復投与後のアトロプ異性体の存在比の検討（4.2.2.7.18 PH-40373 及び 4.2.2.7.19 PH-40388）から得られた

データに基づくと、代謝物 M-1a、M-1b、M-2a 及び M-3a がヒト血漿中での主代謝物であることが明らかとなった。

2.6.4.8.6.2　代謝物の血漿タンパク結合及び血球／血漿分配

参照項目：　4.2.2.7.13　A50452
4.2.2.7.14　PH-38807

ヒト血漿中主代謝物 M-1a、M-1b、M-2a 及び M-3a について、*in vitro* タンパク結合及び血球／血漿分配を検討した。タンパク結合試験の概要を表 2.6.4.8- 14 に、試験成績を代謝物ごとに表 2.6.4.8- 15～表 2.6.4.8- 18 に示す。

表 2.6.4.8- 14　ヒト血漿中主代謝物のタンパク結合試験の概要

Study type	*In vitro* assay, ultrafiltration
Bayer reference	4.2.2.7.13 A50452 4.2.2.7.14 PH-38807
Test compound	[^{3}H]M-1a ([^{3}H]BAY 1117267)[a], [^{14}C]M-1b ([^{14}C]BAY 1117266)[b], [^{3}H]M-2a ([^{3}H]BAY 1117268)[a], [^{3}H]M-3a ([^{3}H]BAY 1117271)[a]

a = specific activity: 10 MBq/mg

b = specific activity: 3.32 MBq/mg

表 2.6.4.8- 15　M-1a（BAY 1117267）の血漿タンパク結合

Species (gender)	**Concentration [µg/L]**	**f_u[a] [%]**
Human (M)	45.9 to 4398	5.82
Wistar rat (M)	47.0 to 4321	6.01
Beagle dog (F)	44.8 to 4488	11.2
Himalayan rabbit (F)	46.0 to 4673	2.17
CD-1 mouse (M)	48.4 to 4463	14.7

Source: 4.2.2.7.13 A50452

a = fraction of free (unbound) drug in plasma

表 2.6.4.8- 16　M-1b（BAY 1117266）の血漿タンパク結合

Species (gender)	**Concentration [µg/L]**	**f_u[a] [%]**
Human (M)	37.0 to 4620	3.88
Wistar rat (M)	37.4 to 4080	11.1
Beagle dog (F)	36.7 to 485	6.36
Beagle dog (F)	4090 to 4180	10.8
Himalayan rabbit (F)	43.2 to 4330	1.25
CD-1 mouse (M)	41.8 to 4430	12.1

Source: 4.2.2.7.14 PH-38807

a = fraction of free (unbound) drug in plasma

表 2.6.4.8- 17 M-2a（BAY 1117268）の血漿タンパク結合

Species (gender)	Concentration [µg/L]	f_u[a] [%]
Human (M)	48.6 to 4297	17.4
Wistar rat (M)	50.7 to 4552	45.4
Beagle dog (F)	51.5 to 4661	48.3
Himalayan rabbit (F)	51.0 to 4907	37.6
CD-1 mouse (M)	50.7 to 4344	58.0

Source: 4.2.2.7.13 A50452

a = fraction of free (unbound) drug in plasma

表 2.6.4.8- 18 M-3a（BAY 1117271）の血漿タンパク結合

Species (gender)	Concentration [µg/L]	f_u[a] [%]
Human (M)	35.1 to 3408	67.8
Wistar rat (M)	37.2 to 3846	74.1
Beagle dog (F)	39.8 to 3834	75.3
Himalayan rabbit (F)	48.2 to 4485	76.1
CD-1 mouse (M)	45.0 to 4186	82.4

Source: 4.2.2.7.13 A50452

a = fraction of free (unbound) drug in plasma

ヒト血漿中主代謝物のタンパク結合率には種差が認められた。しかし、代謝物での種差はフィネレノンのタンパク結合率に比べると小さかった。ヒト、ラット、イヌ、ウサギ及びマウスにおける代謝物 M-1a／M-1b のタンパク結合率は低い～中程度であり、非結合型分率（f_u）はそれぞれ約 5.8%／約 3.9%（ヒト）、約 6.0%／約 11%（ラット）、約 11%／約 6.4%（イヌ）、約 2.1%／約 1.3%（ウサギ）及び約 15%／約 12%（マウス）であった（表 2.6.4.8- 15 及び表 2.6.4.8- 16）。代謝物 M-2a については、ウサギ、ラット、イヌ及びマウスではタンパク結合率が低く非結合型分率が約 38%～58%の範囲であったが、ヒトでのみタンパク結合率がやや高く非結合型分率は約 17%であった（表 2.6.4.8- 17）。代謝物 M-3a のタンパク結合率は検討したすべての動物種で極めて低く、非結合型分率は約 68%～約 82%であった（表 2.6.4.8- 18）。イヌ血漿において約 500 µg/L と 4000 µg/L の濃度の間で M-1b の非結合型分率がわずかに増加したのを除くと、いずれの動物種においても、検討した濃度範囲（約 40～4900 µg/L）ではすべての代謝物でタンパク結合率の濃度依存性はみられなかった。

フィネレノンのヒト血漿中主代謝物は、ラット、イヌ及びヒトの全血中で概して血漿に分布した。C_b/C_p は、約 30～4600 µg/L までの濃度範囲において M-1a では約 0.61～0.65、M-2a では約 0.71～0.97、M-3a では約 0.75～0.76 であった（2.6.5.16 Table 16-21、Table 16-24 及び Table 16-26）。

2.6.4.8.6.3 CYP 分子種に対する代謝物の阻害作用

参照項目： 4.2.2.7.20 PH-37685
4.2.2.4.4 PH-40971
4.2.2.4.5 PH-40973

ヒト血漿中主代謝物の CYP 阻害作用に関する検討試験の概要を表 2.6.4.8- 19 に、試験成績を表 2.6.4.8- 20 に示す。

表 2.6.4.8- 19　CYP 分子種に対するヒト血漿中主代謝物の阻害作用検討試験の概要

Study type	*In vitro* assay, CYP inhibition
Bayer reference	4.2.2.7.20 PH-37685; 4.2.2.4.4 PH-40971; 4.2.2.4.5 PH-40973
Test system	Human liver microsomes, recombinant CYP isoforms 1A1 and 2E1
Test compound	M-1a (BAY 1117267), M-1b (BAY 1117266), M-2a (BAY 1117268), M-3a (BAY 1117271); 1.6 – 50 µM (M-1a/b: 602 – 18821 µg/L, M-2a: 628 – 19621 µg/L, M-3a: 650 – 20320 µg/L)

表 2.6.4.8- 20　CYP 分子種に対するヒト血漿中主代謝物の阻害作用

CYP isoform	**Substrate**	**M-1a IC_{50} [µM[a]]**	**M-1b IC_{50} [µM[a]]**	**M-2a IC_{50} [µM[a]]**	**M-3a IC_{50} [µM[a]]**
1A1	Granisetron	30	29	>50	>50
1A2	Phenacetin	>50	>50	>50	>50
2A6	Coumarin	>50	>50	>50	>50
2B6	Bupropion	>50	>50	>50	>50
2C8	Amodiaquine	>50	>50	>50	>50
2C9	Diclofenac	25	>50	>50	>50
2C19	Mephenytoin	>50	>50	>50	>50
2D6	Dextromethorphan	>50	>50	>50	>50
2E1	Chlorzoxazone	>50	>50	>50	>50
3A4	Midazolam	>50	>50	>50	30
3A4	Testosterone	>50	>50	>50	>50

Source: 4.2.2.7.20 PH-37685; 4.2.2.4.5 PH-40973

a = values in µg/L: 25 µM = 9410 µg/L (M-1a), 29 µM = 10916 µg/L (M-1b), 30 µM = 11292 µg/L (M-1a) and 12192 µg/L (M-3a), >50 µM = >18821 µg/L (M-1a/b), >19621 µg/L (M-2a) and >20320 µg/L (M-3a)

ヒト血漿中におけるフィネレノンの主代謝物 M-1a、M-1b、M-2a 及び M-3a は、検討した CYP 分子種の酵素活性に対し概して影響を及ぼさなかった。ただし、M-1a 及び M-1b による CYP1A1 の阻害（それぞれ IC_{50}：30 及び 29 µM）、M-1a による CYP2C9 の阻害（IC_{50}：25 µM）及び M-3a による CYP3A4 の阻害（IC_{50}：30 µM）がわずかに認められた（表 2.6.4.8- 20）。更に、代謝物を NADPH 存在下でヒト肝ミクロソームと 30 分間プレインキュベーションしたとき、CYP1A2、2B6、2C8、2C9、2C19、2D6 及び 3A4 活性に対する阻害作用の変化は認められなかった。一方、M-1a、M-1b 及び M-3a を NADPH 存在下で CYP1A1 発現系と 30 分間プレインキュベーションしたとき、CYP1A1 阻害作用のわずかな増強が認められた（2.6.5.16 Table 16-27～Table 16-30）。

2.6.4.8.6.4　UGT 分子種に対する代謝物の阻害作用

参照項目：　4.2.2.7.21　PH-40043

ヒト血漿中主代謝物の UGT 阻害作用に関する検討試験の概要を表 2.6.4.8- 21 に、試験成績を表 2.6.4.8- 22 に示す。

表 2.6.4.8- 21　UGT 分子種に対するヒト血漿中主代謝物の阻害作用検討試験の概要

Study type	*In vitro* assay, UGT inhibition
Bayer reference	4.2.2.7.21 PH-40043
Test system	Human liver microsomes
Test compound	M-1a (BAY 1117267), M-1b (BAY 1117266), M-2a (BAY 1117268), M-3a (BAY 1117271); 1.6 – 50 µM (M-1a/b: 602 – 18821 µg/L, M-2a: 628 – 19621 µg/L, M-3a: 650 – 20320 µg/L)

表 2.6.4.8- 22 UGT 分子種に対するヒト血漿中主代謝物の阻害作用

UGT isoform	Substrate	M-1a IC_{50} [μM]	M-1b IC_{50} [μM]	M-2a IC_{50} [μM]	M-3a IC_{50} [μM]
1A1	Estradiol	>50	>50	>50	>50
1A4	Trifluoperazine	>50	>50	>50	>50
1A6	α-Naphthol	>50	>50	>50	>50
1A9	Propofol	>50	>50	>50	>50
2B4	1'-Hydroxymidazolam	>50	>50	>50	>50
2B7	Tarenflurbil	>50	>50	>50	>50

Source: 4.2.2.7.21 PH-40043

フィネレノンのヒト血漿中主代謝物は検討した最高濃度まで UGT1A1、1A4、1A6、1A9、2B4 及び 2B7 のグルクロン酸抱合活性に影響を及ぼさなかった（IC_{50}＞50μM）（表 2.6.4.8- 22）。

2.6.4.8.6.5 CYP 分子種に対する代謝物の誘導作用

参照項目： 4.2.2.4.7 PH-39130

3 名のドナーに由来するヒト初代培養肝細胞を用いて、CYP 分子種に対するフィネレノンの血漿中主代謝物の誘導作用を評価した。ヒト血漿中主代謝物である M-1a、M-1b、M-2a 及び M-3a の CYP 誘導作用検討試験の概要を表 2.6.4.8- 23 に、試験成績を代謝物ごとに表 2.6.4.8- 24～表 2.6.4.8- 27 に示す。

表 2.6.4.8- 23 CYP 分子種に対するヒト血漿中主代謝物の誘導作用検討試験の概要

Study type	*In vitro* assay, induction of CYP1A2, 2B6, 2C19 and 3A4
Bayer reference	4.2.2.4.7 PH-39130
Test system	Cultured human hepatocytes
Test compound	M-1a (BAY 1117267), M-1b (BAY 1117266), M-2a (BAY 1117268), M-3a (BAY 1117271); 14 – 30000 µg/L (approximately 0.03 –80 µM) for M-1a/M-1b/M-3a, 5 – 10000 µg/L (approximately 0.01 – 25 µM) for M-2a

表 2.6.4.8- 24 CYP 分子種に対する M-1a（BAY 1117267）の誘導作用（mRNA 発現量）

CYP	Result
1A2	Concentration-dependent induction up to 2.8-fold
3A4	Concentration-dependent induction up to 16.1-fold
2B6	Concentration-dependent induction up to 10.1-fold
2C19	Concentration-dependent induction up to 5.3-fold

Source: 4.2.2.4.7 PH-39130

表 2.6.4.8- 25 CYP 分子種に対する M-1b（BAY 1117266）の誘導作用（mRNA 発現量）

CYP	Result
1A2	Concentration-dependent induction up to 2.1-fold
3A4	Concentration-dependent induction up to 18.3-fold
2B6	Concentration-dependent induction up to 6.8-fold
2C19	Concentration-dependent induction up to 5.9-fold

Source: 4.2.2.4.7 PH-39130

表 2.6.4.8- 26 CYP 分子種に対する M-2a（BAY 1117268）の誘導作用（mRNA 発現量）

CYP	Result
1A2	No induction up to 10000 µg/L (25 µM)
3A4	Concentration-dependent induction up to 8.5-fold
2B6	Concentration-dependent induction up to 2.2-fold
2C19	No induction up to 10000 µg/L (25 µM)

Source: 4.2.2.4.7 PH-39130

表 2.6.4.8- 27 CYP 分子種に対する M-3a（BAY 1117271）の誘導作用（mRNA 発現量）

CYP	Result
1A2	No induction up to 30000 µg/L (74 µM)
3A4	No induction up to 30000 µg/L (74 µM)
2B6	No induction up to 30000 µg/L (74 µM)
2C19	No induction up to 30000 µg/L (74 µM)

Source: 4.2.2.4.7 PH-39130

3 名すべてのドナー由来の培養肝細胞において、ヒトの血漿中主代謝物 M-1a、M-1b、M-2a 及び M-3a は CYP1A2 の mRNA 発現量及び酵素活性レベルのいずれについても、検討した最高濃度（10000 又は 30000μg/L）まで明確な誘導を示さなかった。わずかに認められた mRNA の増加（最大で 2.8 倍）は臨床的に有意なものではないと考えられる（表 2.6.4.8- 24～表 2.6.4.8- 27）。

一方、すべてのドナー由来の肝細胞において、代謝物 M-1a、M-1b 及び M-2a は概して濃度依存的に CYP3A4 の mRNA 発現を誘導し、その最大誘導作用は M-1a で約 16 倍（陽性対照であるリファンピシンの誘導作用の 69%）、M-1b で約 18 倍（同、79%）、M-2a で 8.5 倍（同、34%）であった。これは、M-1a、M-1b 及び M-2a によって PXR が活性化されることに起因するものである。また、M-1a 及び M-1b による CYP2B6 及び CYP2C19 の誘導が認められた。M-2a による CYP2B6 に対する誘導もわずかに認められたが（mRNA は最大で 2.2 倍）、これは臨床的に有意なものではないと考えられる。mRNA 発現量の結果と一致して、代謝物 M-1a、M-1b 及び M-2a では、CYP3A4 活性においても溶媒対照と比較して増加が認められた。代謝物 M-3a は CYP3A4、CYP2B6 及び CYP2C19 に対して誘導を示さず、臨床において誘導作用を示す可能性は低い（表 2.6.4.8- 24～表 2.6.4.8- 27 及び 2.6.5.16 Table 16-40～Table 16-71）。

2.6.4.8.6.6 排出トランスポーターに対する代謝物の阻害作用

参照項目： 4.2.2.7.3 PH-40886
4.2.2.7.5 PH-40885
4.2.2.7.22 R-11130
4.2.2.7.23 R-11820

排出トランスポーター遺伝子をトランスフェクトした細胞及びサンドイッチ培養ヒト肝細胞を用いて、P-gp、BCRP、BSEP、MATE1 及び MATE2K を介した典型基質の輸送に対する M-1a、M-1b、M-2a 及び M-3a の阻害作用を検討した。試験の概要を表 2.6.4.8- 28 に、試験成績を表 2.6.4.8- 29 に示す。

表 2.6.4.8- 28 排出トランスポーターに対するヒト血漿中主代謝物の阻害作用検討試験の概要

Study type	*In vitro* assay, inhibitory potential towards efflux transporters
Bayer reference	4.2.2.7.3 PH-40886; 4.2.2.7.5 PH-40885; 4.2.2.7.22 R-11130; 4.2.2.7.23 R-11820
Test system	Transfected LLC-PK1 cells: P-gp; transfected MDCKII cells: BCRP Sandwich-Cultured Human Hepatocytes: BSEP Transfected HEK cells: MATE1 and MATE2K
Probe substrates	Digoxin, dipyridamole (P-gp); topotecan, PhIP (BCRP); d8-TCA (BSEP); metformin (MATE1 and MATE2K)
Reference Inhibitors	Ivermectin (P-gp); Ko143 (BCRP); cyclosporin (BSEP); cimetidine (MATE1); pyrimethamine (MATE2K)
Test compound	M-1a (BAY 1117267): 0.1 – 100 µM (37.6 – 37641 µg/L) for P-gp, 20 µM (7528 µg/L) for BCRP, 0.03 – 30 µM (11.3 – 11292 µg/L) for BSEP, 0.5 – 5 µM (188 – 1882 µg/L) for MATE1 and MATE2K M-1b (BAY 1117266): 0.1 – 30 µM (37.6 – 11292 µg/L) for P-gp, 0.1 – 30 µM (37.6 – 11292 µg/L) for BCRP, 0.03 – 30 µM (11.3 – 11292 µg/L) for BSEP, 0.5 – 5 µM (188 – 1882 µg/L) for MATE1 and MATE2K M-2a (BAY 1117268): 0.1 – 30 µM (39.2 – 11772 µg/L) for P-gp, 20 µM (7848 µg/L) for BCRP, 0.03 – 30 µM (11.8 – 11772 µg/L) for BSEP, 0.5 – 5 µM (196 – 1962 µg/L) for MATE1 and MATE2K M-3a (BAY 1117271): 0.1 – 30 µM (40.6 – 12192 µg/L) for P-gp, 20 µM (8128 µg/L) for BCRP, 0.03 – 30 µM (12.2 – 12192 µg/L) for BSEP, 0.5 – 5 µM (203 – 2032 µg/L) for MATE1 and MATE2K

表 2.6.4.8- 29 排出トランスポーターに対するヒト血漿中主代謝物の阻害作用

Transporter	**Probe substrate**	**M-1a IC_{50} [µM[a]]**	**M-1b IC_{50} [µM[a]]**	**M-2a IC_{50} [µM[a]]**	**M-3a IC_{50} [µM[a]]**
P-gp	Digoxin	>100	>30	>30	>30
P-gp	Dipyridamole	70	31	>30	>30
BCRP	Topotecan	>20	>30	>20	>20
BCRP	PhIP	>20	n.a.[b]	>20	>20
BSEP	d8-TCA	>30	>30	>30	>30
MATE1	Metformin	>5	>5	>5	>5
MATE2K	Metformin	>5	>5	>5	>5

Source: 4.2.2.7.3 PH-40886; 4.2.2.7.5 PH-40885; 4.2.2.7.22 R-11130; 4.2.2.7.23 R-11820

a = values in µg/L: 5 µM = 1882 µg/L (M-1a/b), 1962 µg/L (M-2a), 2032 µg/L (M-3a), 20 µM = 7528 µg/L (M-1a), 7848 µg/L (M-2a), 8128 µg/L (M-3a), 30 µM = 11292 µg/L (M-1a/b), 11772 µg/L (M-2a), 12192 µg/L (M-3a), 31 µM = 11669 µg/L (M-1b), 70 µM = 26349 µg/L (M-1a), 100 µM = 37641 µg/L (M-1a)

b = not applicable

M-1a、M-1b、M-2a 及び M-3a は、検討した最高濃度まで BCRP、BSEP、MATE1 及び MATE2K に対して阻害作用を示さなかった。また、P-gp については、M-2a 及び M-3a は阻害作用を示さなかったが、M-1a 及び M-1b は基質としてジピリダモールを用いた場合に、最高濃度で弱い阻害作用（IC_{50}：それぞれ 70 及び 31 µM）を示した（表 2.6.4.8- 29）。

2.6.4.8.6.7 取込みトランスポーターに対する代謝物の阻害作用

参照項目： 4.2.2.7.9 PH-40952
4.2.2.7.24 R-9702
4.2.2.7.25 R-9701

取込みトランスポーター遺伝子をトランスフェクトした細胞において、OATP1B1、OATP1B3、OAT1、OAT3、OCT1 及び OCT2 を介した典型基質の取込み輸送に対する M-1a、M-1b、M-2a 及び M-3a の阻害作用を検討した。試験の概要を表 2.6.4.8- 30 に、試験成績を表 2.6.4.8- 31 に示す。

表 2.6.4.8- 30　取込みトランスポーターに対するヒト血漿中主代謝物の阻害作用検討試験の概要

Study type	*In vitro* assay, inhibitory potential towards uptake transporters	
Bayer reference	4.2.2.7.9 PH-40952; 4.2.2.7.24 R-9702; 4.2.2.7.25 R-9701	
Test system	Transfected HEK cells: OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2	
Probe substrates	Pravastatin (OATPs); PAH (OAT1); furosemide (OAT3); MPP^+ (OCTs)	
Reference inhibitors	Rifamycin (OATPs); probenecid (OATs); repaglinide (OCT1); imipramine (OCT2)	
Test compound	M-1a (BAY 1117267):	0.2 – 10 µM (75.3 – 3764 µg/L) for OATPs, 0.25 – 2.47 µM (94 – 930 µg/L) for OATs, OCT2, 0.85 – 8.5 µM (320 – 3199 µg/L) for OCT1
	M-1b (BAY 1117266):	0.2 – 10 µM (75.3 – 3764 µg/L) for OATPs, 0.52 – 5.16 µM (196 – 1942 µg/L) for OATs, OCT2, 0.72 – 7.17 µM (271 – 2699 µg/L) for OCT1
	M-2a (BAY 1117268):	0.2 – 10 µM (78.5 – 3924 µg/L) for OATPs, 0.31 – 3.1 µM (122 – 1216 µg/L) for OATs, OCT2, 0.36 – 3.57 µM (141 – 1401 µg/L) for OCT1
	M-3a (BAY 1117271):	0.2 – 10 µM (81.3 – 4064 µg/L) for OATPs, 0.43 – 4.25 µM (175 – 1727 µg/L) for OATs, OCTs

表 2.6.4.8- 31　取込みトランスポーターに対するヒト血漿中主代謝物の阻害作用

Transporter	**Probe substrate**	**M-1a IC_{50} [µM[a]]**	**M-1b IC_{50} [µM[a]]**	**M-2a IC_{50} [µM[a]]**	**M-3a IC_{50} [µM[a]]**
OATP1B1	Pravastatin	3.8	3.9	>10	>10
OATP1B3	Pravastatin	7.6	7.3	>10	3.4
OAT1	PAH	>2.5	>5.2	>3.1	>4.3
OAT3	Furosemide	>2.5	>5.2	>3.1	>4.3
OCT1	MPP^+	>8.5	>7.2	>3.6	>4.3
OCT2	MPP^+	>2.5	>5.2	>3.1	>4.3

Source: 4.2.2.7.9 PH-40952; 4.2.2.7.24 R-9702; 4.2.2.7.25 R-9701

a = values in µg/L: (M-1a/b) >2.5 µM = >941 µg/L, 3.8 µM = 1430 µg/L, 3.9 µM = 1468 µg/L, >5.2 µM = >1957 µg/L, >7.2 µM = >2710 µg/L, 7.3 µM = 2748 µg/L, 7.6 µM = 2861 µg/L, >8.5 µM = >3199 µg/L
(M-2a) >3.1 µM = >1216 µg/L, 3.6 µM = 1413 µg/L, >10 µM = >3924 µg/L
(M-3a) 3.4 µM = 1382 µg/L, >4.3 µM = >1747 µg/L, >10 µM = >4064 µg/L

代謝物 M-1a、M-1b、M-2a 及び M-3a は、検討した濃度範囲では OAT1、OAT3、OCT1 及び OCT2 のいずれに対しても阻害作用を示さなかった（表 2.6.4.8- 31）。

OATP については、代謝物 M-2a は OATP1B1 及び OATP1B3 いずれに対しても阻害作用を示さず、M-3a は OATP1B1 を阻害しなかったが OATP1B3 に対して阻害作用を示した（IC_{50}：3.4μM）。また、M-1a 及び M-1b は OATP を介したプラバスタチン取込みに対して阻害作用を示した。すなわち、M-1a 及び M-1b は OATP1B1〔それぞれの IC_{50}：3.8μM（M-1a）及び 3.9μM（M-1b）〕及び OATP1B3〔それぞれの IC_{50}：7.6μM（M-1a）及び 7.3μM（M-1b）〕を阻害した（表 2.6.4.8-31）。

2.6.4.9　考察及び結論

ラットに単回経口投与したとき、フィネレノンはほぼ完全に吸収され、絶対的バイオアベイラビリティは高かった。イヌでは、バイオアベイラビリティは 56.5%～100%の範囲であった。

血漿タンパク結合におけるげっ歯類と非げっ歯類との間での著しい種差と矛盾なく、フィネレノンの血漿クリアランスはマウス（約 0.0062L/(h·kg)）及びラット（約 0.011～0.014L/(h·kg)）で極めて低く、イヌ（約 0.16L/(h·kg)）及びサル（0.39L/(h·kg)）では低かった。分布容積はマウス（約 0.10L/kg）及びラット（約 0.11～0.14L/kg）で小さく、イヌ（約 0.39L/kg）及びサル（約 0.25L/kg）では中程度であった。

ラットでは、フィネレノンは 3mg/kg までの用量では線形の薬物動態を示したが、毒性試験での 30mg/kg まで用量増加した場合の曝露量は用量比例性を下回る傾向がみられた。30mg/kg 未満の用量で 1 日 1 回、26 週間まで反復投与したとき、曝露量の増加が認められ、C_{max}及び AUC の蓄積率はそれぞれ最大で約 525%及び 601%であった。一方、30mg/kg の用量の反復投与ではフィネレノンの蓄積は認められなかった。イヌでは、フィネレノンの 0.3～15mg/kg の用量範囲で曝露量は用量比例性を軽度～中程度に上回って増加した。反復投与後の定常状態における C_{max} は初回投与時から変化しなかったが、AUC(0-24)は初回投与時に比べて中程度に増加した（AUC の蓄積率：最大で約 199%）。

雌雄ラットでの反復投与試験及び臓器・組織分布試験において、それぞれフィネレノン及び放射能濃度の曝露量は雄に比べて雌の方が明らかに高く、性差が認められた。これは、雌ラットの肝 CYP 酵素系の活性が概して雄よりも低いこと[4, 5]に起因するものと考えられる。一方、イヌにおける薬物動態に性差は認められなかった。

臨床濃度範囲においてフィネレノンの血漿タンパク結合率は、げっ歯類（ラット及びマウス）及びウサギで高かったが、非げっ歯類（サル、イヌ及びヒト）では中程度であった。臨床濃度範囲において、非結合型分率は、約 0.047%（ラット）～約 8.3%（ヒト）の範囲であり、種差は最大で約 180 倍であった。臨床濃度の約 500 倍の高濃度では、非結合型分率はわずかに増加した。主要な結合タンパクは、血清アルブミンであった。フィネレノンは、臨床濃度範囲においてラット及びイヌの全血中では主に血漿中に分布した（C_b/C_pがそれぞれ約 0.55 及び約 0.72）。一方、ヒトでは血液と血漿にほぼ均等に分布した（C_b/C_p：約 0.94）。

ヒトにおける血漿中主代謝物 M-1a、M-1b、M-2a 及び M-3a のタンパク結合率には、マウス、ラット、イヌ、ウサギ及びヒトの間で種差が認められ、非結合型分率は M-1a で約 5.8～15%、M-1b で約 1.3～12%、M-2a で約 17～58%、M-3a で約 68～82%であった。代謝物における血漿タンパク結合率の種差は、フィネレノンにおける種差に比べて小さかった。

ラットに[^{14}C]フィネレノンを投与したとき、放射能は種々の臓器・組織に分布し、放射能濃度が最も高かったのは血液及び血流量が多い臓器・組織であった。脳では放射能濃度が極めて低かった（血液中濃度の 2%未満）。この値は、血液脳関門を通過した放射能よりもむしろ、脳に残存した血液中放射能を反映したものである。[^{14}C]フィネレノン由来の放射能は、有色組織への親和性が低かった。また、[^{14}C]フィネレノンはラットの胎盤を中程度に通過した。放射能は時間と共に消失し、ラットにおいて[^{14}C]フィネレノン由来放射能の不可逆的な結合や残留は認められなかった。

[^{14}C]フィネレノンを単回経口投与したとき、マウス及びラット血漿中ではフィネレノンが圧倒的な主成分であり、総放射能 AUC の 96%超を占めた。対照的に、イヌ及びヒト血漿中では、フィネレノンは総放射能 AUC のそれぞれ約 28%及び 7.1%に過ぎなかった。ヒト血漿中では、ナ

フチリジン代謝物 M-1、M-2 及び M-3 が主成分であり、総放射能 AUC に占める割合はそれぞれ約 49%、約 22%及び 9%であった。これらの代謝物は軸性キラリティを示し、それぞれに対応するアトロプ異性体 M-1a、M-1b、M-2a、M-2b、M-3a 及び M-3b から成ることが明らかとなった。ラット、イヌ及びヒトの血漿及び／又は尿試料を分析した結果、いずれの動物種においても、各代謝物について主に一方のアトロプ異性体（「a」を付した一連の異性体であり、異性体存在比はいずれも 80%超）が認められた。ヒトでのマスバランス試験及び腎機能障害を有する患者での試験における代謝物の曝露量並びに単回及び反復投与後のアトロプ異性体存在比のデータに基づくと、代謝物 M-1a、M-1b、M-2a 及び M-3a がヒト血漿中での主代謝物であることが明らかとなった。ヒト血漿中主代謝物は、いずれもミネラルコルチコイド受容体に対する薬理学的な活性を有さず、意味のあるオフターゲット作用もないことが示された（2.6.2.2.1.5 及び 2.6.2.3.1.1）。*In vivo* でフィネレノン（*S*－エナンチオマー）が薬理学的に不活性なエナンチオマー（BAY 94-8863：*R*－エナンチオマー；4.2.1.1.4　PH-35690）に反転しラセミ化が生じる可能性について、ヒト血漿中において検討した結果、フィネレノンのキラル反転／ラセミ化は生じないことが明らかとなった。

授乳ラットにおいて、[^{14}C]フィネレノンを単回静脈内投与したとき、投与量の約 20%が乳汁中に分泌された。

[^{14}C]フィネレノンを単回経口投与したとき、ラットでは放射能は主に胆汁／糞を介する経路（投与量の約 76%）で排泄されたが、イヌでは放射能は胆汁／糞を介する経路（投与量の 42%）及び尿を介する経路（投与量の約 53%）にほぼ均等に排泄された。ヒトでは、放射能は主に尿（投与量の約 80%）を介して排泄された。放射能の回収率は、ヒトで完全（101%）であり、ラット（約 96%）及びイヌ（約 97%）においてもほぼ完全であった。ラット、イヌ及びヒトのすべての動物種で、*in vivo* においてフィネレノンはほぼ酸化的代謝反応のみによって消失し、主にナフチリジン代謝物（M-1、M-2 及び M-3）が産生する経路、及び寄与の程度は少ないが、恐らくエポキシド中間体の産生を経由してジヒドロジオール代謝物（M-4、M-5 及び M-8）が産生する経路が認められた。*In vivo* で得られた代謝プロファイルのデータは *in vitro* でのデータを反映しており、いずれの動物種においても、ナフチリジン代謝物の産生経路（M-1、M-2 及び M-3 の排泄率の合計：ラットで約 41%、イヌで約 48%及びヒトで約 63%）が、ジヒドロジオール代謝物の産生経路（M-4、M-5 及び M-8 の排泄率の合計：ラットで約 17%、イヌで約 17%及びヒトで約 22%）よりも優勢であった。

In vitro 試験に基づくと、フィネレノンは膜透過性が高く、P-gp の基質であった。一方、フィネレノンは BCRP、取込みトランスポーターである OATP1B1、OATP1B3 あるいは OCT1 のいずれに対しても基質とならなかった。フィネレノンの吸収率が高いこと（ヒトにおいて糞中への未変化体としての排泄率は投与量の 1%未満であり、かつ糞中でフィネレノンは安定である）を考慮すると、P-gp 阻害薬と併用してもフィネレノンは吸収過程において薬物動態学的薬物相互作用の被相互作用薬になる可能性は低いと考えられる。*In vitro* 試験の結果、フィネレノンの酸化的代謝は主に CYP3A4 により触媒され、CYP2C8 の寄与もわずかに認められた。中程度の CYP3A4 阻害薬であるエリスロマイシン〔併用時／非併用時のフィネレノンの AUC 比（AUCR）：3.5〕（2.7.2.2.3.1.2.1）及びベラパミル（フィネレノンの AUCR：2.7）（2.7.2.2.3.1.2.2）を併用した 2 つの臨床薬物相互作用試験の結果、フィネレノンの消失における CYP3A4 代謝による寄与率 f_m が 0.87～0.89 と算出されたことから、フィネレノンの消失に CYP3A4 が主要な役割を果たしていることが確認された（2.7.2.3.4.2.2.1）。フィネレノンの消失に寄与する CYP3A4 の f_m 値及び強力な CYP3A4 阻害薬であるケトコナゾール、イトラコナゾール、ボリコナゾール、テリスロマイシン、クラリスロマイシン、リトナビル及びテラプレビルによる *in vivo* での阻害強度の報告値[7, 8] に基づくと、これらの薬物と併用時のフィネレノンの AUCR は 5 を超えることが予測される。また、フィネレノンの消失に対する CYP2C8 の役割がわずかであることは、強い

CYP2C8 阻害薬であるゲムフィブロジルと併用した臨床薬物相互作用試験において意味のある薬物動態学的薬 1 物相互作用が認められなかったことにより確認された（2.7.2.2.3.1.2.3）。

フィネレノンは、*in vitro* において阻害作用を検討した主要な CYP 及び UGT 分子種のうち、CYP2C8（K_i：1.9μM）及び CYP1A1（IC_{50}：6.7μM）に対して競合的阻害作用を示し、CYP3A4 に対しては可逆的阻害作用（IC_{50}：19/12μM）及び不可逆的阻害作用（k_{inact}：0.012min^{-1}、K_I：10.3μM）を示した。ヒト血漿中の主代謝物 M-1a、M-1b、M-2a 及び M-3a は、いずれも主要な CYP 分子種に対して意味のある阻害を示さなかった。ヒト肝細胞において、フィネレノン及び代謝物 M-1a、M-1b 及び M-2a は概して濃度依存的に CYP3A4 の mRNA 発現に対する誘導作用を示した。

ヒトにフィネレノンを 1 日 1 回 20mg 反復経口投与後の定常状態におけるフィネレノンの曝露量に基づいて、FDA[9] 及び EMA[10] により推奨されている方法を用いて *in vivo* における薬物相互作用の可能性を予測した。フィネレノンによる時間依存性／不可逆的阻害については、被相互作用薬としての CYP3A4 基質薬の AUCR（時間依存性阻害の basic model で算出）は 1.25 を超えたが、CYP2C8 基質薬〔静的薬物速度論モデル（mechanistic static model）で算出〕の場合は 1.25 未満であった。これは、フィネレノンが CYP3A4 酵素阻害薬として薬物相互作用を引き起こす可能性を示唆し、一方 CYP2C8 に対しては阻害薬とならないことを示すものである。また、CYP1A1 を含むそのほかのすべての CYP 並びに UGT 分子種に対しては、可逆的阻害の basic model を用いた評価[9、10]により、フィネレノンが *in vivo* で酵素阻害薬とならないことが示された。なお、上記の予測には、フィネレノン 20mg を 1 日 1 回反復経口投与後の C_{max}=I_{max}：0.43μM（161μg/L）、最高血漿中非結合型濃度（$C_{max,u}$=$I_{max,u}$）：0.035μM（13.4μg/L）、臨床試験で得られた吸収速度定数（k_a）：0.153min^{-1}及び 吸収率×消化管アベイラビリティ（F_a×F_g）：0.575 に基づいて算出した肝臓入り口における最高血漿中非結合型濃度（$I_{in,max,u}$）：0.292μM を用いた（2.6.5.12 Table 12-3 及び Table 12-4）。更に、臨床でフィネレノン 20mg を 1 日 1 回反復経口投与後の代謝物の曝露量〔M-1a：0.80μM（302μg/L）、M-1b：0.16μM（61.5μg/L）、M-2a：0.39μM（152μg/L）、M-3a：0.17μM（69.6μg/L）〕を用いて同様に評価したところ、CYP 及び UGT 分子種に関連する臨床的に問題となる薬物動態学的薬物相互作用を引き起こす可能性が低いことが示された（2.6.5.16 Table 16-32～Table 16-39）。なお、代謝物の臨床での曝露量は母集団薬物動態（PopPK）及びアトロプ異性体存在比に基づいて推定した（2.7.2.2.5.2.2 及び 4.2.2.7.19 PH-40388）。フィネレノン及び代謝物の誘導作用については、相対誘導スコア（RIS）モデルを用いることにより、フィネレノンと併用した際のミダゾラムの AUC が最大 55%減少することが予測され、臨床においてフィネレノン及び代謝物 M-2a が弱～中程度の、M-1a は弱い CYP3A4 誘導作用を示す可能性が示唆された（2.6.5.12 Table 12-13 及び 2.6.5.16 Table 16-72～Table 16-74）。しかしながら、フィネレノン 20mg を 1 日 1 回 10 日間反復経口投与後に、CYP3A4 の典型基質薬であるミダゾラムを単回経口投与した臨床での薬物動態学的薬物相互作用試験において、ミダゾラムの曝露量に意味のある変化は認められなかった（ミダゾラムの AUCR：1.11）（2.7.2.2.3.2.2）。また、臨床薬物相互作用試験において、CYP2C8 の典型基質薬であるレパグリニドに対してフィネレノンの影響がないことが確認された（レパグリニドの AUCR：1.11）（2.7.2.2.3.2.3）。更に、臨床薬物相互作用試験において、フィネレノン 20mg の 1 日 1 回反復経口投与により、CYP2C9 の典型基質薬であるワーファリンとの間にも薬物動態学的薬物相互作用がないことが示された（2.7.2.2.3.2.4）。結論として、検討したすべての CYP 及び UGT 分子種の基質薬に対して、臨床においてフィネレノン及び代謝物の阻害又は誘導作用を介して薬物動態学的薬物相互作用が引き起こされる可能性は低いと考えられる。

フィネレノンは *in vitro* において、検討した濃度範囲で BSEP、MATE1、MATE2K、OATP1B3、OAT1、OAT3、OCT1 及び OCT2 のいずれも阻害しなかった（IC_{50}＞3μM）。また、代謝物 M-1a、M-1b、M-2a 及び M-3a は、BCRP、BSEP、MATE1、MATE2K、OAT1、OAT3、OCT1 及び OCT2 のいずれも阻害せず、M-2a 及び M-3a は P-gp を阻害しなかった。更に、M-2a 及び M-3a は OATP1B1 を阻害せず、M-2a は OATP1B3 も阻害しなかった。一方、フィネレノンは *in vitro* において P-gp、BCRP 及び

OATP1B1 を阻害し、それらに対する IC_{50} は 47/121μM（P-gp）、17.4/18.1μM（BCRP）及び 3.2μM（OATP1B1）であった。加えて、代謝物 M-1a 及び M-1b は P-gp に対して弱い阻害作用を示した（IC_{50}≧31μM）。また、代謝物 M-1a 及び M-1b はいずれも OATP1B1 に対して阻害作用を示し（それぞれの IC_{50}：3.8 及び 3.9μM）、M-1a、M-1b 及び M-3a は OATP1B3 を阻害した（それぞれの IC_{50}：7.6、7.3 及び 3.4μM）。

フィネレノン及び代謝物による P-gp 阻害作用を介した *in vivo* での薬物相互作用の可能性については、臨床薬物相互作用試験においてフィネレノン 20mg の 1 日 1 回反復経口投与により、P-gp の典型基質薬であるジゴキシンの薬物動態に対して意味のある影響を及ぼさないことが確認された（2.7.2.2.3.2.5）。フィネレノンによる BCRP 阻害作用については、理論的な消化管内最高濃度（I_{gut}）と IC_{50} 又は K_i との比（I_{gut}/IC_{50} 又は I_{gut}/Ki）は 12.1 となり、FDA 及び EMA のガイドライン [9、10] によるカットオフ基準（I_{gut}/IC_{50} 又は I_{gut}/Ki≧10）をわずかに超えていた。一方、$C_{max,u}/Ki$ は EMA ガイドライン [10] によるカットオフ基準（$C_{max,u}/Ki$≧0.02）を超えなかった（2.6.5.16 Table 16-91 及び Table 16-92）。これらのことから、フィネレノンが消化管において BCRP の基質となる薬物との間で薬物相互作用を引き起こす可能性は否定できない。しかしながら、消化管壁で約 50%が CYP3A4 による代謝を受けることが知られているミダゾラムを併用した臨床薬物相互作用試験〔試験番号 15111（2.7.2.2.3.2.2）〕において、I_{gut}/Ki が BCRP の 12.1 よりも高い 27.5 を示すミダゾラムの曝露量に意味のある増加がみられなかったことから、BCRP の基質となる薬物との間でも臨床的に問題となる薬物相互作用を引き起こす可能性は低いと考えられる。

フィネレノン及び代謝物による OATP に対する阻害作用に関しても、薬物相互作用の可能性を予測した。フィネレノンについては、OATP1B1 に対する $I_{in,max,u}/IC_{50}$ 又は $I_{in,max,u}/K_i$ は 0.091 となり、FDA ガイドライン [9] によるカットオフ基準（$I_{in,max,u}/IC_{50}$≧0.1）を下回っていたが、EMA ガイドライン [10] によるカットオフ基準（$I_{in,max,u}/IC_{50}$≧0.04）をわずかに超えていた（2.6.5.16 Table 16-91 及び Table 16-92）。代謝物に関してはフィネレノン 20mg を 1 日 1 回反復経口投与後の代謝物の曝露量に基づき、FDA 及び EMA ガイドライン [9、10] により推奨されている $C_{max,u}/IC_{50}$ 又は $C_{max,u}/Ki$ に基づく相互作用の予測を行った（FDA ガイドラインに基づく評価：2.6.5.16 Table 16-94、Table 16-97、Table 16-100 及び Table 16-103 並びに EMA ガイドラインに基づく評価：2.6.5.16 Table 16-95、Table 16-98、Table 16-101 及び Table 16-104）。その結果、M-1a、M-1b 及び M-2a については、OATP を含め検討したすべてのトランスポーターの阻害作用を介して臨床的に問題となる薬物動態学的薬物相互作用を引き起こす可能性は低いと考えられる。M-3a については、OATP1B3 に対する比の算出値（0.035）が、EMA ガイドライン [10] によるカットオフ基準（$C_{max,u}/K_i$≧0.02）をわずかに超えていた。しかし、CYP2C8 及び OATP の基質であるレパグリニド[11] を併用した臨床薬物相互作用試験〔試験番号 16541（2.7.2.2.3.2.3〕において、恐らくフィネレノンの CYP2C8 阻害作用（2.6.5.12 Table 12-1 及び Table 12-3）によると考えられる、生物学的同等性の範囲内のわずかな曝露量増加（レパグリニドの AUCR：1.11）が認められたに過ぎなかった。したがって、フィネレノンを 20mg 投与したとき、OATP の基質となる薬物との間で臨床的に問題となる薬物相互作用を生じる可能性は低いと考えられる。結論として、臨床においてフィネレノンを 20mg 投与したとき、検討したトランスポーターの基質薬との間で薬物動態学的薬物相互作用が引き起こされる可能性は低いと考えられる。

2.6.4.10　図表

図表は本文中の適切な位置に配置した。

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2.6.5.1 薬物動態試験： 一覧表

All studies were performed at the Department of DMPK, Bayer AG, Germany unless otherwise mentioned.

Test article: Finerenone

Table 1-1: Overview on pharmacokinetic studies

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
Analytical methods					
Synthesis			[^{14}C]finerenone	PH-35584	4.2.2.1.1
Synthesis			[^{14}C]finerenone	PH-36288	4.2.2.1.2
Synthesis			[^{3}H]finerenone	PH-35642	4.2.2.1.3
Synthesis			[$^{2}H_5$]BAY 85-1980	PH-35402	4.2.2.1.4
Synthesis of metabolites			[^{3}H]BAY 1117267 ([^{3}H]M-1a) [^{3}H]BAY 1117268 ([^{3}H]M-2a) [^{3}H]BAY 1117271 ([^{3}H]M-3a)	A52248	4.2.2.1.5
Synthesis of metabolites			[^{14}C]BAY 1117266 ([^{14}C]M-1b)	PH-37636	4.2.2.1.6
Synthesis of metabolites			[$^{2}H_5$]BAY 1040818 ([$^{2}H_5$]M-1) [$^{2}H_5$]BAY 1088089 ([$^{2}H_5$]M-2) [$^{2}H_5$]BAY 1088090 ([$^{2}H_5$]M-3)	PH-37324	4.2.2.1.7
Analytical methods			Finerenone[a]	R-9602	4.2.2.1.8
Analytical methods			Finerenone[a] BAY 1040818 (M-1)[a] BAY 1088089 (M-2)[a] BAY 1088090 (M-3)[a]	R-9546	4.2.2.1.9
Analytical methods			Finerenone[a] BAY 1040818 (M-1)[a] BAY 1088089 (M-2)[a] BAY 1088090 (M-3)[a]	R-11117	4.2.2.1.10
Analytical methods			Finerenone[a]	R-12055	4.2.2.1.11

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
Analytical methods			Finerenone BAY 1040818 (M-1) BAY 1088089 (M-2) BAY 1088090 (M-3)	PH-41142	4.2.2.1.12
Analytical methods			Finerenone BAY 1040818 (M-1) BAY 1088089 (M-2) BAY 1088090 (M-3)	PH-40958	4.2.2.1.13
Pharmacokinetics					
Pharmacokinetics	Mouse / CD-1	iv / LC-MS/MS	Finerenone	A49288	4.2.2.2.1
Pharmacokinetics	Rat / Wistar	iv, po / LSC, LC-MS/MS	[^{14}C]finerenone Finerenone	A49516	4.2.2.2.2
Pharmacokinetics	Dog / Beagle	iv, po / LC-MS/MS	Finerenone	A49278	4.2.2.2.3
Pharmacokinetics	Dog / Beagle	po / LSC, LC-MS/MS	[^{14}C]finerenone	PH-37447	4.2.2.5.2
Pharmacokinetics	Monkey / Cynomolgus	iv / LC-MS/MS	Finerenone	A49292	4.2.2.2.4
Pharmacokinetics	Rat / Wistar	po / LC-MS/MS	Finerenone	PH-39791	4.2.2.2.5
Distribution					
Plasma protein binding, partitioning between blood cells and plasma	Mouse / CD-1 Rat / Wistar Dog / Beagle Monkey / Cynomolgus Human / Caucasian	*in vitro* / LSC, LC-MS/MS	[^{14}C]finerenone Finerenone	A44959	4.2.2.3.1
Plasma protein binding	Rabbit / CHBB:HM Human / Caucasian	*in vitro* / LSC	[^{14}C]finerenone	A50448	4.2.2.3.2
Plasma protein binding	Human liver microsomes	*in vitro* / LSC	[^{14}C]finerenone	PH-38806	4.2.2.3.3
Single dose tissue distribution	Rat / Wistar Rat / Long Evans	iv, po / QWBA	[^{14}C]finerenone	A47052	4.2.2.3.4
Single dose tissue distribution	Rat / Wistar, pregnant	po / QWBA	[^{14}C]finerenone	PH-38642	4.2.2.3.5

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
Metabolism					
Species comparison	Liver microsomes, hepatocytes / several species	*in vitro* / HPLC-LSC, LC-MS/MS	[^{14}C]finerenone	PH-41146	4.2.2.4.1
CYP phenotyping	Human hepatocytes, human liver microsomes, recombinant CYP isoforms	*in vitro* / HPLC-LSC, LC-HRMS	[^{14}C]finerenone Finerenone	PH-39534	4.2.2.4.2
CYP inhibition	Human liver microsomes, recombinant CYP2E1	*in vitro* / HPLC-LSC, LC-MS/MS, HPLC-FL	Finerenone	PH-37733	4.2.2.4.3
CYP inhibition	Human liver microsomes	*in vitro* / LC-MS/MS	Finerenone	PH-40971	4.2.2.4.4
CYP inhibition	Recombinant CYP1A1	*in vitro* / LC-MS/MS	Finerenone	PH-40973	4.2.2.4.5
UGT inhibition	Human liver microsomes	*in vitro* / LC-MS/MS	Finerenone	A50906	4.2.2.4.6
CYP induction	Human hepatocytes	*in vitro* / LC-MS/MS, qRT-PCR	Finerenone	PH-39130	4.2.2.4.7
Metabolism *in vivo*	Mouse / CD-1	po / HPLC-LSC, LC-MS/MS	[^{14}C]finerenone	A52016	4.2.2.4.8
Metabolism *in vivo*	Rat / Wistar	iv, po / HPLC-LSC, LC-MS/MS, NMR	[^{14}C]finerenone	PH-39348	4.2.2.4.9
Metabolism *in vivo*	Dog / Beagle	po / HPLC-LSC, LC-MS/MS, NMR	[^{14}C]finerenone	PH-39368	4.2.2.4.10
Metabolism *in vivo*	Human / Caucasian	po / HPLC-LSC, LC-MS/MS, NMR	[^{14}C]finerenone	PH-39577	4.2.2.4.11
Metabolism *in vivo*	Human / Caucasian	po / LC-MS/MS	[^{14}C]finerenone	PH-39816	4.2.2.4.12
Excretion					
Excretion	Rat / Wistar	iv, po / LSC	[^{14}C]finerenone	A49457	4.2.2.5.1
Excretion	Dog / Beagle	po / LSC	[^{14}C]finerenone	PH-37447	4.2.2.5.2
Excretion	Rat / Wistar	po / LSC	[^{14}C]finerenone	PH-39224	4.2.2.5.3
Excretion	Rat / Wistar	iv / LSC	[^{14}C]finerenone	PH-40956	4.2.2.5.4
Pharmacokinetic drug interactions					
DDI with SGLT2 inhibitors	Human hepatocytes	*in vitro* / LC-MS/MS	Finerenone	PH-41050	4.2.2.6.1
Other PK studies					
Permeability assessment	Caco-2 cells	*in vitro* / LC-MS/MS	Finerenone[d]	R-12248	4.2.2.7.1

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
P-gp substrate characteristics	MDR1 in LLC-PK1	*in vitro* / LC-MS/MS	Finerenone	PH-40755	4.2.2.7.2
P-gp inhibition	MDR1 in LLC-PK1	*in vitro* / LC-MS/MS	Finerenone BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40886	4.2.2.7.3
BCRP substrate characteristics	BCRP in MDCKII-cells	*in vitro* / LC-MS/MS	Finerenone	PH-40764	4.2.2.7.4
BCRP inhibition	BCRP in MDCKII-cells	*in vitro* / LC-MS/MS	Finerenone BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40885	4.2.2.7.5
BSEP inhibition	Sandwich-cultured human hepatocytes	*in vitro* / LC-MS/MS	Finerenone[c]	R-11129	4.2.2.7.6
MATE1 and MATE2K inhibition	MATE1 and MATE2K in HEK-cells	*in vitro* / LC-MS/MS	Finerenone[d]	R-11196	4.2.2.7.7
OATP1B1 and OATP1B3 substrate characteristics	OATP1B1, OATP1B3 in HEK-cells	*in vitro* / LSC	[^{14}C]finerenone[b]	R-9574	4.2.2.7.8
OATP1B1 and OATP1B3 inhibition (preincubation)	OATP1B1, OATP1B3 in HEK-cells	*in vitro* / LC-MS/MS	Finerenone BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40952	4.2.2.7.9
OAT1 and OAT3 inhibition	OAT1, OAT3 in HEK-cells	*in vitro* / LC-MS/MS	Finerenone[d]	R-9494	4.2.2.7.10
OCT1 substrate characteristics and inhibition	OCT1 in HEK-cells	*in vitro* / LC-MS/MS	Finerenone[d]	R-9495	4.2.2.7.11
OCT2 inhibition	OCT2 in HEK-cells	*in vitro* / LC-MS/MS	Finerenone[d]	R-9440	4.2.2.7.12

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
Plasma protein binding of metabolites, partitioning between blood cells and plasma	Mouse / CD-1 (protein binding only) Rat / Wistar Dog / Beagle Rabbit / CHBB:HM (protein binding only) Human / Caucasian	*in vitro* / LSC	[^{3}H]BAY 1117267 ([^{3}H]M-1a) [^{3}H]BAY 1117268 ([^{3}H]M-2a) [^{3}H]BAY 1117271 ([^{3}H]M-3a)	A50452	4.2.2.7.13
Plasma protein binding of metabolites	Mouse / CD-1 Rat / Wistar Dog / Beagle Rabbit / CHBB:HM Human / Caucasian William's medium 10% FCS Human liver microsomes	*in vitro* / LSC	[^{14}C]BAY 1117266 ([^{14}C]M-1b) Human liver microsomes only: [^{3}H]BAY 1117267 ([^{3}H]M-1a) [^{3}H]BAY 1117268 ([^{3}H]M-2a) [^{3}H]BAY 1117271 ([^{3}H]M-3a)	PH-38807	4.2.2.7.14
Protein binding of metabolites	William's medium 10% FCS	*in vitro* / LSC	[^{3}H]BAY 1117267 ([^{3}H]M-1a) [^{3}H]BAY 1117268 ([^{3}H]M-2a) [^{3}H]BAY 1117271 ([^{3}H]M-3a)	A56949	4.2.2.7.15
Atropisomer ratio	Liver microsomes/ several species	*in vitro* / LC-MS/MS	Finerenone	PH-41146	4.2.2.4.1
Atropisomer ratio	Rat / Wistar	po / HPLC-LSC, LC-MS/MS	[^{14}C]finerenone	PH-40365	4.2.2.7.16
Atropisomer ratio	Rat / Wistar	po / LC-MS/MS	Finerenone	PH-39791	4.2.2.2.5
Atropisomer ratio	Dog / Beagle	po / HPLC-LSC, LC-MS/MS	[^{14}C]finerenone	PH-40326	4.2.2.7.17
Atropisomer ratio	Human / Caucasian	po / LC-MS/MS, LC-HRMS	[^{14}C]finerenone	PH-40373	4.2.2.7.18
Atropisomer ratio	Human / Caucasian	po / LC-MS/MS	Finerenone	PH-40388	4.2.2.7.19
CYP inhibition of metabolites	Human liver microsomes, recombinant CYP2E1	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117270 (M-2b) BAY 1117271 (M-3a) BAY 1117272 (M-3b)	PH-37685	4.2.2.7.20

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
CYP inhibition of metabolites	Human liver microsomes	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40971	4.2.2.4.4
CYP inhibition of metabolites	Recombinant CYP1A1	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40973	4.2.2.4.5
UGT imhibition of metabolites	Human microsomes	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-40043	4.2.2.7.21
CYP induction of metabolites	Human hepatocytes	*in vitro* / LC-MS/MS, qRT-PCR	BAY 1117267 (M-1a) BAY 1117266 (M-1b) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	PH-39130	4.2.2.4.7
BSEP inhibition of metabolites	Sandwich-cultured human hepatocytes	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a)[c] BAY 1117266 (M-1b)[c] BAY 1117268 (M-2a)[c] BAY 1117271 (M-3a)[c]	R-11130	4.2.2.7.22
MATE1 and MATE2K inhibition of metabolites	MATE1 and MATE2K in HEK-cells	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a)[d] BAY 1117266 (M-1b)[d] BAY 1117268 (M-2a)[d] BAY 1117271 (M-3a)[d]	R-11820	4.2.2.7.23
OAT1 and OAT3 inhibition of metabolites	OAT1, OAT3 in HEK-cells	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a)[d] BAY 1117266 (M-1b)[d] BAY 1117268 (M-2a)[d] BAY 1117271 (M-3a)[d]	R-9702	4.2.2.7.24
OCT1 and OCT2 inhibition of metabolites	OCT1, OCT2 in HEK-cells	*in vitro* / LC-MS/MS	BAY 1117267 (M-1a)[d] BAY 1117266 (M-1b)[d] BAY 1117268 (M-2a)[d] BAY 1117271 (M-3a)[d]	R-9701	4.2.2.7.25

Type of study	Test system / Species / strain	Route of administration / method	Test compound	Report no.	Location
a = testing facility: [redacted] Switzerland b = testing facility: [redacted] Germany c = testing facility: [redacted] USA d = testing facility: [redacted] USA					

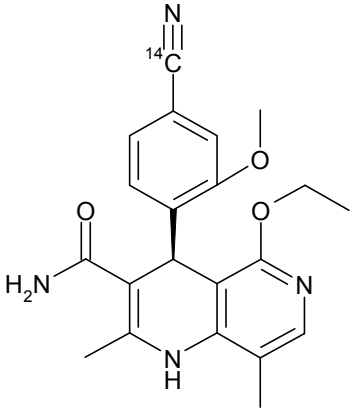
2.6.5.2 分析方法及びバリデーション試験

Test article: Finerenone

Table 2-1: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.1, 4.2.2.1.2
Report no.: PH-35584, PH-36288

Chemical structure / labeling position: [^{14}C]BAY 94-8862 ([^{14}C]finerenone)



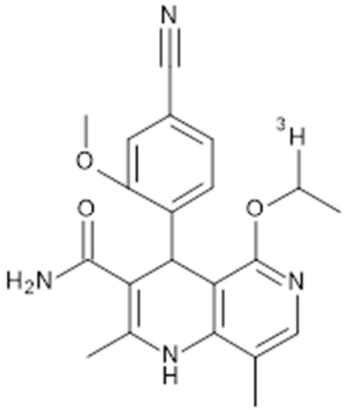
SXD 1876

Test article: Finerenone

Table 2-2: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.3
Report no.: PH-35642

Chemical structure / labeling position: [^{3}H]BAY 94-8862 ([^{3}H]finerenone)



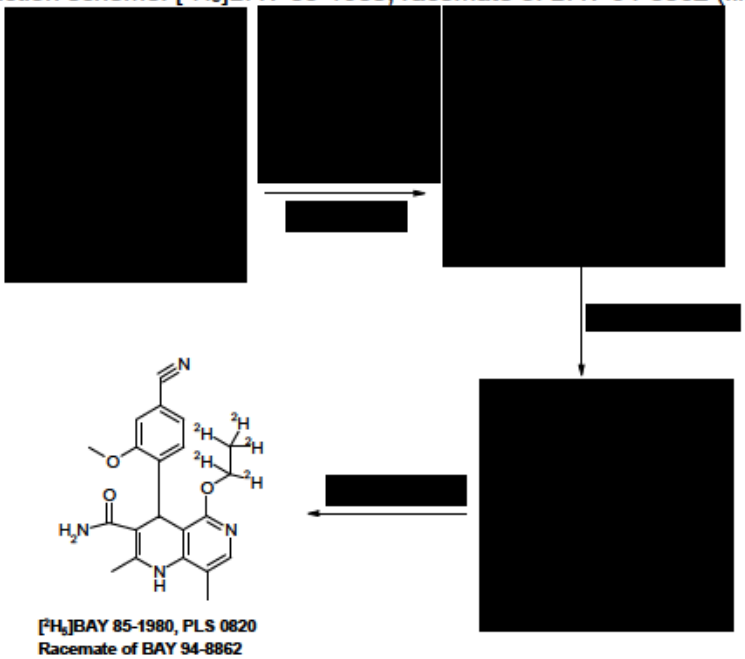
PLS 0838

Test article: Finerenone

Table 2-3: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.4
Report no.: PH-35402

Chemical structure / labeling position, see reaction scheme: [$^2H_5$]BAY 85-1980, racemate of BAY 94-8862 (finerenone)



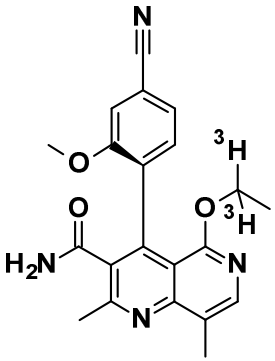
[$^2H_5$]BAY 85-1980, PLS 0820
Racemate of BAY 94-8862

Test article: Finerenone

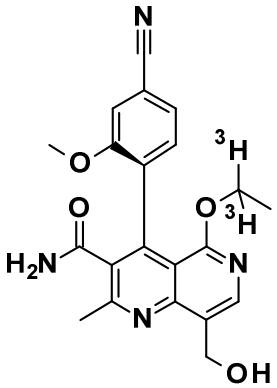
Table 2-4: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.5
Report no.: A52248

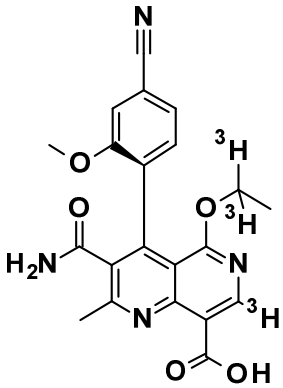
Chemical structure / labeling position: [^{3}H]BAY 1117267 ([^{3}H]M-1a), [^{3}H]BAY 1117268 ([^{3}H]M-2a), [^{3}H]BAY 1117271 ([^{3}H]M-3a)



[^{3}H]BAY 1117267 ([^{3}H]M-1a)



[^{3}H]BAY 1117268 ([^{3}H]M-2a)



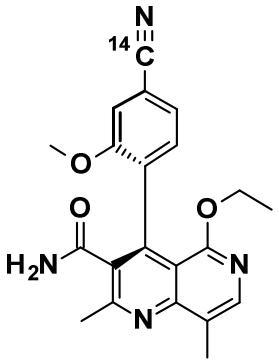
[^{3}H]BAY 1117271 ([^{3}H]M-3a)

Test article: Finerenone

Table 2-5: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.6
Report no.: PH-37636

Chemical structure / labeling position: [^{14}C]BAY 1117266 ([^{14}C]M-1b)



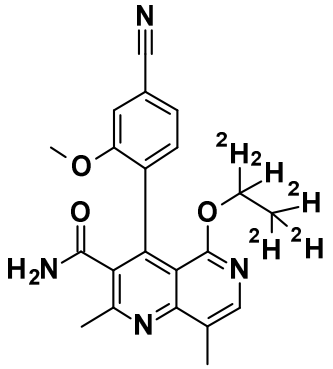
[^{14}C]BAY 1117266
([^{14}C]M-1b)

Test article: Finerenone

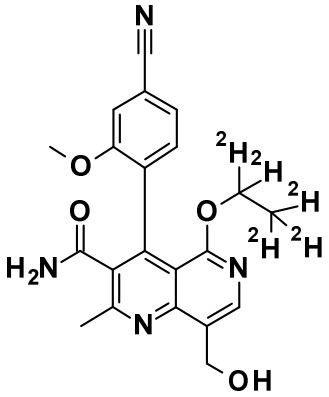
Table 2-6: Pharmacokinetics: Isotope labeled finerenone and its metabolites

Location: 4.2.2.1.7
Report no.: PH-37324

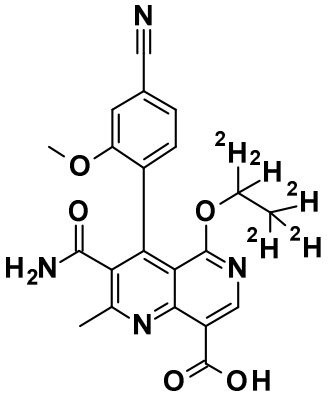
Chemical structure / labeling position of metabolites: [$^2H_5$]BAY 1040818 ([$^2H_5$]M-1), [$^2H_5$]BAY 1088089 ([$^2H_5$]M-2), [$^2H_5$]BAY 1088090 ([$^2H_5$]M-3)



[$^2H_5$]BAY 1040818
([$^2H_5$]M-1)



[$^2H_5$]BAY 1088089
([$^2H_5$]M-2)



[$^2H_5$]BAY 1088090
($^2H_5$]M-3)

Test article: Finerenone

Table 2-7: Pharmacokinetics: Analytical methods and validation reports

Overview on Bioanalytical Methods

Type of Study	Method	Analyte	Matrix	Testing Facility	Report no.	Location in CTD
Validation and cross validation of a method for the quantitative determination of BAY 94-8862 in human plasma by LC-MS/MS	LC-MS/MS	Finerenone (BAY 94-8862)	Human plasma	[redacted]	R-9602	4.2.2.1.8
Method validation of a HPLC-MS/MS method for the determination of BAY 94-8862, BAY 1040818, BAY 1088089 and BAY 1088090 in human plasma	LC-MS/MS	Finerenone (BAY 94-8862), BAY 1040818 (M-1), BAY 1088089 (M-2), BAY 1088090 (M-3)	Human plasma	[redacted]	R-9546	4.2.2.1.9
Method validation of a HPLC-MS/MS method for the determination of BAY 94-8862, BAY 1040818, BAY 1088089 and BAY 1088090 in human urine	LC-MS/MS	Finerenone (BAY 94-8862), BAY 1040818 (M-1), BAY 1088089 (M-2), BAY 1088090 (M-3)	Human urine	[redacted]	R-11117	4.2.2.1.10
Additional Stability Investigations for BAY 94-8862 in human plasma	LC-MS/MS	Finerenone (BAY 94-8862)	Human plasma	[redacted]	R-12055	4.2.2.1.11
Bioanalytical Methods and Validation Data for Clinical Studies	LC-MS/MS	Finerenone (BAY 94-8862), BAY 1040818 (M-1), BAY 1088089 (M-2), BAY 1088090 (M-3)	Human plasma, urine	Bayer AG	PH-41142	4.2.2.1.12
Bioanalytical Methods and Validation Data for Preclinical and Toxicokinetic Studies	LC-MS/MS	Finerenone (BAY 94-8862), BAY 1040818 (M-1), BAY 1088089 (M-2), BAY 1088090 (M-3)	Plasma of rat, dog, mouse, rabbit	Bayer AG	PH-40958	4.2.2.1.13
		Finerenone (BAY 94-8862)	Monkey plasma			

2.6.5.3 薬物動態試験： 単回投与後の吸収

Test article: Finerenone

Table 3-1: Pharmacokinetics: Absorption / basic PK after a single dose, mouse

Location: 4.2.2.2.1
Report no.: A49288

Species / strain:		Mouse / CD-1
Test compound:		Finerenone
Analyte:		Finerenone
Dose:	[mg/kg]	0.3
Route:		iv
Gender / No. of animals:		Male / 3 / time point
Feeding condition:		Fed
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)
Duration:	[h]	168
Assay:		LC-MS/MS
Parameter	**Unit**	**Pharmacokinetic parameters were calculated from the geometric means of the concentrations**
AUC	[µg·h/L]	48527
AUC_{norm}	[kg·h/L]	162
$AUC(0\text{-}t_n)$	[µg·h/L]	47794
t_n	[h]	72
C_{max}	[µg/L]	4349
$C_{max,norm}$	[kg/L]	14.5
t_{max}	[h]	0.0833
$t_{1/2}$	[h]	11.7
Interval	[h]	0.5 - 72
CL	[L/(kg·h)]	0.00618
V_{ss}	[L/kg]	0.0996

Test article: Finerenone

Table 3-2: Pharmacokinetics: Absorption / basic PK after a single dose, rat

Location: 4.2.2.2.2
Report no.: A49516

Species / strain:		Rat / Wistar	Rat / Wistar	Rat / Wistar	Rat / Wistar	Rat / Wistar
Test compound:		Finerenone	[^{14}C]finerenone	Finerenone	[^{14}C]finerenone	Finerenone
Analyte:		Finerenone	Finerenone	Finerenone	Finerenone	Finerenone
Dose:	[mg/kg]	0.3	1	0.3	1	3
Route:		iv	iv	po	po	po
Gender / No. of animals:		Male / 3 / time point	Male / 3 / time point	Male / 3 / time point	Male / 3 time point	Male / 3 / time point
Feeding condition:		Fasted	Fasted	Fasted	Fasted	Fasted
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)				
Duration:	[h]	168	168	168	168	168
Assay:		LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Parameter	**Unit**	**Pharmacokinetic parameters were calculated from the geometric means of the concentrations**				
AUC	[µg·h/L]	28106	72200	25473	59998	260257
AUC_{norm}	[kg·h/L]	93.7	72.2	84.9	60.0	86.8
AUC(0-t_n)	[µg·h/L]	28024	72048	25357	59897	259188
t_n	[h]	72	72	72	72	72
C_{max}	[µg/L]	5502	14725	1870	7465	24471
$C_{max,norm}$	[kg/L]	18.3	14.7	6.23	7.47	8.16
t_{max}	[h]	0.0333	0.0333	2.00	0.750	0.750
$t_{1/2}$	[h]	8.60	8.13	9.12	7.79	9.14
Interval	[h]	2 - 72	2 - 72	3 - 72	2 - 72	8 - 72
CL	[L/(kg·h)]	0.0107	0.0139	n.c.[b]	n.c.[b]	n.c.[b]
V_{ss}	[L/kg]	0.112	0.135	n.c.[b]	n.c.[b]	n.c.[b]
F[a]	[%]	n.a.[c]	n.a.[c]	90.6	83.1	120[d]

a = bioavailability related to the corresponding AUC_{norm} at the same dose level
b = not calculated
c = not applicable
d = calculated with the iv AUC_{norm} value of 1 mg/kg

Test article: Finerenone

Table 3-3: Pharmacokinetics: Absorption / basic PK after a single dose, dog

Location: 4.2.2.2.3
Report no.: A49278

Species / strain:		Dog / Beagle		Dog / Beagle		Dog / Beagle		Dog / Beagle	
Test compound:		Finerenone		Finerenone		Finerenone		Finerenone	
Analyte:		Finerenone		Finerenone		Finerenone		Finerenone	
Dose:	[mg/kg]	0.3		0.03		0.3		3	
Route:		iv [T = 0.25 h]		po		po		po	
Gender / No. of animals:		Female / 3		Female / 3		Female / 3		Female / 3	
Feeding condition:		Fasted		Fasted		Fasted		Fasted	
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)							
Duration:	[h]	24		24		24		72	
Assay:		LC-MS/MS		LC-MS/MS		LC-MS/MS		LC-MS/MS	
Parameter	**Unit**	**Geometric mean of individual pharmacokinetic parameters**							
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
AUC	[µg·h/L]	1908	1.25	108	1.09	1137	1.09	18503	1.18
AUC_{norm}	[kg·h/L]	6.36	1.25	3.59	1.09	3.79	1.09	6.17	1.18
$AUC(0-t_n)$	[µg·h/L]	1869	1.25	105	1.10	1104	1.07	18499	1.18
t_n	[h]	10	1.00	10	1.00	10	1.00	32	1.00
C_{max}	[µg/L]	730	1.04	29.6	1.04	303	1.10	4033	1.17
$C_{max,norm}$	[kg/L]	2.43	1.04	0.986	1.04	1.01	1.10	1.34	1.17
t_{max}	[h]	0.25	1.00	2.00	1.00	0.909	1.18	0.630	1.49
$t_{1/2}$	[h]	1.68	1.24	1.47	1.31	1.76	1.29	2.35	1.10
Interval	[h]	0.333-10		2-10		2-10		0.75-32	
CL	[L/(kg·h)]	0.157	1.25	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]
V_{ss}	[L/kg]	0.388	1.32	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]	n.c.[b]
F[a]	[%]	n.a.[c]	n.a.[c]	56.5	1.15	59.6	1.26	97.0	1.09

a = bioavailability, calculated with the iv AUC_{norm} value of 0.3 mg/kg
b = not calculated
c = not applicable

Test article: Finerenone

Table 3-4: Pharmacokinetics: Absorption / basic PK after a single dose, monkey

Location: 4.2.2.2.4
Report no.: A49292

Species / strain:		Monkey / Cynomolgus	
Test compound:		Finerenone	
Analyte:		Finerenone	
Dose:	[mg/kg]	1	
Route:		iv [T = 0.25 h]	
Gender / No. of animals:		Female / 3	
Feeding condition:		Fasted	
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)	
Duration:	[h]	24	
Assay:		LC-MS/MS	
Parameter	**Unit**	**Geometric mean of individual pharmacokinetic parameters**	
		Mean	**S.D.**
AUC	[µg·h/L]	2565	1.12
AUC_{norm}	[kg·h/L]	2.57	1.12
$AUC(0\text{-}t_n)$	[µg·h/L]	2563	1.12
t_n	[h]	10	1.00
C_{max}	[µg/L]	3998	1.02
$C_{max,norm}$	[kg/L]	4.00	1.02
t_{max}	[h]	0.250	1.00
$t_{1/2}$	[h]	1.31	1.11
Interval	[h]	3-10	
CL	[L/(kg·h)]	0.390	1.12
V_{ss}	[L/kg]	0.247	1.06

Test article: Finerenone

Table 3-5: Pharmacokinetics: Absorption and disposition of radioactivity, rat

Location: 4.2.2.2.2
Report no.: A49516

Species / strain:		Rat / Wistar	Rat / Wistar
Test compound:		[^{14}C]finerenone	[^{14}C]finerenone
Analyte:		Radioactivity	Radioactivity
Dose:	[mg/kg]	1	1
Route:		iv	po
Gender / No. of animals:		Male / 3 / time point	Male / 3 / time point
Feeding condition:		fasted	fasted
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)	
Duration:	[h]	168	168
Assay:		LSC	LSC
Parameter	**Unit**	**Pharmacokinetic parameters were calculated from the geometric means of the concentrations**	
AUC	[µg-eq·h/L]	88620	73498
AUC_{norm}	[kg·h/L]	88.6	73.5
$AUC(0\text{-}t_n)$	[µg-eq·h/L]	88595	73352
t_n	[h]	168	168
$C_{eq,max}$	[µg-eq/L]	17428	9015
$C_{eq,max,norm}$	[kg/L]	17.4	9.02
t_{max}	[h]	0.0333	0.750
$t_{1/2}$	[h]	19.3	8.1
Interval	[h]	72-168	4-72
$t_{1/2\ apparent}$	[h]	7.15	n.c.[a]
Interval	[h]	2-48	n.c.[a]

a = not calculated

2.6.5.4 薬物動態試験： 反復投与後の吸収

Test article: Finerenone

Table 4-1: Pharmacokinetics: Absorption after repeated dosing, rat

Comparison of pharmacokinetic parameters of finerenone, BAY 1040818 (M-1), BAY 1088089 (M-2) and BAY 1088090 (M-3) after repeated daily oral administration of 30 mg/kg finerenone to 3 male and 3 female Wistar rats	Location: 4.2.2.2.5 Report no.: PH-39791

Species / strain:	Rat / Wistar
Test compound:	Finerenone
Dose:	30 mg/kg, 7 days
Route:	po
Gender / No. of animals:	Male and female / 3 / time point
Feeding condition:	Fasted
Formulation:	10% Ethanol + 40% Solutol HS50 + 50% demineralized water (v / v / v)
Assay:	LC-MS/MS

Male, Day 7:		**Pharmacokinetic parameters were calculated from the geometric means of the concentrations**			
Equiv. dose	[mg/kg]	**29.8**	**31.1**	**32.2**	**30**
Analyte		**BAY 1040818 (M-1)**	**BAY 1088089 (M-2)**	**BAY 1088090 (M-3)**	**Finerenone**
AUC(0-24)	[µg·h/L]	32500	9770	1210	1960000
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	1.09	0.314	0.0376	65.2
C_{max}	[µg/L]	2230	645	120	122000
$C_{max,norm}$	[kg/L]	0.0747	0.0207	0.00371	4.05
t_{max}	[h]	7.00	4.00	1.00	4.00
$C(24)/C_{max}$	[%]	25.2	29.1	29.4	34.5
MR[a](BAY 94-8862)AUC	[%]	1.5	0.4	0.1	n.a.[b]
Female, Day 7:		**Pharmacokinetic parameters were calculated from the geometric means of the concentrations**			
Equiv. dose	[mg/kg]	**29.8**	**31.1**	**32.2**	**30**
Analyte		**BAY 1040818 (M-1)**	**BAY 1088089 (M-2)**	**BAY 1088090 (M-3)**	**Finerenone**
AUC(0-24)	[µg·h/L]	9100	4220	1100	2950000
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	0.305	0.136	0.0342	98.4
C_{max}	[µg/L]	606	263	158	141000
$C_{max,norm}$	[kg/L]	0.0203	0.00846	0.00489	4.70
t_{max}	[h]	7.00	2.00	4.00	7.00

Equiv. dose Analyte	[mg/kg]	**29.8** **BAY 1040818 (M-1)**	**31.1** **BAY 1088089 (M-2)**	**32.2** **BAY 1088090 (M-3)**	**30** **Finerenone**
$C(24)/C_{max}$	[%]	32.4	30.3	13.2	69.5
MR[a](BAY 94-8862)AUC	[%]	0.2	0.1	<0.1	n.a.[b]

a = metabolic ratio
b = not applicable

反復投与後のトキシコキネティクスは 2.6.7.3 を参照のこと。

2.6.5.5 薬物動態試験： 分布

Test article: Finerenone

Table 5-1: Pharmacokinetics: Quantitative organ and tissue distribution after a single dose, rat

Location: 4.2.2.3.4
Report no.: A47052

Species / strain:	Rat / Wistar	Route:	po	Assay:	Radioluminography
Test compound:	[^{14}C]finerenone	Gender / no.:	Male / 1 per time point		
Analyte:	Radioactivity	Feeding conditions:	Fasted		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	**Equivalent concentration C_{eq} [µg-eq/L]**						
	1 h	**2 h**	**4 h**	**8 h**	**24 h**	**72 h**	**168 h**
Adipose tissue, brown	1490	2137	1608	652	63.4	4.40	<3.30[b]
Adipose tissue, white	656	544	685	313	35.1	<3.36[b]	<3.26[b]
Adrenal cortex	5100	3600	2919	1577	270	76.5	27.7
Adrenal medulla	5356[a]	3913[a]	4239[a]	1584[a]	187[a]	23.7[a]	9.58[a]
Adrenal glands (average)	5107	3624	3043	1567	264	69.4	25.1
Blood (heart)	**9919**	**7945**	**7906**	**3338**	**410**	**21.7**	**9.94**
Bone marrow	3124	2536	1210	1239	148	4.57	<3.26[b]
Brain	191	132	132	56.8	8.52	<3.36[b]	<3.30[b]
Cardiac muscle	4409	3190	2754	1502	163	11.6	4.83
Eye wall	1436	864	3155	1473	190	<3.27[b]	<3.19[b]
Harderian gland	1223	1189	1686	616	84.4	9.14	3.16
Kidney cortex	2769	1894	1732	985	163	27.9	11.2
Kidney, inner medulla	5050	4115	3348	1805	186	9.38	4.31
Kidney, outer medulla	2406	2277	1916	920	172	31.1	9.22
Kidney papilla	5841	4706	3729	1866	238	7.7	<3.19[b]
Kidneys (average)	3782	2980	2447	1322	184	20.7	7.93
Liver	6110	4544	5529	2584	400	73.7	25.2
Lung	8729	6661	5431	2716	334	13.2	6.40
Pancreas	1618	1131	1337	563	78.5	6.78	<3.19[b]
Prostate	1431	828	1160	470	72.6	4.50	<3.30[b]
Seminal vesicles	421	143	455	286	31.7	3.76	<3.30[b]

Organ / tissue	Equivalent concentration C_{eq} [µg-eq/L]						
	1 h	2 h	4 h	8 h	24 h	72 h	168 h
Skeletal muscle	772	565	689	299	37.2	3.58	<3.26[b]
Skin, dorsal	864	782	1728	894	124	10.3	3.75
Spleen	1191	917	1171	497	64.9	4.87	<3.19[b]
Submandibular gland	2851	1991	2634	1050	113	6.67	<3.26[b]
Testes	730	742	1766	869	115	3.64	<3.30[b]
Thymus	685	560	783	279	45.0	<3.36[b]	<3.32[b]
Thyroid	4279	2441	2476	945[a]	144	6.85	<3.32[b]

a = reduced accuracy, measured area of interest below 1 mm^2 (on average)
b = below lower limit of quantitation (LLOQ)

Test article: Finerenone

Table 5-2: Pharmacokinetics: Quantitative organ and tissue distribution after a single dose, rat

Location: 4.2.2.3.4
Report no.: A47052

Species / strain:	Rat / Wistar	Route:	po	Assay:	Radioluminography
Test compound:	[^{14}C]finerenone	Gender / no.:	Male / 1 per time point		
Analyte:	Radioactivity	Feeding conditions:	Fasted		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	AUC(0-24) [µg-eq·h/L]	AUC [µg-eq·h/L]	$C_{eq,max}$ [µg-eq/L]	$C_{eq,max}$ ratio Organ / blood	t_{max} [h]	$t_{1/2}$ [h]	Truncated evaluation Regression range [h]	Truncated evaluation $t_{1/2}$ [h]	Truncated evaluation Regression range [h]
Adipose tissue, brown	14553	14944	2137	0.215	2	n.c.[a]	n.c.[a]	4.41	4-24
Adipose tissue, white	6087	6323	685	0.0690	4	n.c.[a]	n.c.[a]	4.78	4-24
Adrenal cortex	33925	48537	5100	0.514	1	65.6[b]	72-168	5.95	4-24
Adrenal medulla	36671	42976	5356	0.540	1	73.4[b]	72-168	4.63	4-24
Adrenal glands (average)	34124	47659	5107	0.515	1	65.4[b]	72-168	5.82	4-24
Blood (heart)	**73245**	**82263**	**9919**	**1**	**1**	**85.0[b]**	**72-168**	**4.84**	**4-24**
Bone marrow	21069	22445	3124	0.315	1	n.c.[a]	n.c.[a]	6.13	4-24
Brain	1283	1346	191	0.0193	1	n.c.[a]	n.c.[a]	5.26	4-24
Cardiac muscle	29815	33840	4409	0.445	1	75.8[b]	72-168	4.93	4-24
Eye wall	24716	26069	3155	0.318	4	n.c.[a]	n.c.[a]	5.06	4-24
Harderian gland	13225	15678	1686	0.170	4	62.7[b]	72-168	4.87	4-24
Kidney cortex	19920	26519	2769	0.279	1	72.5[b]	72-168	5.95	4-24
Kidney, inner medulla	35918	39913	5050	0.509	1	85.5[b]	72-168	4.82	4-24
Kidney, outer medulla	20296	26706	2406	0.243	1	54.8[b]	72-168	5.97	4-24
Kidney papilla	39976	41704	5841	0.589	1	n.c.[a]	n.c.[a]	5.13	4-24
Kidneys (average)	27209	32870	3782	0.381	1	69.4[b]	72-168	5.44	4-24
Liver	52626	68475	6110	0.616	1	62.0[b]	72-168	5.45	4-24
Lung	57922	64441	8729	0.880	1	91.8[b]	72-168	5.06	4-24
Pancreas	12154	12710	1618	0.163	1	n.c.[a]	n.c.[a]	5.08	4-24
Prostate	10266	10792	1431	0.144	1	n.c.[a]	n.c.[a]	5.24	4-24
Seminal vesicles	4370	4608	455	0.0458	4	n.c.[a]	n.c.[a]	5.16	4-24
Skeletal muscle	6180	6435	772	0.0778	1	n.c.[a]	n.c.[a]	4.90	4-24

Organ / tissue	AUC(0-24) [µg-eq·h/L]	AUC [µg-eq·h/L]	$C_{eq,max}$ [µg-eq/L]	$C_{eq,max}$ ratio Organ / blood	t_{max} [h]	$t_{1/2}$ [h]	Regression range [h]	Truncated evaluation $t_{1/2}$ [h]	Truncated evaluation Regression range [h]
Skin, dorsal	15064	18235	1728	0.174	4	66.0[b]	72-168	5.36	4-24
Spleen	10274	10723	1191	0.120	1	n.c.[a]	n.c.[a]	4.96	4-24
Submandibular gland	22065	22783	2851	0.287	1	n.c.[a]	n.c.[a]	4.55	4-24
Testes	14636	15480	1766	0.178	4	n.c.[a]	n.c.[a]	5.18	4-24
Thymus	6314	6630	783	0.0789	4	n.c.[a]	n.c.[a]	5.15	4-24
Thyroid	23501	24517	4279	0.431	1	n.c.[a]	n.c.[a]	5.13	4-24

a = not calculated
b = rough estimate due to regression with only 2 time points

Test article: Finerenone

Table 5-3: Pharmacokinetics: Quantitative organ and tissue distribution after a single dose, rat

Location: 4.2.2.3.4
Report no.: A47052

Species / strain:	Rat / Wistar	Route:	iv	Assay:	Radioluminography
Test compound:	[^{14}C]finerenone	Gender / no.:	Male / 1 per time point		
Analyte:	Radioactivity	Feeding conditions:	Fasted		
Dose:	1 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	**Equivalent concentration C_{eq} [µg-eq/L]**	
	0.0833 h	**2 h**
Adipose tissue, brown	1004	505
Adipose tissue, white	430	277
Adrenal cortex	3341	1674
Adrenal glands (average)	3393	1696
Adrenal medulla	4176[a]	1897[a]
Blood (heart)	**9281**	**3612**
Bone marrow	1573	686
Brain	131	54.6
Cardiac muscle	3129	1422
Eye wall	363	549
Harderian gland	264	711
Kidney cortex	1195	881
Kidney papilla	93.2	1833
Kidney, inner medulla	2264	1827
Kidney, outer medulla	1143	1052
Kidneys (average)	1211	1326
Liver	4814	2291
Lungs	6914	3813
Pancreas	869	614
Prostate	483	545
Seminal vesicles	141	191
Skeletal muscle, dorsal	300	339
Skin, dorsal	187	823
Spleen	1066	476

Organ / tissue	Equivalent concentration C_{eq} [µg-eq/L]	
	0.0833 h	2 h
Submandibular gland	1751	1313
Testes	152	650
Thymus	242	344
Thyroid	756	1020

a = reduced accuracy, measured area of interest below 1 mm^2 (on average)

Test article: Finerenone

Table 5-4: Pharmacokinetics: Quantitative organ and tissue distribution after a single dose, rat

Location: 4.2.2.3.4
Report no.: A47052

Species / strain:	Rat / Wistar	Route:	po	Assay:	Radioluminography
Test compound:	[^{14}C]finerenone	Gender / no.:	Female / 1 per time point		
Analyte:	Radioactivity	Feeding conditions:	Fasted		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	**Equivalent concentration C_{eq} [µg-eq/L]**	
	2 h	**24 h**
Adipose tissue, brown	2528	1387
Adipose tissue, white	717	362
Adrenal cortex	7388	3779
Adrenal glands (average)	7544	3899
Adrenal medulla	8289[a]	5038[a]
Blood (heart)	**15069**	**7149**
Bone marrow	3290	2090
Brain	218	110
Cardiac muscle	4679	2839
Eye wall	2640	2889
Harderian gland	3309	1327
Kidney cortex	3326	1930
Kidney papilla	5943	2951
Kidney, inner medulla	6741	3428
Kidney, outer medulla	3392	1830
Kidneys (average)	4946	2629
Liver	8601	3430
Lungs	8279	6979
Ovaries	5937	1756
Pancreas	2160	1212
Skeletal muscle, dorsal	824	391
Skin, dorsal	1590	1958
Spleen	2192	1067
Submandibular gland	3608	1851

Organ / tissue	Equivalent concentration C_{eq} [µg-eq/L]	
	2 h	24 h
Thymus	1226	790
Thyroid	4804	2786
Uterus	2800	3754

a = reduced accuracy, measured area of interest below 1 mm^2 (on average)

Test article: Finerenone

Table 5-5: Pharmacokinetics: Quantitative organ and tissue distribution after a single dose, pigmented rat

Location: 4.2.2.3.4
Report no.: A47052

Species / strain:	Rat / Long Evans	Route:	po	Assay:	Radioluminography
Test compound:	[^{14}C]finerenone	Gender / no.:	Male / 1 per time point		
Analyte:	Radioactivity	Feeding conditions:	Fasted		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	**Equivalent concentration C_{eq} [µg-eq/L]**				**$t_{1/2}$**	**AUC(t_1-t_n)**
	24 h	**72 h**	**168 h**	**336 h**	**[h]**	**[µg-eq·h/L]**
Adipose tissue, brown	126	5.88	<3.22[c]	<3.07[c]	n.c.[b]	n.c.[b]
Adipose tissue, white	34.5	3.56	<3.31[c]	<3.07[c]	n.c.[b]	n.c.[b]
Adrenal cortex	251	43.1	19.5	8.38	114	10727
Adrenal medulla	246[a]	28.9[a]	5.04[a]	4.32[a]	107	6968
Adrenal glands (average)	252	40.7	17.8	8.03	116	10286
Blood (heart)	**351**	**19.2**	**10.7**	**7.74**	**212**	**8406**
Bone marrow	107	4.03	<3.21[c]	<3.07[c]	n.c.[b]	n.c.[b]
Brain	7.74	<3.31[c]	<3.31[c]	<3.05[c]	n.c.[b]	n.c.[b]
Cardiac muscle	174	11.7	7.30	4.08	176	4713
Eye wall, pigmented	395	49.9	21.9	10.6	122	13886
Harderian gland	119	10.8	4.08	<3.08[c]	68.7[d]	2824
Kidney cortex	201	29.4	15.3	5.49	109	7966
Kidney, inner medulla	198	14.4	5.50	<3.07[c]	69.2[d]	4250
Kidney, outer medulla	213	29.1	14.9	3.80	89.4	7830
Kidney papilla	232	7.78	<3.25[c]	<3.07[c]	n.c.[b]	n.c.[b]
Kidneys (average)	206	23.8	10.5	3.89	103	6736
Liver	517	78.4	29.3	8.96	85.7	18844
Lungs	336	13.6	4.51	<3.07[c]	60.4[d]	5609
Pancreas	95.7	6.33	<3.25[c]	<3.07[c]	n.c.[b]	n.c.[b]
Prostate	93.2	4.17	<3.22[c]	<3.05[c]	n.c.[b]	n.c.[b]
Seminal vesicles	114	4.53	<3.31[c]	<3.05[c]	n.c.[b]	n.c.[b]
Skeletal muscle, dorsal	45.0	3.93	<3.21[c]	<3.07[c]	n.c.[b]	n.c.[b]
Skin, high pigmented	131	7.85	<3.21[c]	<3.07[c]	n.c.[b]	n.c.[b]
Skin, less pigmented	174	7.24	<3.21[c]	<3.07[c]	n.c.[b]	n.c.[b]

Organ / tissue	Equivalent concentration C_{eq} [µg-eq/L]				$t_{1/2}$	AUC(t_1-t_n)
	24 h	72 h	168 h	336 h	[h]	[µg-eq·h/L]
Spleen	60.7	5.60	<3.25[c]	<3.07[c]	n.c.[b]	n.c.[b]
Submandibular gland	112	7.07	<3.31[c]	<3.07[c]	n.c.[b]	n.c.[b]
Testes	85.4	<3.31[c]	<3.22[c]	<3.07[c]	n.c.[b]	n.c.[b]
Thymus	50.2	<3.36[c]	<3.22[c]	<3.05[c]	n.c.[b]	n.c.[b]
Thyroid	128	5.91[a]	<3.31[c]	<3.07[c]	n.c.[b]	n.c.[b]

a = reduced accuracy, measured area of interest below 1 mm^2 (on average)
b = not calculated
c = below LLOQ
d = rough estimate, evaluation with only two time points

2.6.5.6 薬物動態試験： タンパク結合

Test article: Finerenone

Table 6-1: Pharmacokinetics: Plasma protein binding *in vitro*

Location: 4.2.2.3.1, 4.2.2.3.2, 4.2.2.3.3
Report no.: A44959, A50448, PH-38806

Test compound:	[^{14}C]finerenone, finerenone	Method:	Ultrafiltration
Analyte:	Radioactivity, finerenone	Assay:	LSC, LC-MS/MS
Table:	Binding of finerenone to plasma proteins in different species, William's medium and human liver microsomes *in vitro*		

Species / strain / Test system	Gender / N[a]	Matrix	Concentration [µg/L]	Fraction bound [%]	Fraction unbound [%]
Human / Caucasian	Male / 2 - 3	Plasma	94.5 to 4289	91.7	8.33
Human / Caucasian	Male / 3	Plasma	87549	87.4	12.6
Monkey / Cynomolgus	Female / 3	Plasma	95.5 to 4396	97.5	2.55
Monkey / Cynomolgus	Female / 3	Plasma	85069	95.8	4.20
Dog / Beagle	Female / 3	Plasma	99.0 to 4394	94.5	5.49
Dog / Beagle	Female / 3	Plasma	83087	93.9	6.09
Rat / Wistar	Male / 3	Plasma	515 to 5270	99.9	0.0465
Rat / Wistar	Male / 3	Plasma	100000	99.9	0.0682
Mouse / CD-1	Male / 3	Plasma	440 to 3150	99.9	0.0772
Mouse / CD-1	Male / 3	Plasma	66500	99.9	0.120
Rabbit / CHBB:HM	Female / 3	Plasma	529 to 10135	99.8	0.183
Human Serum Albumin	n.a.[b] / 3	Dissolved in buffer	5287	83.5	16.5
Alpha-1 acidic glycoprotein	n.a.[b] / 3	Dissolved in buffer	4934	40.7	59.3
Alpha-globulin	n.a.[b] / 3	Dissolved in buffer	4988	41.1	58.9
Gamma-globulin	n.a.[b] / 3	Dissolved in buffer	4948	15.6	84.4
LDL	n.a.[b] / 3	Dissolved in buffer	4984	40.2	59.8
William's medium 10% FCS[c]	n.a.[b] / 3	Dissolved in buffer	105	43.8	56.2
William's medium 10% FCS[c]	n.a.[b] / 3	Dissolved in buffer	10420	39.6	60.4
Human liver microsomes (0.05 mg/mL)	n.a.[b] / 3	-	357 to 7261	13.2	86.8
Human liver microsomes (0.1 mg/mL)	n.a.[b] / 3	-	369 to 7293	19.0	81.0
Human liver microsomes (0.5 mg/mL)	n.a.[b] / 3	-	379 to 7362	39.4	60.6

a = number of determinations / concentration, b = not applicable, c = William's medium containing 10% fetal calf serum

Test article: Finerenone

Table 6-2: Pharmacokinetics: Blood Cell/ Plasma Partitioning *in vitro*

Location: 4.2.2.3.1
Report no.: A44959

Test compound: [^{14}C]finerenone
Analyte: Radioactivity

Species / strain	Gender / N[a]	Conc. in blood (C_b) [µg/L]	Conc. in plasma (C_p) [µg/L]	C_b/C_p
Rat / Wistar	Male / 3	103 to 5115	188 to 9298	0.549
Rat / Wistar	Male / 3	102040	169800	0.601
Dog / Beagle	Female / 3	107 to 5105	148 to 7056	0.723
Dog / Beagle	Female / 3	104423	134240	0.779
Human / Caucasian	Male / 3	119 to 6587	133 to 6793	0.935
Human / Caucasian	Male / 3	126870	116700	1.09

a = number of determinations / concentration

2.6.5.7 薬物動態試験： 妊娠または授乳動物における試験（胎盤移行性）

Test article: Finerenone

Table 7-1: Pharmacokinetics: Qualitative and quantitative organ and tissue distribution after a single dose, pregnant rat

Location: 4.2.2.3.5
Report no.: PH-38642

Species / strain:	Rat / Wistar	Route:	po	Feeding conditions:	Fasted
Test compound:	[^{14}C]finerenone	Gender / no.:	Female / 1 per time point	Assay:	Radioluminography
Analyte:	Radioactivity	Gestation day:	18		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	**Equivalent concentration C_{eq} [µg-eq/L]**				
	2 h	**4 h**	**8 h**	**24 h**	**48 h**
Adipose tissue, brown	1200	1670	1440	983	832
Adipose tissue, white	415	1030	600	150	287
Adrenal glands (average)	4980	5680	5650	3350	3490
Amnion	5690	8760	8470	6300	6720
Amniotic fluid	28.8	98.8	200	211	549
Blood (heart)	**11800**	**14200**	**13000**	**8450**	**7740**
Brain	164	193	151	104	100
Cardiac muscle	3110	4150	3450	2710	2170
Kidney cortex	2340	2980	2940	3000	1700
Kidney, inner medulla	4800	7090	5800	5440	3560
Kidney, outer medulla	2450	3550	3520	2920	1470
Kidneys (average)	4000	4830	4580	4130	2570
Liver	5170	6170	4730	3270	3240
Lungs	9430	9820	9530	6730	4920
Mammary glands	2820	3060	2820	2320	3040
Ovaries	4450	5930	5200	3460	1820
Placenta	7180	10700	7500	5430	4220
Skeletal muscle, dorsal	531	607	606	376	365
Skin, dorsal	939	1530	2360	1110	756
Spleen	1320	1340	1240	996	1090
Submandibular gland	1870	2250	2470	1340	1370
Uterus	4650	6670	6120	5980	3150

Organ / tissue	Equivalent concentration C_{eq} [µg-eq/L]				
	2 h	4 h	8 h	24 h	48 h
Fetal blood	532	600	1240[a]	1130	1730
Fetal brain	102	95.3	110	92.2	129
Fetal kidney	434	567	899	804	902
Fetal liver	308	418	666	603	1150
Fetal lung	285	338	417	454	718
Fetal skeletal muscle	417	483	1590	805	1380
Fetal skin	511	555	1130	1240	1480
Fetuses (average)	**374**	**430**	**819**	**776**	**1030**

a = reduced accuracy, measured area of interest below 1 mm^2 (on average)

Test article: Finerenone

Table 7-2: Pharmacokinetics: Qualitative and quantitative organ and tissue distribution after a single dose, pregnant rat

Location: 4.2.2.3.5
Report no.: PH-38642

Species / strain:	Rat / Wistar	Route:	po	Feeding conditions:	Fasted
Test compound:	[^{14}C]finerenone	Gender / no.:	Female / 1 per time point	Assay:	Radioluminography
Analyte:	Radioactivity	Gestation day:	18		
Dose:	3 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)		

Organ / tissue	$C_{eq,max}$ [µg-eq/L]	$C_{eq,max}$ ratio Organ/Blood	t_{max} [h]	AUC(0-24) [µg-eq·h/L]	AUC(0-t_n) [µg-eq·h/L]	AUC [µg-eq·h/L]	$t_{1/2}$ [h]	Regression range [h]
Adipose tissue, brown	1670	0.118	4	29400	51100	102000[a]	45.0	4.00-48.0
Adipose tissue, white	1030	0.0725	4	10200	15500	n.c.[b]	n.c.[b]	n.c.[b]
Adrenal glands (average)	5680	0.400	4	109000	191000	n.c.[b]	n.c.[b]	n.c.[b]
Amnion	8760	0.617	4	172000	328000	n.c.[b]	n.c.[b]	n.c.[b]
Amniotic fluid	549	0.0387	48	4040	13200	n.c.[b]	n.c.[b]	n.c.[b]
Blood (heart)	**14200**	**1.00**	**4**	**261000**	**455000**	**969000[a]**	**49.6**	**4.00-48.0**
Brain	193	0.0136	4	3220	5670	12400[a]	51.0	4.00-48.0
Cardiac muscle	4150	0.292	4	74600	133000	286000[a]	50.6	4.00-48.0
Kidney cortex	3000	0.211	24	67000	122000	271000[a]	55.8	4.00-48.0
Kidney, inner medulla	7090	0.499	4	132000	239000	497000[a]	49.4	4.00-48.0
Kidney, outer medulla	3550	0.250	4	74000	125000	201000[a]	34.1	4.00-48.0
Kidneys (average)	4830	0.340	4	101000	180000	370000[a]	49.3	4.00-48.0
Liver	6170	0.435	4	101000	180000	400000[a]	52.2	4.00-48.0
Lungs	9820	0.692	4	196000	335000	631000[a]	42.7	4.00-48.0
Mammary glands	3060	0.215	4	61500	126000	n.c.[b]	n.c.[b]	n.c.[b]
Ovaries	5930	0.418	4	105000	167000	235000[a]	26.1	4.00-48.0
Placenta	10700	0.754	4	164000	279000	488000[a]	36.8	4.00-48.0
Skeletal muscle, dorsal	607	0.0427	4	11800	20700	49500[a]	58.8	8.00-48.0
Skin, dorsal	2360	0.166	8	37700	59800	85300[a]	25.3	8.00-48.0
Spleen	1340	0.0944	4	27000	52000	n.c.[b]	n.c.[b]	n.c.[b]
Submandibular gland	2470	0.174	8	45000	77600	n.c.[b]	n.c.[b]	n.c.[b]
Uterus	6679	0.470	4	138000	244000	452000[a]	42.5	4.00-48.0

Organ / tissue	$C_{eq,max}$ [µg-eq/L]	$C_{eq,max}$ ratio Organ/Blood	t_{max} [h]	AUC(0-24) [µg-eq·h/L]	AUC(0-t_n) [µg-eq·h/L]	AUC [µg-eq·h/L]	$t_{1/2}$ [h]	Regression range [h]
Fetal blood	1730	0.122	48	24300	58600	n.c.[b]	n.c.[b]	n.c.[b]
Fetal brain	129	0.00908	48	2320	4970	n.c.[b]	n.c.[b]	n.c.[b]
Fetal kidney	902	0.0635	48	18000	38400	n.c.[b]	n.c.[b]	n.c.[b]
Fetal liver	1150	0.0810	48	13300	34400	n.c.[b]	n.c.[b]	n.c.[b]
Fetal lung	718	0.0506	48	9380	23400	n.c.[b]	n.c.[b]	n.c.[b]
Fetal skeletal muscle	1590	0.112	8	23900	50200	n.c.[b]	n.c.[b]	n.c.[b]
Fetal skin	1480	0.104	48	23900	56600	n.c.[b]	n.c.[b]	n.c.[b]
Fetuses (average)	1030	0.0725	48	16400	38100	n.c.[b]	n.c.[b]	n.c.[b]

a = rough estimate due to high (>30%) extrapolated portion of AUC
b = not calculated due to terminally strongly increasing radioactivity concentrations

2.6.5.7 薬物動態試験： 妊娠または授乳動物における試験（乳汁排泄）

Test article: Finerenone

Table 7-3: Pharmacokinetics: Secretion into milk, rat

Location: 4.2.2.5.4
Report no.: PH-40956

Species / strain:	Rat / Wistar lactating	Route:	iv	Feeding conditions:	Fed	
Test compound:	[^{14}C]finerenone	Gender / no.:	Female / 5			
Analyte:	Radioactivity	Assay:	LSC			
Dose:	1 mg/kg	Formulation:	10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)			
Animal Sampling time:		**1** **24 h**	**2** **24 h**	**3** **24 h**	**Mean**	**C.V.** **[%]**
Dose:	[µg/kg]	984	978	1024	996	2.51
Body weight:	[g]	320	322	328	323	1.29
Dose:	[µg/animal]	315	315	336	322	3.77
Amount / Litter:	[µg]	69.3	60.4	80.0	69.9	14.0
% of Dose:		22.0	19.2	23.8	21.6	10.7
Animal Sampling time:			**4** **48 h**	**5** **48 h**	**Mean**	**C.V.** **[%]**
Dose:	[µg/kg]		977	969	973	0.545
Body weight:	[g]		301	325	313	5.42
Dose:	[µg/animal]		294	315	304	4.88
Amount / Litter:	[µg]		51.4	58.6	55.0	9.18
% of Dose:			17.5	18.6	18.0	4.45

2.6.5.8 薬物動態試験： その他の分布試験

その他の分布試験は実施していない。

2.6.5.9 薬物動態試験： In Vivo における代謝

Test article: Finerenone

Table 9-1: Pharmacokinetics: Metabolism *in vivo*

Location: 4.2.2.4.8, 4.2.2.4.9, 4.2.2.4.10, 4.2.2.4.11
Report no.: A52016, PH-39348, PH-39368, PH-39577

PK and Mass balance studies								
Analyte(s):	Finerenone and metabolites		Assays:	LC-MS/MS, HPLC-LSC, NMR				
Species/Strain:	Mouse/CD-1			Rat/Wistar			Dog/Beagle	Human
Gender/Number of animals/subjects:	M/3[a]	M/3[a] (intact)	M/5 (intact)	M/3 (intact)	M/5 (BDC)	M/4 (BDC)	F/4	M/4
Feeding conditions:	Fed			Fasted			Fasted	Fasted
Vehicle / Formulation:	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	10% Ethanol, 40% PEG 400, 50% demin. Water (v/v/v)	water
Route:	po	po	po	po	iv	po	po	po
Dose:	1 mg/kg	1 mg/kg	1 mg/kg	10 mg/kg	1 mg/kg	1 mg/kg	3 mg/kg	10 mg
Radionuclide:				[^{14}C]finerenone				
Specific Activity (MBq/mg):	3.09	3.09	3.09	3.13	3.09	3.09	1.545	0.31
Radioactivity Dose (MBq/kg):	3.09	3.09	3.09	31.3	3.09	3.09	4.71	~2.89[b]
Biological Samples:	Plasma	Plasma	Urine, feces	Urine, feces	Urine, feces, bile	Urine, feces, bile	Plasma, urine, feces	Plasma, urine, feces

a = numbers of animals per time point
b = actual radioactivity dose per body

Test article: Finerenone

Table 9-2: Pharmacokinetics: Metabolism *in vivo*

Location: 4.2.2.4.8, 4.2.2.4.9, 4.2.2.4.10, 4.2.2.4.11
Report no.: A52016, PH-39348, PH-39368, PH-39577

Presence of Finerenone and Metabolites in Plasma and Excreta from Non-Clinical Species and Human

Species:	Mouse	Rat (Intact)					Rat (BDC)						Dog			Human		
Route:	po	po (1 mg/kg)			po (10 mg/kg)		po				iv		po			po		
Matrix:	Plasma	Plasma	Urine	Feces	Urine	Feces[a]	Bile	Urine	Feces	Bile	Urine	Feces	Plasma	Urine	Feces	Plasma	Urine	Feces
Unit	[%][e]	[%][e]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][f]	[%][e]	[%][f]	[%][f]	[%][e]	[%][f]	[%][f]
Finerenone	96.8	96.4	0.640	7.85	0.936	-	n.d.[d]	0.698	2.43	n.d.[d]	0.586	2.77	28.2	1.26	2.86	7.1	0.825	0.184
M-1	0.4	1.0	0.165	0.953	0.352	-	n.d.[d]	0.239	0.114	n.d.[d]	0.0917	0.161	8.1	0.122	0.246	48.9	n.d.[d]	0.0506
M-2	n.d.[d]	n.d.[d]	4.98	8.10	7.97	-	2.16	2.78	2.77	0.661	2.08	2.40	36.0	27.8	14.7	21.5	13.1	1.86
M-3	n.d.[d]	n.d.[d]	6.91	19.9	6.53	-	24.2	3.58	0.163	24.2	3.22	0.173	1.6	4.16	0.856	9.0	46.3	1.48
M-4	0.9[b]	2.4[b]	2.36[b]	4.86[b]	2.11[b]	-	n.d.[d]	1.40[b]	2.59[b]	n.d.[d]	1.28[b]	1.50[b]	11.1[b]	3.81[b]	3.44[b]	2.4	3.95	0.823
M-5	n.d.[d]	n.d.[d]	0.356	7.30	0.685	-	5.47	0.270	0.508	5.03	0.504	0.280	0.6	2.46	6.08	1.4	2.72	9.40
M-7	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]	-	n.d.[d]	n.a.[c]	n.a.[c]	n.d.[d]	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]	n.a.[c]	n.d.[d]	0.376	1.25
M-8	n.d.[d]	n.d.[d]	n.d.[d]	2.21	n.d.[d]	-	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	0.889	n.d.[d]	2.44	2.61
M-9	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	-	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	0.443	3.24	n.d.[d]	n.d.[d]	1.11
M-10	n.d.[d]	n.d.[d]	n.d.[d]	3.13	n.d.[d]	-	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	0.794
Other	-	-	3.01	16.7	3.58	-	20.8	3.09	0.696	14.3	3.15	0.489	4.3	11.4	8.66	-	8.76	1.61
not balanced	-	-	1.08	4.70	-	-	-	-	-	-	-	-	-	1.31	1.02	-	1.11	0.0726

a = not investigated
b = coeluting with M-7
c = not applicable
d = not detected
e = percent AUC of total radioactivity
f = percent of radioactivity dose

Test article: Finerenone

Table 9-3: Pharmacokinetics: Metabolism *in vivo*

Assessment of the potential for chiral inversion of finerenone (BAY 94-8862) in plasma after administration of [^{14}C]finerenone to humans within the frame of study BAY 94-8862/14502	Location: Report no.:	4.2.2.4.12 PH-39816
In none of the analyzed plasma samples chiral inversion/racemization of finerenone (BAY 94-8862) to its enantiomer BAY 94-8863 was observed for the present finerenone concentrations in the range of 11.5 to 102.8 µg/L, representative for a 10 mg dose of finerenone (LLOQ for BAY 94-8863: 1 µg/L)		

2.6.5.10 薬物動態試験： In Vitro 代謝

Test article: Finerenone

Table 10-1: Pharmacokinetics: Metabolism *in vitro*, species comparison

Location: 4.2.2.4.1
Report no.: PH-41146

Species / strain:	Several	Route:	*in vitro*
Material:	Pooled liver microsomes	Assay:	HPLC-LSC, LC-MS/MS
Test compound:	[^{14}C]finerenone	Nuclide:	^{14}C
Table:	Metabolite profiles of 1 h incubations of [^{14}C]finerenone (1 µM) with liver microsomes of different species		

	[% of radioactivity]							
Species / strain (gender)	**Mouse / NMRI (M)[a]**	**Mouse / CD-1 (M)[a]**	**Rat / Wistar (M)[a]**	**Rat / Wistar (F)[b]**	**Rabbit / Himalayan (F)[b]**	**Dog / Beagle (F)[b]**	**Monkey / Cynomolgus (Mix)**	**Human (Mix)**
M-1	18.9	16.4	35.5	4.71	7.97	21.4	0.94	14.2
M-2(major)[c]/M-6	19.1	28.2	15.0	0.39	19.3	15.6	42.3	35.5
M-3	0.54	2.11	0.60	n.d.[d]	0.90	n.d.[d]	10.8	1.09
M-4	16.7	14.7	19.6	6.11	37.5	17.9	5.16	14.5
M-5	16.9	19.6	7.49	0.94	12.6	5.29	28.6	19.2
M-7	1.73	1.56	2.26	0.88	1.38	2.27	n.d.[d]	0.93
M-8	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	n.d.[d]	3.47	n.d.[d]
M-14	trace[e]	trace[e]	trace[e]	n.d.[d]	trace[e]	trace[e]	trace[e]	trace[e]
Finerenone	23.2	11.8	11.5	85.5	11.0	35.3	trace[e]	6.94
Turnover	76.9	88.2	88.5	14.5	89.0	64.7	~100	93.1

a = male
b = female
c = major component of the peak, based on peak area obtained by LC-MS/MS
d = not detected
e = below LOD of HPLC-LSC, detected by LC-MS/MS

Test article: Finerenone

Table 10-2: Pharmacokinetics: Metabolism *in vitro*, species comparison

Location: 4.2.2.4.1
Report no.: PH-41146

Species / strain:	Several	Route:	*in vitro*	
Material:	Hepatocytes	Assay:	HPLC-LSC, LC-MS/MS	
Test compound:	[^{14}C]finerenone	Nuclide:	^{14}C	
Table:	Metabolite profiles of 2 h incubations of [^{14}C]finerenone with hepatocytes of rat, dog, monkey and human in suspension culture			

	[% of radioactivity]					
Species / strain (gender)	**Rat / Wistar (M)[a,c]**		**Dog / Beagle (F)[b]**	**Monkey / Cynomolgus (F)[b]**	**Human[c]**	
M-1	31.2	3.71	17.6	6.84	20.3	17.5
M-2 (major)[d]/M-6	13.4	28.7	36.6	32.5	6.80	5.31
M-3	3.00	26.7	n.d.[e]	3.89	n.d.[e]	n.d.[e]
M-4	11.8	7.06	13.6	13.2	13.2	12.1
M-5	5.69	9.86	4.04	13.3	8.68	6.50
M-7	n.d.[e]	0.45	3.16	2.67	1.63	1.69
M-8	1.55	8.31	n.d.[e]	Trace[f]	n.d.[e]	n.d.[e]
M-9	0.88	3.19	2.56	n.d.[e]	n.d.[e]	n.d.[e]
M-10	2.60	1.84	n.d.[e]	1.66	n.d.[e]	n.d.[e]
M-11	n.d.[e]	n.d.[e]	n.d.[e]	3.02	n.d.[e]	n.d.[e]
M-13	n.d.[e]	n.d.[e]	n.d.[e]	6.00	n.d.[e]	n.d.[e]
Finerenone	16.5	Trace[f]	18.0	14.7	47.6	55.7
Turnover	83.5	~100	82.0	85.3	52.4	44.3

a = male
b = female
c = two different hepatocyte preparations
d = major component of the peak, based on peak area obtained by LC-MS/MS
e = not detected
f = below LOD of HPLC-LSC, detected by LC-MS/MS

Test article: Finerenone

Table 10-3: Pharmacokinetics: Metabolism *in vitro*

Location: 4.2.2.4.2
Report no.: PH-39534

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Recombinant CYPs	Assay:	HPLC-LCS, LC-HRMS
Test compound:	[^{14}C]finerenone	Nuclide:	^{14}C
Table:	Mass balance of 1 µM [^{14}C]finerenone incubates with CYP isoforms		

Incubation RMA1487	CYP Isoform	[^{14}C]finerenone [%]	M-1 [%]	M-2[b] [%]	M-2 + M-6[b] [%]	M-3 [%]	M-4 [%]	M-5 [%]	M-6[b] [%]	M-7 [%]	M-11 [%]	M-12 [%]	M-13 [%]	M-14 [%]
B21	Insect cell Ctr	99.5	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B01	1A1	65.0	5.2	n.a.[a]	3.5	n.d.[c]	3.9	n.d.[c]	n.a.[a]	1.6	n.d.[c]	n.d.[c]	19.6	n.d.[c]
B02	1A2	98.1	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B03	2A6	97.0	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B04	2B6	97.4	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B05	2C8	23.0	19.4	n.d.[c]	n.a.[a]	n.d.[c]	24.5	n.d.[c]	3.9	5.5	13.7	1.0	n.d.[c]	6.7
B06	2C9	99.0	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B07	2C18	96.1	<2	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B08	2C19	96.3	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B09	2D6	97.2	<2	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B10	2E1	97.4	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B11	2J2	97.7	<2	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B12	3A4	7.6	9.7	37.1	n.a.[a]	1.1	14.2	20.2	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	3.5
C04	3A5	85.5	4.1	n.a.[a]	1.3	n.d.[c]	5.7	1.0	n.a.[a]	1.0	n.d.[c]	n.d.[c]	n.d.[c]	0.5
C05	3A7	86.9	6.6	n.a.[a]	1.2	n.d.[c]	4.9	n.d.[c]	n.a.[a]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	0.5
B16	4A11	98.5	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B17	4F2	99.3	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B18	4F3A	98.2	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B19	4F3B	99.0	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
B20	4F12	99.4	<1	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]

a = not applicable
b = insufficient chromatographic separation of M-2 and M-6: depending on their occurrence in MS, they were balanced separately or together
c = not detected

Test article: Finerenone

Table 10-4: Pharmacokinetics: Metabolism *in vitro*

Location: 4.2.2.4.2
Report no.: PH-39534

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Human liver microsomes, recombinant CYPs	Assay:	LC-HRMS
Test compound:	Finerenone	Nuclide:	-
Table:	Clearance and metabolite formation in 50 nM finerenone incubates with CYP1A1, 2C8, 3A4 and HLM		

Time [min]	Finerenone [%]	CL_{int}	M-1	M-2	M-3	M-4	M-5	M-7	M-13
						[MS response]			
CYP1A1 100 pmol/mL (LAND0607K01)									
0	100.0		n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
6	90.4		2245	n.d.[b]	n.d.[b]	15368	n.d.[b]	n.d.[b]	44685
10	82.1	0.22	15127	n.d.[b]	n.d.[b]	18258	n.d.[b]	n.d.[b]	75153
15	73.1	µL/min/pmol	17558	n.d.[b]	n.d.[b]	19567	n.d.[b]	n.d.[b]	108277
25	62.1		20099	5223	n.d.[b]	32292	n.d.[b]	5374	158466
45	49.0		27497	5489	n.d.[b]	46192	n.d.[b]	8120	225801
CYP2C8 100 pmol/mL (LAND0607K05)									
0	100		n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
6	97.2		3095	n.d.[b]	n.d.[b]	94534	n.d.[b]	n.d.[b]	n.d.[b]
10	89.9	0.12	23983	n.d.[b]	n.d.[b]	155661	n.d.[b]	n.d.[b]	n.d.[b]
15	82.0	µL/min/pmol	45440	n.d.[b]	n.d.[b]	220092	n.d.[b]	n.d.[b]	n.d.[b]
25	72.0		97967	n.d.[b]	n.d.[b]	324382	n.d.[b]	8855	n.d.[b]
45	55.8		142209	n.d.[b]	n.d.[b]	489685	n.d.[b]	8141	n.d.[b]

Time [min]	Finerenone [%]	CL_{int}	M-1	M-2	M-3	M-4 [MS response]	M-5	M-7	M-13
CYP3A4 75 pmol/mL (LAND0607K09)									
0	100		n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
6	40.7		471477	212425	n.d.[b]	264971	128121	n.d.[b]	n.d.[b]
10	22.3	1.91	456503	404322	n.d.[b]	334647	153460	n.d.[b]	n.d.[b]
15	11.1	µL/min/pmol	323734	563419	n.d.[b]	347500	199526	n.d.[b]	n.d.[b]
25	1.5		161595	639213	31589	290294	225092	n.d.[b]	n.d.[b]
45	0.2		28907	594262	115054	186778	248024	n.d.[b]	n.d.[b]
HLM 0.5 mg/mL (LAND0607Q01)									
0	100.0		n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]	n.d.[b]
5	92.1		86308	n.d.[b]	n.d.[b]	52423	n.d.[b]	n.d.[b]	n.d.[b]
10	83.2	38.83	164771	n.d.[b]	n.d.[b]	114502	4740	n.d.[b]	n.d.[b]
15	75.4	µL/min/mg	264012	n.d.[b]	n.d.[b]	169739	23318	n.d.[b]	n.d.[b]
25	64.1		373499	6208	n.d.[b]	222275	41159	n.d.[b]	n.d.[b]
45	40.7		484183	59056	n.d.[b]	330524	65860	n.d.[b]	n.d.[b]

a = not applicable
b = not detected

Test article: Finerenone

Table 10-5: Pharmacokinetics: Metabolism *in vitro*

Location: 4.2.2.4.2
Report no.: PH-39534

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Human hepatocytes	Assay:	LC-HRMS
Test compound:	Finerenone	Nuclide:	-
Table:	Clearance and calculated hepatic f_m in 0.2 µM finerenone incubates with human hepatocytes and CYP3A4/2C8 selective inhibitors		

	CL_{int} [L/h/kg]	**Inhibition [%]**	**Calculated hepatic f_m**	
			CYP3A4	**CYP2C8**
Without inhibitor	2.33	-		
Gemfibrozil	1.29	45	0.55	0.45
Verapamil	0.30	87	0.87	0.13
Verapamil + gemfibrozil	0.01	100		
Erythromycin	0.53	77	0.79	0.21
Erythromycin + gemfibrozil	0.07	97		

a = not applicable

Test article: Finerenone

Table 10-6: Pharmacokinetics: Metabolism *in vitro*

Location: 4.2.2.4.2
Report no.: PH-39534

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Recombinant CYP isoforms	Assay:	HPLC-LSC
Test compound:	[^{14}C]finerenone	Nuclide:	^{14}C
Table:	Overview of enzyme kinetics parameters		

	K_m [µM]	**V_{max} [pmol/pmol CYP/min]**	**CL_{int} [µL/min/pmol]**
CYP2C8			
Dihydrodiol pathway	17.7	1.1	0.06
Naphthyridine pathway	70.9	1.2	0.02
CYP3A4			
Dihydrodiol pathway	18.5	11.0	0.59
Naphthyridine pathway	10.5	12.8	1.22

a = not applicable

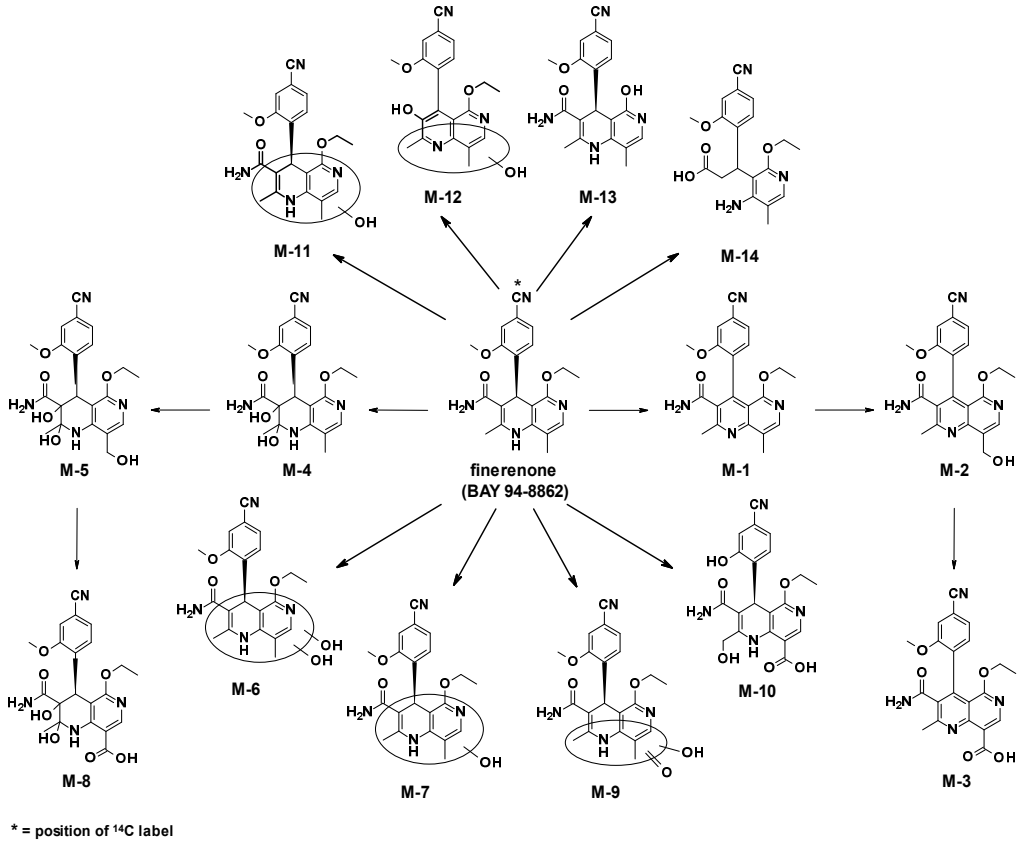
2.6.5.11 薬物動態試験： 推定代謝経路

Test article: Finerenone

Table 11-1: Pharmacokinetics: Metabolic pathways observed *in vitro* and *in vivo*

Location: 4.2.2.4.1, 4.2.2.4.2, 4.2.2.4.8, 4.2.2.4.9, 4.2.2.4.10, 4.2.2.4.11
Report no.: PH-41146, PH-39534, A52016, PH-39348, PH-39368, PH-39577

Table: Proposed metabolic pathways observed *in vitro* and *in vivo*



2.6.5.12 薬物動態試験： 薬物代謝酵素の誘導／阻害

Test article: Finerenone

Table 12-1: Pharmacokinetics: Inhibitory potential towards human CYP isoforms

Location: 4.2.2.4.3, 4.2.2.4.4, 4.2.2.4.5
Report no.: PH-37733, PH-40971, PH-40973

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes, recombinant CYP1A1, 2E1	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS, HPLC-FL, HPLC-LSC
Table:	Inhibitory effects of finerenone on formation of metabolites of standard probes mediated by cytochrome P450 isoforms		

CYP isoform	Probe reaction	Reversible inhibition IC_{50} [µM]	30-Minute pre-incubation without NADPH IC_{50} [µM]	30-Minute pre-incubation with NADPH IC_{50} [µM]	Potential for TDI
1A1	Granisetron 7-hydroxylation	6.7	9.5	3.7	Yes[c]
1A2	Phenacetin *O*-deethylation	>50	>50	>50	No
2A6	Coumarin 7-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
2B6	Bupropion hydroxylation	>50	>50	>50	No
2C8	Amodiaquine *N*-deethylation	6.8 (1.9)[b]	6.5	2.7	Yes[d]
2C9	Diclofenac 4'-hydroxylation	29 (16)[b]	46	35	No
2C19	Mephenytoin 4'-hydroxylation	31	19	21	No
2D6	Dextromethorphan *O*-demethylation	>50	>50	>50	No
2E1	Chlorzoxazone 6-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
3A4	Midazolam 1'-hydroxylation	19	n.a.[a]	10	Yes[c]
3A4	Testosterone 6β-hydroxylation	12	n.a.[a]	6.4	Yes[e]

a = not applicable
b = K_i value
c = no investigations on mechanism-based inhibition performed
d = no mechanism-based inhibition detected
e = mechanism-based inhibition parameters: k_{inact} = 0.012 min^{-1} and K_I = 10.3 µM

Test article: Finerenone

Table 12-2: Pharmacokinetics: Inhibitory potential towards human UGT isoforms

Location: 4.2.2.4.6
Report no.: A50906

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Inhibitory effects of finerenone on formation of metabolites of standard probes mediated by UGT isoforms		

UGT isoform	Substrate	IC_{50} [µM]
1A1	Estradiol	>50
1A4	Trifluoperazine	>50
1A6	α-Naphthol	>50
1A9	Propofol	>50
2B4	1'-Hydroxymidazolam	>50
2B7	3'-Azido-3'-deoxythymidine (AZT)	>50

a = not applicable

Test article: Finerenone

Table 12-3: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by finerenone (FDA)

Table:	Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]						
Enzyme	**Model**	**$[I]_{max,u}$ [µM]**	**$[I]_{in,max,u}$ [µM]**	**$[I]_{gut}$ [µM]**	**K_i[b] [µM]**	**$1+[I]/K_i$**	**Threshold cutoff for potential DDI**
				Systemic			
CYP1A1	Basic	0.035	-	-	2.91[c]	1.012	$1+[I]/K_i \geq 1.02$
CYP1A2	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
CYP2A6	Basic	0.035	-	-	>21.7[f]	<1.002	$1+[I]/K_i \geq 1.02$
CYP2B6	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
CYP2C8	Basic	0.035	-	-	1.65[g]	1.021	$1+[I]/K_i \geq 1.02$
CYP2C8	Mechanistic static[d]	-	0.292	-	1.65[g]	1.18	$1+[I]/K_i \geq 1.25$
CYP2C9	Basic	0.035	-	-	13.9[h]	1.003	$1+[I]/K_i \geq 1.02$
CYP2C19	Basic	0.035	-	-	9.39[i]	1.004	$1+[I]/K_i \geq 1.02$
CYP2D6	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
CYP2E1	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
CYP3A4/midazolam, reversible	Basic	0.035	-	-	7.70[j]	1.005	$1+[I]/K_i \geq 1.02$
CYP3A4/testosterone, reversible	Basic	0.035	-	-	4.86[k]	1.007	$1+[I]/K_i \geq 1.02$
CYP3A4, TDI	Basic	0.035	-	-	6.24[l]	9.29[m]	$(k_{obs} + k_{deg}) / k_{deg} \geq 1.25$
				Intestinal			
CYP3A4/midazolam	Basic	-	-	211	7.70[j]	28.5	$1+[I]/K_i \geq 11$
CYP3A4/testosterone	Basic	-	-	211	4.86[k]	44.5	$1+[I]/K_i \geq 11$
				Systemic			
UGT1A1	Basic	0.035	-	-	>20.3[n]	<1.002	$1+[I]/K_i \geq 1.02$
UGT1A4	Basic	0.035	-	-	>20.3[n]	<1.002	$1+[I]/K_i \geq 1.02$
UGT1A6	Basic	0.035	-	-	>20.3[n]	<1.002	$1+[I]/K_i \geq 1.02$
UGT1A9	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
UGT2B4	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$
UGT2B7	Basic	0.035	-	-	>15.2[e]	<1.002	$1+[I]/K_i \geq 1.02$

Table: Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = Unbound K_i for CYP1A1 (2.91 µM; K_i = 3.35 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.868))

d = The mechanistic static model for CYP2C8 inhibition assumed no enzyme inhibition in the gut

e = Unbound K_i (>15.2 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606; unbound fraction in 100 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.606))

f = Unbound K_i (>21.7 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)

g = Unbound K_i (1.65 µM; K_i = 1.9 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)

h = Unbound K_i (13.9 µM; K_i = 16 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)

i = Unbound K_i (9.39 µM; K_i 15.5 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606)

j = Unbound K_i (7.70 µM; K_i = 9.5 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)

k = Unbound K_i (4.86 µM; K_i = 6.0 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)

l = Unbound K_I (6.24 µM; K_I = 10.3 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606)

m = Calculated according to $(k_{obs} + k_{deg}) / k_{deg}$ with $k_{obs} = [(k_{inact} \times 50 \times [I]_{max,u}) / (K_I + 50 \times [I]_{max,u})]$ and k_{deg} = 0.00032 min^{-1}(Obach RS et al., Drug Metab Dispos 2007:35:246-255)

n = Unbound K_i (>20.3 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for finerenone calculated under assumption of dose-linearity from exposures of finerenone at steady state observed in patients receiving 10 mg finerenone (5.3.3.5.3 R-9543) (finerenone total $[I]_{max}$ = 0.43 µM [161 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.292 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/R_B)$, where fraction absorbed (F_a) = 1, fraction escaping gut metabolism (F_g) = 0.575 [Heinig R et al., Eur J Drug Metab Pharmacokinet 2018:43:715–727 (4.3.48)], observed absorption rate constant (k_a) = 0.153 min^{-1} (5.3.3.5.2 PH-36697), hepatic blood flow (Q_h) = 1617 mL/min, R_B (blood-to-plasma ratio) = 0.935; unbound fraction = 0.0833); $[I]_{gut}$ = theoretical maximum gastrointestinal drug concentration, calculated as the highest clinical dose on a molar basis in a volume of 250 mL; [I] = $[I]_{max,u}$ or $[I]_{in,max,u}$ or $[I]_{gut}$ used for IC_{50} ratio formation depending on specific guideline requirement; K_i = inhibition constant (reversible); K_I = concentration causing half maximal inactivation (irreversible); k_{inact} = maximal inactivation rate constant; IC_{50} = concentration required for 50% inhibition; k_{obs} = observed (apparent first order) inactivation rate of the affected enzyme; k_{deg} = apparent first-order degradation rate constant of the affected enzyme; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

Test article: Finerenone

Table 12-4: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by finerenone (EMA)

Table: Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	$[I]_{in,max,u}$ [µM]	$[I]_{gut}$ [µM]	K_i[b] [µM]	$[I]/K_i$	Threshold cutoff for potential DDI
				Systemic			
CYP1A1	Basic	0.035	-	-	2.91[c]	0.012	$[I]/K_i \geq 0.02$
CYP1A2	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
CYP2A6	Basic	0.035	-	-	>21.7[f]	<0.002	$[I]/K_i \geq 0.02$
CYP2B6	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
CYP2C8	Basic	0.035	-	-	1.65[g]	0.021	$[I]/K_i \geq 0.02$
CYP2C8	Mechanistic static[d]	-	0.292	-	1.65[g]	0.18	$[I]/K_i \geq 0.25$
CYP2C9	Basic	0.035	-	-	13.9[h]	0.003	$[I]/K_i \geq 0.02$
CYP2C19	Basic	0.035	-	-	9.39[i]	0.004	$[I]/K_i \geq 0.02$
CYP2D6	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
CYP2E1	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
CYP3A4/midazolam, reversible	Basic	0.035	-	-	7.70[j]	0.005	$[I]/K_i \geq 0.02$
CYP3A4/testosterone, reversible	Basic	0.035	-	-	4.86[k]	0.007	$[I]/K_i \geq 0.02$
CYP3A4, TDI	Basic	0.035	-	-	6.24[l]	9.29[m]	$(k_{obs} + k_{deg}) / k_{deg} \geq 1.25$
				Intestinal			
CYP3A4/midazolam	Basic	-	-	211	7.70[j]	27.5	$[I]/K_i \geq 10$
CYP3A4/testosterone	Basic	-	-	211	4.86[k]	43.5	$[I]/K_i \geq 10$
				Systemic			
UGT1A1	Basic	0.035	-	-	>20.3[n]	<0.002	$[I]/K_i \geq 0.02$
UGT1A4	Basic	0.035	-	-	>20.3[n]	<0.002	$[I]/K_i \geq 0.02$
UGT1A6	Basic	0.035	-	-	>20.3[n]	<0.002	$[I]/K_i \geq 0.02$
UGT1A9	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
UGT2B4	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$
UGT2B7	Basic	0.035	-	-	>15.2[e]	<0.002	$[I]/K_i \geq 0.02$

Table: Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012
b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition
c = Unbound K_i for CYP1A1 (2.91 µM; K_i = 3.35 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.868))
d = The mechanistic static model for CYP2C8 inhibition assumed no enzyme inhibition in the gut
e = Unbound K_i (>15.2 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606; unbound fraction in 100 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.606))
f = Unbound K_i (>21.7 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)
g = Unbound K_i (1.65 µM; K_i = 1.9 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)
h = Unbound K_i (13.9 µM; K_i = 16 µM; unbound fraction in 0.05 mg/mL microsomes = 0.868)
i = Unbound K_i (9.39 µM; K_i 15.5 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606)
j = Unbound K_i (7.70 µM; K_i = 9.5 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)
k = Unbound K_i (4.86 µM; K_i = 6.0 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)
l = Unbound K_I (6.24 µM; K_I = 10.3 µM; unbound fraction in 0.5 mg/mL microsomes = 0.606)
m = Calculated according to $(k_{obs} + k_{deg}) / k_{deg}$ with $k_{obs} = [(k_{inact} \times 50 \times [I]_{max,u}) / (K_I + 50 \times [I]_{max,u})]$ and $k_{deg} = 0.00032\ min^{-1}$
n = Unbound K_i (>20.3 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.810)
Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for finerenone calculated under assumption of dose-linearity from exposures of finerenone at steady state observed in patients receiving 10 mg finerenone (5.3.3.5.3 R-9543) (finerenone total $[I]_{max}$ = 0.43 µM [161 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.292 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/R_B)$, where fraction absorbed (F_a) = 1, fraction escaping gut metabolism (F_g) = 0.575 [Heinig R et al., Eur J Drug Metab Pharmacokinet 2018:43:715–727 (4.3.48)], observed absorption rate constant (k_a) = 0.153 min^{-1} (5.3.3.5.2 PH-36697) , hepatic blood flow (Q_h) = 1617 mL/min, R_B (blood-to-plasma ratio) = 0.935; unbound fraction = 0.0833); $[I]_{gut}$ = theoretical maximum gastrointestinal drug concentration, calculated as the highest clinical dose on a molar basis in a volume of 250 mL; [I] = $[I]_{max,u}$ or $[I]_{in,max,u}$ or $[I]_{gut}$ used for IC_{50} ratio formation depending on specific guideline requirement; K_i = inhibition constant (reversible); K_I = concentration causing half maximal inactivation (irreversible); k_{inact} = maximal inactivation rate constant; IC_{50} = concentration required for 50% inhibition; k_{obs} = observed (apparent first order) inactivation rate of the affected enzyme; k_{deg} = apparent first-order degradation rate constant of the affected enzyme; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase
Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

Test article: Finerenone

Table 12-5: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP1A2 mRNA: The effect of treating cultured human hepatocytes with finerenone on CYP1A2 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
Finerenone	0.041	1.2	1.5	1.3
	0.123	1.2	1.4	1.2
	0.370	1.3	1.3	1.3
	1.1	1.4	1.4	1.5
	3.3	1.7	1.9	1.6
	10	2.1	2.1	2.1
	30	2.1	2.0	2.3
	90	1.1	0.9	1.8
Omeprazole	16.7/16.7/50	13.2	15.7	9.5

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 12-6: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP1A2 activity: The effect of treating cultured human hepatocytes with finerenone on the rate of phenacetin O-dealkylase activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	37.7	1.0	47.0	1.0	51.0
Finerenone	0.041	0.8	30.8	1.2	55.4	0.8	43.2
	0.123	0.9	35.1	1.0	45.0	0.9	47.5
	0.370	1.0	37.7	0.9	43.7	0.8	40.6
	1.1	0.9	35.7	1.0	48.9	0.7	35.4
	3.3	1.2	45.4	0.6	28.1	0.8	41.4
	10	0.7	27.0	0.4	18.1	0.6	29.6
	30	0.4	15.4	0.3	12.1	0.3	15.5
	90	0.3	10.1	0.2	9.5	0.2	7.8
Omeprazole	16.7/5.6/16.7	10.2	382.3	9.9	467.4	14.3	727.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol acetaminophen/min/10^6 cells

Test article: Finerenone

Table 12-7: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP2B6 mRNA: The effect of treating cultured human hepatocytes with finerenone on CYP2B6 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
Finerenone	0.041	0.9	1.4	1.1
	0.123	0.9	1.1	0.7
	0.370	1.0	1.2	0.9
	1.1	1.3	1.4	1.2
	3.3	1.7	2.6	1.5
	10	3.5	6.7	3.3
	30	7.0	6.5	6.5
	90	7.9	3.6	5.6
Rifampicin	30/10/30	8.3	10.2	8.3
Phenobarbital	333/333/333	13.8	7.6	8.1

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 12-8: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP2B6 activity: The effect of treating cultured human hepatocytes with finerenone on the rate of S-mephenytoin N-demethylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	7.1	1.0	4.3	1.0	5.8
Finerenone	0.041	0.7	5.3	0.7	3.2	0.8	4.7
	0.123	0.9	6.3	0.8	3.6	0.8	4.8
	0.370	0.8	5.9	1.0	4.3	0.9	5.1
	1.1	0.9	6.4	0.9	3.8	0.8	4.8
	3.3	1.2	8.4	1.2	5.2	1.1	6.4
	10	1.4	9.9	1.3	5.4	1.3	7.5
	30	1.8	12.5	1.1	4.6	1.2	6.7
	90	1.1	7.9	0.6	2.4	0.7	4.3
Rifampicin	10/3.3/3.3	4.8	34.1	4.1	17.6	5.5	31.4
Phenobarbital	333/111/333	8.5	60.3	4.5	19.5	6.2	35.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol nirvanol/min/10^6 cells

Test article: Finerenone

Table 12-9: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP2C19 mRNA: The effect of treating cultured human hepatocytes with finerenone on CYP2C19 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
Finerenone	0.041	1.3	1.4	1.3
	0.123	1.1	1.8	1.1
	0.370	1.1	1.5	1.2
	1.1	1.2	1.5	1.2
	3.3	1.4	1.7	1.3
	10	2.2	2.6	1.5
	30	3.0	2.4	1.7
	90	1.9	1.6	1.6
Rifampicin	30/30/30	6.3	4.0	2.4
Phenobarbital	333/333/333	6.5	3.7	2.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 12-10: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP2C19 activity: The effect of treating cultured human hepatocytes with finerenone on the rate of S-mephenytoin 4'-hydroxylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	14.37	1.0	12.71	1.0	0.81
Finerenone	0.041	0.5	9.64	0.6	10.71	0.6	0.65
	0.123	0.7	13.27	0.8	13.72	0.6	0.67
	0.370	0.8	14.59	1.1	17.78	0.8	0.84
	1.1	0.9	16.96	1.0	16.34	0.9	0.91
	3.3	1.4	25.46	1.5	25.09	1.6	1.66
	10	1.6	29.91	1.1	18.55	2.2	2.24
	30	1.5	26.77	0.5	8.50	1.9	1.91
	90	0.4	7.74	0.0	0.69	0.5	0.48
Rifampicin	10/30/30	7.1	101.8	5.5	67.5	16.2	13.1
Phenobarbital	333/111/333	4.1	59.4	3.0	37.4	13.3	10.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 4'-OH mephenytoin/min/10^6 cells

Test article: Finerenone

Table 12-11: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP3A4 mRNA: The effect of treating cultured human hepatocytes with finerenone on CYP3A4 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
Finerenone	0.041	0.8	1.3	1.1
	0.123	1.0	1.5	1.3
	0.370	1.3	1.5	1.6
	1.1	2.2	2.0	2.6
	3.3	5.2	6.7	6.0
	10	9.2	14.2	12.1
	30	12.5	18.2	21.2
	90	10.5	6.0	25.0
Rifampicin	1.1/10/30	16.0	13.7	22.8
Phenobarbital	111/333/333	13.9	10.5	18.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 12-12: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential *in vitro* in cultured human hepatocytes		

CYP3A4/5 activity: The effect of treating cultured human hepatocytes with finerenone on the rate of testosterone 6β-hydroxylation activity

	Concentration [µg/mL]	Donor 1		Donor 2		Donor 3	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	64.2	1.0	67.1	1.0	70.5
Finerenone	0.041	0.7	42.3	1.0	70.2	0.9	61.4
	0.123	0.8	53.1	0.8	56.7	0.8	58.7
	0.370	1.0	62.6	0.8	52.9	0.7	51.9
	1.1	0.9	58.0	0.9	62.7	0.6	44.9
	3.3	1.4	90.5	0.4	26.0	0.7	48.9
	10	0.7	46.2	0.2	15.2	0.5	37.1
	30	0.3	17.1	0.1	8.6	0.2	16.7
	90	0.1	6.0	0.1	4.4	0.1	7.2
Rifampicin	30/3.3/3.3	8.6	550.6	11.2	753.9	12.2	858.9
Phenobarbital	333/111/333	10.1	650.0	10.2	686.6	12.5	881.0

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 6β-hydroxytestosterone/min/10^6 cells

Test article: Finerenone

Table 12-13: Pharmacokinetics: Induction potential towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	Quantitative real time PCR
Table:	Kinetic parameters generated *in vitro* (CYP3A4 mRNA) and prediction of CYP3A4 induction effects *in vivo* based on different models		

Test compound Finerenone		**Donor 1**	**Donor 2**	**Donor 3**	**CYP induction assessment**
E_{max}	[fold induction]	12.5	19.1	27.4	
EC_{50}	[µg/L]	3823	5563	12363	
Dose[a]	[mg]	20	20	20	
Total $C_{max,ss}$[a]	[µg/L]	161	161	161	
Unbound $C_{max,ss}$	[µg/L]	13.4	13.4	13.4	
PXR regulation					yes
RIS model					
RIS score *in vitro*		0.044	0.046	0.030	
% Decrease in AUC of midazolam predicted		54	55	43	weak to moderate

a = Median $C_{max,ss}$ for finerenone was calculated under assumption of dose-linearity from exposures of finerenone at steady state observed in patients receiving 10 mg finerenone (5.3.3.5.3 R-9543)

2.6.5.13 薬物動態試験： 累積排泄

Test article: Finerenone

Table 13-1: Pharmacokinetics: Excretion, rat

Location: 4.2.2.5.1
Report no.: A49457

Study no.:		I 5036-4	I 5036-4	I 5075-7	I 5036-4
Species / strain:		Rat / Wistar	Rat / Wistar	Rat / Wistar (BDC)	Rat / Wistar (BDC)
Test compound:		[^{14}C]finerenone	[^{14}C]finerenone	[^{14}C]finerenone	[^{14}C]finerenone
Analyte:		Radioactivity	Radioactivity	Radioactivity	Radioactivity
Dose:	[mg/kg]	1	1	1	1
Route:		iv	po	iv	po
Gender / No. of animals:		Male / 5	Male / 5	Male / 5	Male / 4
Feeding condition:		fasted	fasted	fasted	fasted
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)			
Duration:	[h]	168	168	24	24
Assay:		LSC	LSC	LSC	LSC

		% of administered dose							
Matrix	**Interval**	**Arithmetic**		**Arithmetic**		**Arithmetic**		**Arithmetic**	
		Mean	**C.V. [%]**	**Mean**	**C.V. [%]**	**Mean**	**C.V. [%]**	**Mean**	**C.V. [%]**
Urine	0-24 h	16.2	6.63	14.6	6.60	10.9	27.3	12.1	13.1
	0-168 h	21.4	3.47	19.5	8.36	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]
Bile	0-24 h	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]	44.1	29.2	52.7	15.8
Feces	0-24 h	51.1	5.87	31.3	29.6	7.78	38.4	9.27	19.8
	0-168 h	74.0	1.37	75.7	3.95	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]
Expired air	0 - 24 h	n.a.[c]	n.c.[a]	n.c.[a,d]	n.c.[a]	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]
Body excl. GIT[b]	24 h	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]	27.1	27.9	17.4	23.1
	168 h	0.167	8.41	0.153	8.57	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]
GIT[b]	24 h	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]	5.80	55.1	4.78	38.8
	168 h	0.0149	11.8	0.0152	35.3	n.a.[c]	n.c.[a]	n.a.[c]	n.c.[a]
Recovery		95.8	0.828	95.5	1.55	97.3	4.67	97.6	3.33

a = not calculated, b = gastrointestinal tract, c = not applicable
d = no radioactivity was expired as $^{14}CO_2$ within 24 h after oral administration

Test article: Finerenone

Table 13-2: Pharmacokinetics: Excretion, rat

Location: 4.2.2.5.3
Report no.: PH-39224

Species / strain:		Rat / Wistar	
Test compound:		[^{14}C]finerenone	
Analyte:		Radioactivity	
Dose:	[mg/kg]	10	
Route:		po	
Gender / No. of animals:		Male / 3	
Feeding condition:		fasted	
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)	
Duration:	[h]	72	
Assay:		LSC	
Matrix	**Interval**	**% of administered dose Arithmetic Mean**	**C.V. [%]**
Urine	0–72 h	22.2	6.62
Feces	0–72 h	75.7	2.62
Recovery		97.9	1.03

Test article: Finerenone

Table 13-3: Pharmacokinetics: Excretion, dog

Location: 4.2.2.5.2
Report no.: PH-37447

Species / strain:		Dog / Beagle
Test compound:		[^{14}C]finerenone
Analyte:		Radioactivity
Dose:	[mg/kg]	3
Route:		po
Gender / No. of animals:		Female / 4
Feeding condition:		fasted
Formulation:		10% Ethanol, 40% PEG 400, 50% demineralized water (v / v / v)
Duration:	[h]	336
Assay:		LSC

Matrix	**Interval**	**% of administered dose**	
		Arithmetic Mean	**C.V. [%]**
Urine	0–336 h	52.7	5.08
Feces	0–336 h	42.0	8.54
Cage wash	336 h	2.42	11.7
Recovery		97.2	1.17

2.6.5.14 薬物動態試験： 胆汁中排泄

2.6.5.13 Table 13-1 参照。

2.6.5.15 薬物動態試験： 薬物相互作用

Test article: Finerenone

Table 15-1: Pharmacokinetics: Drug-drug interaction of finerenone with SGLT2 inhibitors, *in vitro*

Location: 4.2.2.6.1
Report no.: PH-41050

Species:	Human	Route:	*in vitro*
Material:	Hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Determined clearance ratios ($CL_{h,inh}/CL_{h,w/o\ inh}$) from *in vitro* experiments in human hepatocytes of two donors (HUM4070A, TZU) and derived predicted AUCRs of respective SGLT2 inhibitors in the presence of 5 µM finerenone		

Victim	Ratio $CL_h = CL_{h,inh}/CL_{h,w/o\ inh}$		AUCR	
	HUM4070A	TZU	HUM4070A	TZU
Canagliflozin	0.972	0.906	1.03	1.10
Dapagliflozin	0.980	1.04	1.02	n.c.[b]
Empagliflozin	n.a.[a]	n.a.[a]	n.a.[a]	n.a.[a]
Ertugliflozin	1.01	1.13	n.c.[b]	n.c.[b]
Ipragliflozin	0.978	0.922	1.02	1.08
Tofogliflozin	1.16	1.43	n.c.[b]	n.c.[b]

a = not applicable due to low turnover
b = not calculated

代謝を介する薬物相互作用の可能性については 2.6.5.10 Table 10-1～Table 10-6、2.6.5.12 Table 12-1～Table 12-13 及び 2.6.5.16 Table 16-27～Table 16-74 を参照。トランスポーターを介する薬物相互作用の可能性については 2.6.5.16 Table 16-1～Table 16-13 及び Table 16-75～Table 16-104 を参照。

2.6.5.16 薬物動態試験： その他

Test article: Finerenone

Table 16-1: Pharmacokinetics: *In vitro* studies to evaluate the permeability

Location: 4.2.2.7.1
Report no.: R-12248

Species:	Human	Route:	*in vitro*	
Material:	Caco-2 cells	Nuclide:	-	
Test compound:	Finerenone	Assay:	LC-MS/MS	

Cell type	Test compound	Conc. [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean
Caco-2	Finerenone	2	191	22	439	30	2.30
Caco-2	Finerenone	21	245	n.c.[a]	368	29	1.50
Caco-2	Finerenone	210	322	26	276	50	0.857
Caco-2	Atenolol	100	2.87	0.5	5.04	n.c.[a]	1.76
Caco-2	Fluvastatin	10	90.1	13.1	252	n.c.[a]	2.80
Caco-2	Metoprolol	10	227	24	243	n.c.[a]	1.07
Caco-2	Propranolol	10	286	28	285	n.c.[a]	0.998
Caco-2	Sulfasalazine	100	2.00	0.6	149	n.c.[a]	74.9

a = not calculated (duplicate determinations)

Test article: Finerenone

Table 16-2: Pharmacokinetics: *In vitro* studies to evaluate substrate characteristics towards human efflux transporter P-gp

Location: 4.2.2.7.2
Report no.: PH-40755

Species:	Human	Route:	*in vitro*		
Material:	L-MDR1 cells, LLC-PK1 cells	Nuclide:	-		
Test compound:	Finerenone	Assay:	LC-MS/MS		

Cell type	Test compound	Conc. [µM]	Inhibitor ivermectin [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio	
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.
L-MDR1	Finerenone	0.20	-	70	2.5	505	20	7.2	0.39
L-MDR1	Finerenone	2.0	-	72	14	502	16	6.9	1.40
L-MDR1	Finerenone	2.0	5	353	22	258	18	0.7	0.07
L-MDR1	Finerenone	20	-	90	14	518	21	5.8	0.93
L-MDR1	Finerenone	100	-	116	32	489	133	4.2	1.63
LLC-PK1	Finerenone	2.0	-	274	18	215	19	0.8	0.09
LLC-PK1	Finerenone	2.0	5	353	21	212	7.2	0.6	0.04
LLC-PK1	Finerenone	20	-	291	11	187	11	0.6	0.05
LLC-PK1	Finerenone	100	-	460	53	293	5.1	0.6	0.07
L-MDR1	Dipyridamole	1	-	17	2.4	590	54	35	5.9
L-MDR1	Dipyridamole	1	5	135	15	526	18	3.9	0.5
LLC-PK1	Dipyridamole	1	-	64	7	205	126	3.2	2.0
LLC-PK1	Dipyridamole	1	5	174	26	262	0.5	1.5	0.2

Test article: Finerenone

Table 16-3: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human efflux transporter P-gp

Location: 4.2.2.7.3
Report no.: PH-40886

Species: Human
Material: L-MDR1 cells
Test compound: Finerenone
Route: *in vitro*
Nuclide: -
Assay: LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean	Efflux ratio S.D.	Efflux ratio % of control
Digoxin[a]	20	Control	0.0	3.5		55.4	15.5	15.9	4.4	100 ± S.D.
Digoxin[a]	20	Finerenone	0.6	5.0	0.1	49.6	11.6	9.9	2.3	62.1
Digoxin[a]	20	Finerenone	2.0	4.5	1.3	31.0	4.4	6.9	2.2	43.1
Digoxin[a]	20	Finerenone	6.0	5.0	0.8	37.9	1.9	7.5	1.2	47.3
Digoxin[a]	20	Finerenone	20.0	7.2	1.9	51.9	3.6	7.2	2.0	45.5
Digoxin[a]	20	Finerenone	60.0	7.4	0.5	48.9	7.4	6.6	1.1	41.8
Digoxin[a]	20	Finerenone	200.0	15.8	4.5	36.0	1.8	2.3	0.7	14.3
Digoxin[a]	20	Finerenone	600.0	44.6	21.1	29.7	1.3	0.7	0.3	4.2
Dipyridamole[b]	2	Control	0.0	21.5	0.1	980.3	27.8	45.6	1.3	100 ± S.D.
Dipyridamole[b]	2	Finerenone	0.6	26.5	1.2	922.5	2.2	34.8	1.6	76.3
Dipyridamole[b]	2	Finerenone	2.0	25.6	0.9	854.4	23.0	33.4	1.5	73.3
Dipyridamole[b]	2	Finerenone	6.0	21.4	0.5	874.5	54.8	40.9	2.7	89.8
Dipyridamole[b]	2	Finerenone	20.0	34.4	8.9	1009.8	30.5	29.3	7.6	64.3
Dipyridamole[b]	2	Finerenone	60.0	42.8	3.3	670.8	52.8	15.7	1.7	34.4
Dipyridamole[b]	2	Finerenone	200.0	100.5	12.2	630.6	24.6	6.3	0.8	13.8
Dipyridamole[b]	2	Finerenone	600.0	228.7	17.9	400.1	15.4	1.7	0.2	3.8

a = IC_{50} of finerenone (BAY 94-8862) against this probe substrate = 121 µM
b = IC_{50} of finerenone (BAY 94-8862) against this probe substrate = 47 µM

Test article: Finerenone

Table 16-4: Pharmacokinetics: *In vitro* studies to evaluate substrate characteristics towards human efflux transporter BCRP

Location: 4.2.2.7.4
Report no.: PH-40764

Species:	Human	Route:	*in vitro*		
Material:	MDCKII-BCRP cells, MDCKII-WT cells	Nuclide:	-		
Test compound:	Finerenone	Assay:	LC-MS/MS		

Cell Type	Test compound	Conc. [µM]	Inhibitor Ko143 [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean	Efflux ratio S.D.
MDCKII-BCRP	Finerenone	0.2	-	233	22	310	9.4	1.3	0.13
MDCKII-BCRP	Finerenone	2.0	-	246	5.1	280	8.5	1.1	0.04
MDCKII-BCRP	Finerenone	2.0	1	380	10	174	3.3	0.46	0.02
MDCKII-BCRP	Finerenone	20	-	270	23	231	9.6	0.86	0.08
MDCKII-BCRP	Finerenone	100	-	377	34	187	5.1	0.50	0.05
MDCKII-WT	Finerenone	0.2	-	235	8.8	254	7.0	1.1	0.05
MDCKII-WT	Finerenone	2.0	-	247	24	243	7.7	0.99	0.10
MDCKII-WT	Finerenone	2.0	1	285	5.0	224	28	0.79	0.10
MDCKII-WT	Finerenone	20	-	282	15	224	15	0.80	0.07
MDCKII-WT	Finerenone	100	-	332	35	181	9.9	0.55	0.06
MDCKII-BCRP	Topotecan	2.0	-	8.2	1.3	214	13	26	4.5
MDCKII-BCRP	Topotecan	2.0	1	45	4.3	45	0.57	0.98	0.09
MDCKII-WT	Topotecan	2.0	-	28	1.4	78	3.7	2.8	0.19
MDCKII-WT	Topotecan	2.0	1	32	5.3	91	5.5	2.9	0.52

Test article: Finerenone

Table 16-5: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human efflux transporter BCRP

Location: 4.2.2.7.5
Report no.: PH-40885

Species:	Human	Route:	*in vitro*
Material:	MDCKII-BCRP cells	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio		
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.	% of control
Topotecan[a]	2	Control	0	5.4	0.4	124.3	9.5	23.1	2.50	100 ± S.D.
Topotecan[a]	2	Finerenone	0.1	5.0	0.2	122.8	15.1	24.3	3.11	105.3
Topotecan[a]	2	Finerenone	1	5.2	0.2	126.7	2.1	24.3	1.18	105.2
Topotecan[a]	2	Finerenone	3	5.5	0.2	115.5	4.3	20.9	1.19	90.4
Topotecan[a]	2	Finerenone	10	6.4	0.5	108.7	12.8	16.9	2.33	73.2
Topotecan[a]	2	Finerenone	30	9.2	1.0	85.0	6.7	9.2	1.25	39.9
Topotecan[a]	2	Finerenone	200	16.7	1.0	40.0	5.6	2.4	0.37	10.4
PhIP[b,c]	2	Control	0	51.7	5.7	642.8	19.8	12.4	1.41	100 ± S.D.
PhIP[b,c]	2	Finerenone	1	63.3	11.0	672.0	12.3	10.6	1.86	85.5
PhIP[b,c]	2	Finerenone	3	65.6	12.4	606.3	15.1	9.2	1.77	74.4
PhIP[b,c]	2	Finerenone	10	79.8	7.7	632.0	3.7	7.9	0.77	63.7
PhIP[b,c]	2	Finerenone	30	140.5	20.9	518.3	58.7	3.7	0.69	29.7
PhIP[b,c]	2	Finerenone	100	247.4	25.2	417.2	7.3	1.7	0.17	13.6
PhIP[b,c]	2	Finerenone	300	272.7	114.3	341.6	4.1	1.3	0.53	10.1

a = IC_{50} of finerenone (BAY 94-8862) against this probe substrate = 18.1 µM
b = 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine
c = IC_{50} of finerenone (BAY 94-8862) against this probe substrate = 17.4 µM

Test article: Finerenone

Table 16-6: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human efflux transporter BSEP using B-CLEAR®

Location: 4.2.2.7.6
Report no.: R-11129

Species:	Human	Route:	*in vitro*
Material:	Sandwich-cultured human hepatocytes	Nuclide:	-
Test compound:	Finerenone	Assay:	LC-MS/MS

Inhibitor	Inhibitor concentration	$CL_{Biliary}$[a]				BEI[b]			
	[µM]	[mL/min/kg]	S.D.	% control	S.D.	[%]	S.D.	% control	S.D.
MeOH control (0.1%)		0.675	0.11	100	16	80.1	3.1	100	3.8
Cyclosporine[c]	0.78	0.563	0.044	83.4	6.6	77.5	5.8	96.8	7.2
Cyclosporine[c]	1.56	0.435	0.065	64.4	9.6	69.1	4.0	86.3	5.0
Cyclosporine[c]	3.16	0.189	0.054	28.0	8.0	48.7	11	60.8	13
Cyclosporine[c]	6.25	0.142	0.061	21.0	9.1	46.6	15	58.2	18
Cyclosporine[c]	12.5	0.0867	0.029	12.8	4.3	40.0	11	49.9	14
Cyclosporine[c]	25	0.0144	0.035	2.13	5.1	8.71	22	10.9	28
DMSO control (0.1%)		0.475	0.060	100	13	72.2	3.0	100	4.1
Finerenone[d]	0.1	0.572	0.092	120	19	78.2	3.2	108	4.4
Finerenone[d]	0.3	0.551	0.034	116	7.2	78.2	3.1	108	4.3
Finerenone[d]	1	0.495	0.046	104	9.6	76.4	3.1	106	4.3
Finerenone[d]	3	0.516	0.073	109	15	77.7	5.0	108	6.9
Finerenone[d]	10	0.578	0.028	122	6.0	76.9	2.6	107	3.6
Finerenone[d]	30	0.578	0.13	122	27	73.6	9.7	102	13
Finerenone[d]	100	0.713	0.21	150	44	76.1	6.3	105	8.7

a = of probe substrate d8-taurocholic acid (d8-TCA) at a concentration of 5 µM
b = BEI = biliary excretion index [100 x Bile Accumulation / Total Accumulation (where, Bile Accumulation = Total Accumulation - Cellular Accumulation)]
c = IC_{50} of cyclosporine against d8-TCA as probe substrate = 1.82 µM
d = IC_{50} of finerenone (BAY 94-8862) against d8-TCA as probe substrate not reached in the investigated concentration range (IC_{50} >100 µM)

Test article: Finerenone

Table 16-7: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human efflux transporters MATE1 and MATE2K

Location: 4.2.2.7.7
Report no.: R-11196

Species: Human | Route: *in vitro*
Material: hMATE1, hMATE2K transfected HEK-cells, vector-HEK cells
Test compound: Finerenone | Assay: LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of metformin mediated by MATE1 [pmol/mg protein/min]							
					Vector-HEK		hMATE1-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Metformin[a]	50	10 min	Finerenone	0.5	8.25	0.62	1033	77	1024	77	6.49	8.66
Metformin[a]	50	10 min	Finerenone	5	9.25	1.55	995	35	985	35	10.1	5.8
Metformin[a]	50	10 min	-	-	7.70	0.78	1103	59	1096	59	-	-
Metformin[a]	50	10 min	Cimetidine	100	9.54	1.31	6.71	1.29	-2.82	1.84	100[b]	

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of metformin mediated by MATE2K [pmol/mg protein/min]							
					Vector-HEK		hMATE2K-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Metformin[a]	50	2 min	Finerenone	0.5	38.2	9.2	129	9	90.5	12.8	6.47	13.59
Metformin[a]	50	2 min	Finerenone	5	53.1	11.1	116	9	62.7	14.3	35.2	14.9
Metformin[a]	50	2 min	-	-	23.6	3.1	120	1	96.8	3.2	-	-
Metformin[a]	50	2 min	Pyrimethamine	1	66.8	20.5	43.7	7.6	-23.0	21.8	100[a]	

a = IC_{50} of finerenone (BAY 94-8862) against this probe substrate not reached in the investigated concentration range (IC_{50} >5 µM)
b = The calculated percentage inhibition was greater than 100 but the value of 100 is reported as the maximal value

Test article: Finerenone

Table 16-8: Pharmacokinetics: *In vitro* studies to evaluate substrate characteristics towards human uptake transporters OATP1B1 and OATP1B3

Location: 4.2.2.7.8
Report no.: R-9574

Species: Human Route: *in vitro*
Material: hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells
Test compound: [^{14}C]finerenone Assay: LSC

Test compound	Test concentration [µM]	Time [min]	Inhibitor rifampicin [µM]	Uptake mediated by OATP1B1 (pmol/mg protein/5 min) Vector-HEK cells Mean	Av.Dev.[a]	hOATP1B1 cells Mean	Av.Dev.[a]	Net uptake Mean	Av.Dev.[a]	Uptake ratio Mean
[^{14}C]finerenone	0.5	5	0	10	0.01	11	0.4	0.2	0.4	1
[^{14}C]finerenone	5	5	0	111	0.1	112	2.1	1.4	2.1	1
[^{14}C]finerenone	0.5	5	50	11	0.3	10	0.5	-0.5	0.3	1
[^{14}C]finerenone	5	5	50	105	1.9	105	0.6	-0.1	2.5	1
Uptake mediated by OATP1B1 (pmol/mg protein/min)										
[^{3}H]ES[b]	0.03	1	0	0.03	0.00	1.17	0.01	1.14	0.01	43
[^{3}H]ES[b]	0.03	1	50	0.03	0.00	0.23	0.00	0.20	0.00	8.9
Test compound	**Test concentration [µM]**	**Time [min]**	**Inhibitor rifampicin [µM]**	**Uptake mediated by OATP1B3 (pmol/mg protein/10 min) Vector-HEK cells Mean**	**Av.Dev.[a]**	**hOATP1B3 cells Mean**	**Av.Dev.[a]**	**Net uptake Mean**	**Av.Dev.[a]**	**Uptake ratio Mean**
[^{14}C]finerenone	0.5	10	0	12	0.9	12	0.4	-0.8	1.2	0.9
[^{14}C]finerenone	5	10	0	121	1	114	7	-7	8.1	0.9
[^{14}C]finerenone	0.5	10	5	13	0.01	12	0.7	-0.9	0.7	0.9
[^{14}C]finerenone	5	10	5	120	1	114	7	-6.4	8.7	0.9
Uptake mediated by OATP1B3 (pmol/mg protein/min)										
[^{3}H]BSP[c]	0.05	7	0	0.31	0.02	1.24	0.13	0.93	0.11	4
[^{3}H]BSP[c]	0.05	7	5	0.33	0.01	0.43	0.02	0.11	0.01	1.3

a = average deviation
b = estrone-3-sulfate
c = bromosulfophthalein

Test article: Finerenone

Table 16-9: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human uptake transporters OATP1B1 and OATP1B3 in a preincubation assay

Location: 4.2.2.7.9
Report no.: PH-40952

Species:	Human	Route:	*in vitro*
Material:	hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells		
Test compound:	Finerenone	Assay:	LC-MS/MS

Uptake of pravastatin mediated by OATP1B1 (pmol/mg protein/min)										
Inhibitor	**Inhibitor concentration**	**Vector-HEK cells**		**hOATP1B1 cells**		**Net uptake**		**Uptake ratio**		**% of net uptake**
	[µM]	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**[%]**
Finerenone[a]	0	0.58	0.02	19.87	1.48	19.29	1.48	34.00	2.82	100
Finerenone[a]	0.2	0.87	0.07	19.25	0.35	18.38	0.36	22.23	1.85	95.3
Finerenone[a]	0.5	0.52	0.09	16.09	1.24	15.57	1.24	31.23	5.92	80.7
Finerenone[a]	2	0.62[b]	n.c.[c]	12.10	0.95	11.48	0.95	19.53	1.54	59.5
Finerenone[a]	5	0.48[b]	n.c.[c]	7.10	0.71	6.62	0.71	14.92	1.49	34.3
Finerenone[a]	10	0.51	0.07	4.49	0.68	3.97	0.68	8.75	1.75	20.6
Uptake of pravastatin mediated by OATP1B3 (pmol/mg protein/min)										
Inhibitor	**Inhibitor concentration**	**Vector-HEK cells**		**hOATP1B3 cells**		**Net uptake**		**Uptake ratio**		**% of net uptake**
	[µM]	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**[%]**
Finerenone[d]	0	1.21	0.06	33.72	0.87	32.51	0.87	27.91	1.59	100
Finerenone[d]	0.2	1.26	0.18	31.42	2.77	30.16	2.78	24.93	4.11	92.8
Finerenone[d]	0.5	1.16	0.12	25.82	1.34	24.66	1.35	22.29	2.60	75.9
Finerenone[d]	2	1.19	0.06	21.48	1.25	20.29	1.25	18.04	1.43	62.4
Finerenone[d]	5	1.02	0.15	17.21	0.48	16.19	0.51	16.91	2.52	49.8
Finerenone[d]	10	0.99	0.15	18.25	1.01	17.27	1.02	18.49	2.95	53.1

a = IC_{50} of finerenone (BAY 94-8862) against pravastatin (5 µM) as probe substrate = 3.2 µM
b = n = 1
c = not calculated
d = IC_{50} of finerenone (BAY 94-8862) against pravastatin (5 µM) as probe substrate not reached in the investigated concentration range (IC_{50} >10 µM)

Test article: Finerenone

Table 16-10: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human uptake transporters OAT1 and OAT3

Location: 4.2.2.7.10
Report no.: R-9494

Species:	Human	Route:	*in vitro*
Material:	hOAT1, hOAT3 transfected HEK-cells, vector-HEK cells		
Test compound:	Finerenone	Assay:	LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of PAH[a] mediated by OAT1 [pmol/mg protein/min] Vector-HEK Mean	Vector-HEK S.D.	hOAT1-HEK Mean	hOAT1-HEK S.D.	Net uptake Mean	Net uptake S.D.	Inhibition [%] Mean	Inhibition [%] S.D.
PAH[a,b]	10	5 min	Finerenone	0.3	0.944	0.203	590	19	589	19	-18.9	5.0
PAH[a,b]	10	5 min	Finerenone	3	1.17	0.18	519	23	518	23	-4.6	5.7
PAH[a]	10	5 min	-	-	0.704	0.143	496	14	495	14	-	-
PAH[a]	10	5 min	Probenecid	100	1.49	0.16	54	2.7	52.5	2.7	89.4	0.7

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of furosemide mediated by OAT3 [pmol/mg protein/min] Vector-HEK Mean	Vector-HEK S.D.	hOAT3-HEK Mean	hOAT3-HEK S.D.	Net uptake Mean	Net uptake S.D.	Inhibition [%] Mean	Inhibition [%] S.D.
Furosemide[b]	5	5 min	Finerenone	0.3	2.28	0.23	327	14	325	14	-27.3	7.5
Furosemide[b]	5	5 min	Finerenone	3	2.41	0.08	290	9	287	9	-12.6	5.9
Furosemide	5	5 min	-	-	1.89	0.16	257	10	255	10	-	-
Furosemide	5	5 min	Probenecid	100	2.01	0.21	3.32	0.18	1.30	0.28	99.5	0.1

a = p-aminohippuric acid
b = IC_{50} of finerenone (BAY 94-8862) against this probe substrate not reached in the investigated concentration range (IC_{50} >3 µM)

Test article: Finerenone

Table 16-11: Pharmacokinetics: *In vitro* studies to evaluate substrate characteristics towards human uptake transporter OCT1

Location: 4.2.2.7.11
Report no.: R-9495

Species:	Human	Route:	*in vitro*
Material:	hOCT1 transfected HEK-cells, vector-HEK cells		
Test compound:	Finerenone	Assay:	LC-MS/MS

Test compound	Conc. [µM]	Incubation time	Influx rate [pmol/mg protein /min] Vector-HEK Mean	Vector-HEK S.D.	hOCT1-HEK Mean	hOCT1-HEK S.D.	Uptake ratio Mean	Uptake ratio S.D.
Finerenone	0.1	2 min	1.37	0.02	1.46	0.04	1.07	0.04
Finerenone	0.1	5 min	0.663	0.011	0.664	0.031	1.00	0.05
Finerenone	0.1	10 min	0.317	0.005	0.348	0.022	1.10	0.07
Finerenone	0.5	2 min	6.47	0.21	7.21	0.21	1.11	0.05
Finerenone	0.5	5 min	3.04	0.03	3.16	0.21	1.04	0.07
Finerenone	0.5	10 min	1.56	0.04	1.67	0.03	1.07	0.03
MPP^{+} [a]	5	2 min	6.55	0.75	230	5	35.1	4.1

a = 1-methyl-4-phenylpyridinium

Test article: Finerenone

Table 16-12: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human uptake transporter OCT1

Location: 4.2.2.7.11
Report no.: R-9495

Species:	Human	Route:	*in vitro*
Material:	hOCT1 transfected HEK-cells, vector-HEK cells		
Test compound:	Finerenone	Assay:	LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of MPP+ [a] mediated by OCT1 [pmol/mg protein/min] Vector-HEK Mean	Vector-HEK S.D.	hOCT1-HEK Mean	hOCT1-HEK S.D.	Net uptake Mean	Net uptake S.D.	Inhibition [%] Mean	Inhibition [%] S.D.
MPP+ [a,b]	5	2 min	Finerenone	0.5	16.2	0.7	398	38	382	38	-40.5	16.7
MPP+ [a,b]	5	2 min	Finerenone	5	13.7	0.8	359	48	345	48	-26.9	21.9
MPP+ [a]	5	2 min	-	-	12.1	1.2	284	17	272	17	-	-
MPP+ [a]	5	2 min	Repaglinide	600	6.85	0.79	56.5	6.2	49.9	6.3	81.7	3.4

a = 1-methyl-4-phenylpyridinium
b = IC_{50} of finerenone (BAY 94-8862) against this probe substrate not reached in the investigated concentration range (IC_{50} >5 µM)

Test article: Finerenone

Table 16-13: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human uptake transporter OCT2

Location: 4.2.2.7.12
Report no.: R-9440

Species:	Human	Route:	*in vitro*
Material:	hOCT2 transfected HEK-cells, vector-HEK cells		
Test compound:	Finerenone	Assay:	LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of MPP+ [a] mediated by OCT2 [pmol/mg protein/min] Vector-HEK Mean	Vector-HEK S.D.	hOCT2-HEK Mean	hOCT2-HEK S.D.	Net uptake Mean	Net uptake S.D.	Inhibition [%] Mean	Inhibition [%] S.D.
MPP+ [a,b]	5	2 min	Finerenone	0.3	15.9	0.9	309	14	293	14	3.66	5.39
MPP+ [a,b]	5	2 min	Finerenone	3	17.8	1.0	318	24	300	24	1.14	8.34
MPP+ [a]	5	2 min	-	-	8.09	0.35	312	9	304	9	-	-
MPP+ [a]	5	2 min	Imipramine	300	4.56	1.20	25.3	0.9	20.7	1.5	93.2	0.6

a = 1-methyl-4-phenylpyridinium
b = IC_{50} of finerenone (BAY 94-8862) against this probe substrate not reached in the investigated concentration range (IC_{50} >3 µM)

Test article: Finerenone

Table 16-14: Pharmacokinetics: Atropisomer ratio [%] in *in vitro* incubations of finerenone in pooled liver microsomes

Location: 4.2.2.4.1
Report no.: PH-41146

Material:	Pooled liver microsomes	Route:	*in vitro*
Test compound:	Finerenone	Assay:	LC-MS/MS
Table:	Atropisomer ratio [%] of M-1a : M-1b, M-2a : M-2b and M-3a : M-3b after *in vitro* incubations in liver microsomes of mouse, rat, dog and human (1 µM, except dog: 2 µM)		

Species	**Human**	**Wistar rat**		**CD-1 mice**		**Beagle dog**
Gender	**Mix**	**Male**	**Female**	**Male**	**Female**	**Female**
Turnover finerenone	62.9	68.0	5.17	68.6	63.6	30.9
M-1a	94.6	95.5	82.0	96.7	91.4	92.5
M-1b	5.41	4.46	18.0	3.28	8.60	7.50
M-2a	96.2	96.8	86.7	97.0	93.8	91.9
M-2b	3.83	3.20	13.3	2.96	6.21	8.11
M-3a	n.a.[a]	93.7	n.a.[a]	n.a.[a]	96.5	n.a.[a]
M-3b	n.a.[a]	6.33	n.a.[a]	n.a.[a]	3.49	n.a.[a]

a = not applicable

Test article: Finerenone

Table 16-15: Pharmacokinetics: Atropisomer ratio [%] after single dose, rat

Location: 4.2.2.7.16
Report no.: PH-40365

Test compound: [^{14}C]finerenone Assay: LC-MS/MS, HPLC-LSC
Table: Atropisomer ratio [%] of M-1a : M-1b, M-2a : M-2b and M-3a : M-3b after single oral dose administration of 10 mg/kg b.w. [^{14}C]finerenone to 3 male Wistar rats

Species		**Rat**	
Matrix	**Plasma[a]**	**Urine[b]**	**Feces[a]**
Duration		**0-72 h**	**0-72 h**
M-1a : M-1b	n.a.[c]	85.6 : 14.4	88.3 : 11.7
M-2a : M-2b	n.a.[c]	93.2 : 6.8	94.1 : 5.9
M-3a : M-3b	n.a.[c]	88.2 : 11.8	87.3 : 12.7

a = LC-MS/MS
b = HPLC-LSC
c = not applicable

Test article: Finerenone

Table 16-16: Pharmacokinetics: Atropisomer ratio [%] after single dose, dog

Location: 4.2.2.7.17
Report no.: PH-40326

Test compound: [^{14}C]finerenone Assay: LC-MS/MS, HPLC-LSC
Table: Atropisomer ratio [%] of M-1a : M-1b; M-2a : M-2b and M-3a : M-3b after single oral dose administration of 3 mg/kg b.w. [^{14}C]finerenone to 4 female Beagle dogs [study No. I 4852-9/B]

Species		**Dog**	
Matrix	**Plasma[a]**	**Urine[b]**	**Feces[a]**
Duration	**AUC(0-48)**	**0-72 h**	**0-72 h**
M-1a : M-1b	91.2 : 8.8	89.3 : 10.7	86.6 : 13.4
M-2a : M-2b	89.1 : 10.9	81.3 : 18.7	87.1 : 12.9
M-3a : M-3b	90.7 : 9.3	83.7 : 16.3	84.3 : 15.7

a = LC-MS/MS
b = HPLC-LSC

Test article: Finerenone

Table 16-17: Pharmacokinetics: Atropisomer ratio [%] after single dose, human

Location: 4.2.2.7.18
Report no.: PH-40373

Test compound: [^{14}C]finerenone Assay: LC-MS/MS, LC-HRMS
Table: Atropisomer ratio [%] of M-1a : M-1b, M-2a : M-2b and M-3a : M-3b after single oral dose administration of 10 mg [^{14}C]finerenone to 4 healthy male subjects [study No. 14502]

Species		**Human**	
Matrix	**Plasma[a,c]**	**Urine[b,d]**	**Feces[a,d]**
Duration	**AUC(0-48)**	**0-48 h**	**0-96 h**
M-1a : M-1b	79.3 : 20.7	n.a.[e]	86.0 : 14.0
M-2a : M-2b	94.6 : 5.4	93.9 : 6.1	91.6 : 8.4
M-3a : M-3b	99.1 : 0.9	97.8 : 2.2	78.7 : 21.3

a = LC-MS/MS, plasma: geometric mean, feces: arithmetic mean
b = LC-HRMS, arithmetic mean based on total excretion
c = calculation based on geometric mean AUC, source: 4.2.2.4.11, PH-39577
d = calculation based on arithmetic excreted amounts, source: 4.2.2.4.11, PH-39577
e = not applicable

Test article: Finerenone

Table 16-18: Pharmacokinetics: Atropisomer ratio [%] after repeated administration, rat

Location: 4.2.2.2.5
Report no.: PH-39791

Test compound: Finerenone Assay: LC-MS/MS
Table: Atropisomer ratio [%] of metabolites M-1a : M-1b, M-2a : M-2b and M-3a : M-3b on day 7 after repeated daily oral administration of 30 mg/kg finerenone to 3 male and 3 female Wistar rats for 7 days

Species	**Rat**	
Matrix	**Plasma**	
Duration	**AUC(0-24)**	
Gender	**Male**	**Female**
M-1a : M-1b	96.2 : 3.8	84.4 : 15.6
M-2a : M-2b	94.9 : 5.1	87.8 : 12.2
M-3a : M-3b	89.6 : 10.4	89.4 : 10.6

Test article: Finerenone

Table 16-19: Pharmacokinetics: Atropisomer ratio [%] after repeated administration, human

Location: 4.2.2.7.19
Report no.: PH-40388

Test compound: Finerenone Assay: LC-MS/MS
Table: Atropisomer ratio of M-1a : M-1b, M-2a : M-2b and M-3a : M-3b on day 10 after multiple oral dose administration of 40 mg QD finerenone to 9 healthy male subjects [study No. 13785]

Species	**Human**			
Matrix	**Plasma[a]**	**Plasma[a]**	**Plasma[a]**	**Plasma[a]**
Parameter	**$AUC_{\tau,md}$[b]**	**C(2 h post dose)**	**C(3 h post dose)**	**C(6 h post dose)**
M-1a : M-1b	83.1 : 16.9	89.7 : 10.3	89.1 : 10.9	86.3 : 13.7
M-2a : M-2b	95.3 : 4.7	96.7 : 3.3	96.8 : 3.2	96.6 : 3.4
M-3a : M-3b	98.0 : 2.0	98.7 : 1.3	98.8 : 1.2	98.8 : 1.2

a = geometric mean
b = $AUC_{\tau,md} = C_{pool} \times 24$ h; The pooled samples were prepared according to the method in which appropriate aliquots of the plasma samples obtained from all time points at steady state in the dosing interval within 24 h

Test article: Finerenone

Table 16-20: Pharmacokinetics: Plasma protein binding of metabolites *in vitro*

Location: 4.2.2.7.13, 4.2.2.7.15, 4.2.2.7.14
Report no.: A50452, A56949, PH-38807

Test compound: [^{3}H]BAY 1117267 (M-1a) Method: Ultrafiltration
Analyte: Radioactivity Assay: LSC
Table: Binding of BAY 1117267 (M-1a) to plasma proteins in different species, William's medium and human liver microsomes *in vitro*

Species / strain / Test system	Gender / N[a]	Matrix	Concentration [µg/L]	Fraction bound [%]	Fraction unbound [%]
Human / Caucasian	Male / 3	Plasma	45.9 - 4398	94.2	5.82
Dog / Beagle	Female / 3	Plasma	44.8 - 4488	88.8	11.2
Rat / Wistar	Male / 3	Plasma	47.0 - 4321	94.0	6.01
Mouse / CD-1	Male / 3	Plasma	48.4 - 4463	85.3	14.7
Rabbit / CHBB:HM	Female / 3	Plasma	46.0 - 4673	97.8	2.17
William's medium 10% FCS[b]	n.a.[c] / 3	Dissolved in buffer	65.7 - 6714	26.9	73.1
Human liver microsomes (0.05 mg/mL)	n.a.[c] / 3	-	571 - 14901	8.9	91.1
Human liver microsomes (0.1 mg/mL)	n.a.[c] / 3	-	584 - 14705	15.2	84.8
Human liver microsomes (0.5 mg/mL)	n.a.[c] / 3	-	604 - 14882	33.8	66.2

a = number of determinations / concentration
b = William's medium containing 10% fetal calf serum
c = not applicable

Test article: Finerenone

Table 16-21: Pharmacokinetics: Blood Cell/ Plasma Partitioning of metabolites *in vitro*

Location: 4.2.2.7.13
Report no.: A50452

Test compound: [^{3}H]BAY 1117267 (M-1a) Assay: LSC
Analyte: Radioactivity
Table: Determination of blood/plasma partitioning of BAY 1117267 (M-1a) *in vitro*

Species / strain	Gender / N[a]	Conc. in blood (C_b) [µg/L]	Conc. in plasma (C_p) [µg/L]	C_b/C_p
Human / Caucasian	Male / 3	43.5 - 4200	75.0 - 6611	0.609
Dog / Beagle	Female / 3	48.6 - 4602	81.7 - 6649	0.623
Rat / Wistar	Male / 3	48.6 - 4047	74.0 - 6176	0.653

a = number of determinations / concentration

Test article: Finerenone

Table 16-22: Pharmacokinetics: Plasma protein binding of metabolites *in vitro*

Location: 4.2.2.7.14
Report no.: PH-38807

Test compound: [^{14}C]BAY 1117266 (M-1b) Method: Ultrafiltration
Analyte: Radioactivity Assay: LSC
Table: Binding of BAY 1117266 (M-1b) to plasma proteins in different species, William's medium and human liver microsomes *in vitro*

Species / strain / Test system	Gender / N[a]	Matrix	Concentration [µg/L]	Fraction bound [%]	Fraction unbound [%]
Human / Caucasian	Male / 3	Plasma	37.0 - 4620	96.1	3.88
Dog / Beagle	Female / 3	Plasma	36.7 - 485	93.6	6.36
Dog / Beagle	Female / 3	Plasma	4090 - 4180	89.2	10.8
Rat / Wistar	Male / 3	Plasma	37.4 - 4080	88.9	11.1
Mouse / CD-1	Male / 3	Plasma	41.8 - 4430	87.9	12.1
Rabbit / CHBB:HM	Female / 1	Plasma	43.2 - 4330	98.8	1.25
William's medium 10% FCS[b]	n.a.[c] / 3	Dissolved in buffer	38.1 - 4599	77.6	22.4
Human liver microsomes (0.05 mg/mL)	n.a.[c] / 3	-	340 - 6623	10.9	89.1
Human liver microsomes (0.1 mg/mL)	n.a.[c] / 3	-	354 - 6667	15.8	84.2
Human liver microsomes (0.5 mg/mL)	n.a.[c] / 3	-	369 - 7044	42.0	58.0

a = number of determinations / concentration
b = William's medium containing 10% fetal calf serum
c = not applicable

Test article: Finerenone

Table 16-23: Pharmacokinetics: Plasma protein binding of metabolites *in vitro*

Location: 4.2.2.7.13, 4.2.2.7.15, 4.2.2.7.14
Report no.: A50452, A56949, PH-38807

Test compound: [^{3}H]BAY 1117268 (M-2a) Method: Ultrafiltration
Analyte: Radioactivity Assay: LSC
Table: Binding of BAY 1117268 (M-2a) to plasma proteins in different species, William's medium and human liver microsomes *in vitro*

Species / strain / Test system	Gender / N[a]	Matrix	Concentration [µg/L]	Fraction bound [%]	Fraction unbound [%]
Human / Caucasian	Male / 3	Plasma	48.6 - 4297	82.6	17.4
Dog / Beagle	Female / 3	Plasma	51.5 - 4661	51.7	48.3
Rat / Wistar	Male / 3	Plasma	50.7 - 4552	54.6	45.4
Mouse / CD-1	Male / 3	Plasma	50.7 - 4344	42.0	58.0
Rabbit / CHBB:HM	Female / 3	Plasma	51.0 - 4907	62.4	37.6
William's medium 10% FCS[b]	n.a.[c] / 3	Dissolved in buffer	36.7 - 4458	16.8	83.2
Human liver microsomes (0.05 mg/mL)	n.a.[c] / 3	-	499 - 10530	7.1	92.9
Human liver microsomes (0.1 mg/mL)	n.a.[c] / 3	-	481 - 10768	8.5	91.5
Human liver microsomes (0.5 mg/mL)	n.a.[c] / 3	-	508 - 11607	17.2	82.8

a = number of determinations / concentration
b = William's medium containing 10% fetal calf serum
c = not applicable

Test article: Finerenone

Table 16-24: Pharmacokinetics: Blood Cell/ Plasma Partitioning of metabolites *in vitro*

Location: 4.2.2.7.13
Report no.: A50452

Test compound: [^{3}H]BAY 1117268 (M-2a) Assay: LSC
Analyte: Radioactivity
Table: Determination of blood/plasma partitioning of BAY 1117268 (M-2a) *in vitro*

Species / strain	**Gender / N[a]**	**Conc. in blood (C_b) [µg/L]**	**Conc. in plasma (C_p) [µg/L]**	**C_b/C_p**
Human / Caucasian	Male / 3	46.1 - 3561	65.1 - 4869	0.713
Dog / Beagle	Female / 3	45.7 - 4141	47.7 - 4432	0.941
Rat / Wistar	Male / 3	47.5 - 4432	48.1 - 3865	0.970

a = number of determinations / concentration

Test article: Finerenone

Table 16-25: Pharmacokinetics: Plasma protein binding of metabolites *in vitro*

Location: 4.2.2.7.13, 4.2.2.7.15, 4.2.2.7.14
Report no.: A50452, A56949, PH-38807

Test compound: [^{3}H]BAY 1117271 (M-3a) Method: Ultrafiltration
Analyte: Radioactivity Assay: LSC
Table: Binding of BAY 1117271 (M-3a) to plasma proteins in different species, William's medium and human liver microsomes *in vitro*

Species / strain / Test system	Gender / N[a]	Matrix	Concentration [µg/L]	Fraction bound [%]	Fraction unbound [%]
Human / Caucasian	Male / 3	Plasma	35.1 - 3408	32.2	67.8
Dog / Beagle	Female / 3	Plasma	39.8 - 3834	24.7	75.3
Rat / Wistar	Male / 3	Plasma	37.2 - 3846	25.9	74.1
Mouse / CD-1	Male / 3	Plasma	45.0 - 4186	17.6	82.4
Rabbit / CHBB:HM	Female / 3	Plasma	48.2 - 4485	23.9	76.1
William's medium 10% FCS[b]	n.a.[c] / 3	Dissolved in buffer	44.4 - 4582	10.2	89.8
Human liver microsomes (0.05 mg/mL)	n.a.[c] / 3	-	356 - 7740	6.6	93.4
Human liver microsomes (0.1 mg/mL)	n.a.[c] / 3	-	374 - 7598	7.2	92.8
Human liver microsomes (0.5 mg/mL)	n.a.[c] / 3	-	387 - 7838	16.2	83.8

a = number of determinations / concentration
b = William's medium containing 10% fetal calf serum
c = not applicable

Test article: Finerenone

Table 16-26: Pharmacokinetics: Blood Cell/ Plasma Partitioning of metabolites *in vitro*

Location: 4.2.2.7.13
Report no.: A50452

Test compound: [^{3}H]BAY 1117271 (M-3a) Assay: LSC
Analyte: Radioactivity
Table: Determination of Blood/Plasma Partitioning of BAY 1117271 (M-3a) *in vitro*

Species / strain	**Gender / N[a]**	**Conc. in blood (C_b) [µg/L]**	**Conc. in plasma (C_p) [µg/L]**	**C_b/C_p**
Human / Caucasian	Male / 3	26.9 - 3250	35.0 - 4383	0.754
Dog / Beagle	Female / 3	25.9 - 3214	33.3 - 4293	0.764
Rat / Wistar	Male / 3	32.0 - 3663	41.5 - 4797	0.760

a = number of determinations / concentration

Test article: Finerenone

Table 16-27: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms

Location: 4.2.2.7.20, 4.2.2.4.4, 4.2.2.4.5
Report no.: PH-37685, PH-40971, PH-40973

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes, recombinant CYP1A1, 2E1	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS
Table:	Inhibitory effects of M-1a on formation of metabolites of standard probes mediated by cytochrome P450 isoforms		

CYP isoform	Probe reaction	Reversible Inhibition IC_{50} [µM]	30-Minute pre-incubation without NADPH IC_{50} [µM]	30-Minute pre-incubation with NADPH IC_{50} [µM]	Potential for TDI
1A1	Granisetron 7-hydroxylation	30	35	23	Yes[b]
1A2	Phenacetin *O*-deethylation	>50	>50	>50	No
2A6	Coumarin 7-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
2B6	Bupropion hydroxylation	>50	>50	>50	No
2C8	Amodiaquine *N*-deethylation	>50	35	35	No
2C9	Diclofenac 4'-hydroxylation	25	16	13	No
2C19	Mephenytoin 4'-hydroxylation	>50	>50	>50	No
2D6	Dextromethorphan *O*-demethylation	>50	>50	>50	No
2E1	Chlorzoxazone 6-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
3A4	Midazolam 1'-hydroxylation	>50	n.a.[a]	>50	No
3A4	Testosterone 6β-hydroxylation	>50	n.a.[a]	>50	No

a = not applicable
b = no investigations on mechanism-based inhibition performed

Test article: Finerenone

Table 16-28: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms

Location: 4.2.2.7.20, 4.2.2.4.4, 4.2.2.4.5
Report no.: PH-37685, PH-40971, PH-40973

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes, recombinant CYP1A1, 2E1	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS
Table:	Inhibitory effects of M-1b on formation of metabolites of standard probes mediated by cytochrome P450 isoforms		

CYP isoform	Probe reaction	Reversible Inhibition IC_{50} [µM]	30-Minute pre-incubation without NADPH IC_{50} [µM]	30-Minute pre-incubation with NADPH IC_{50} [µM]	Potential for TDI
1A1	Granisetron 7-hydroxylation	29	32	13	Yes[b]
1A2	Phenacetin *O*-deethylation	>50	>50	>50	No
2A6	Coumarin 7-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
2B6	Bupropion hydroxylation	>50	>50	>50	No
2C8	Amodiaquine *N*-deethylation	>50	42	32	No
2C9	Diclofenac 4'-hydroxylation	>50	>50	>50	No
2C19	Mephenytoin 4'-hydroxylation	>50	>50	>50	No
2D6	Dextromethorphan *O*-demethylation	>50	>50	>50	No
2E1	Chlorzoxazone 6-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
3A4	Midazolam 1'-hydroxylation	>50	n.a.[a]	>50	No
3A4	Testosterone 6β-hydroxylation	>50	n.a.[a]	>50	No

a = not applicable
b = no investigations on mechanism-based inhibition performed

Test article: Finerenone

Table 16-29: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms

Location: 4.2.2.7.20, 4.2.2.4.4, 4.2.2.4.5
Report no.: PH-37685, PH-40971, PH-40973

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes, recombinant CYP1A1, 2E1	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS
Table:	Inhibitory effects of M-2a on formation of metabolites of standard probes mediated by cytochrome P450 isoforms		

CYP isoform	Probe reaction	Reversible Inhibition IC_{50} [µM]	30-Minute pre-incubation without NADPH IC_{50} [µM]	30-Minute pre-incubation with NADPH IC_{50} [µM]	Potential for TDI
1A1	Granisetron 7-hydroxylation	>50	>50	>50	No
1A2	Phenacetin *O*-deethylation	>50	>50	>50	No
2A6	Coumarin 7-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
2B6	Bupropion hydroxylation	>50	>50	>50	No
2C8	Amodiaquine *N*-deethylation	>50	>50	>50	No
2C9	Diclofenac 4'-hydroxylation	>50	>50	>50	No
2C19	Mephenytoin 4'-hydroxylation	>50	>50	>50	No
2D6	Dextromethorphan *O*-demethylation	>50	>50	>50	No
2E1	Chlorzoxazone 6-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
3A4	Midazolam 1'-hydroxylation	>50	n.a.[a]	>50	No
3A4	Testosterone 6β-hydroxylation	>50	n.a.[a]	>50	No

a = not applicable

Test article: Finerenone

Table 16-30: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms

Location: 4.2.2.7.20, 4.2.2.4.4, 4.2.2.4.5
Report no.: PH-37685, PH-40971, PH-40973

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes, recombinant CYP1A1, 2E1	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Inhibitory effects of M-3a on formation of metabolites of standard probes mediated by cytochrome P450 isoforms		

CYP isoform	Probe reaction	Reversible Inhibition IC_{50} [µM]	30-Minute pre-incubation without NADPH IC_{50} [µM]	30-Minute pre-incubation with NADPH IC_{50} [µM]	Potential for TDI
1A1	Granisetron 7-hydroxylation	>50	>50	>50	Yes[b]
1A2	Phenacetin *O*-deethylation	>50	>50	>50	No
2A6	Coumarin 7-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
2B6	Bupropion hydroxylation	>50	>50	>50	No
2C8	Amodiaquine *N*-deethylation	>50	>50	>50	No
2C9	Diclofenac 4'-hydroxylation	>50	>50	>50	No
2C19	Mephenytoin 4'-hydroxylation	>50	>50	>50	No
2D6	Dextromethorphan *O*-demethylation	>50	>50	>50	No
2E1	Chlorzoxazone 6-hydroxylation	>50	n.a.[a]	n.a.[a]	n.a.[a]
3A4	Midazolam 1'-hydroxylation	30	n.a.[a]	>50	No
3A4	Testosterone 6β-hydroxylation	>50	n.a.[a]	>50	No

a = not applicable
b = no investigations on mechanism-based inhibition performed; probe reaction was ~90% of control without NADPH but ~58% of control with NADPH in presence of M-3a at 50 µM

Test article: Finerenone

Table 16-31: Pharmacokinetics: Inhibitory potential of metabolites towards human UGT isoforms

Location: 4.2.2.7.21
Report no.: PH-40043

Species / strain:	Human / n.a.[a]	Route:	*in vitro*
Material:	Liver microsomes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Inhibitory effects of M-1a, M-1b, M-2a and M-3a on formation of metabolites of standard probes mediated by UGT isoforms		

UGT isoform	Substrate	M-1a IC_{50} [µM]	M-1b IC_{50} [µM]	M-2a IC_{50} [µM]	M-3a IC_{50} [µM]
1A1	Estradiol	>50	>50	>50	>50
1A4	Trifluoperazine	>50	>50	>50	>50
1A6	α-Naphthol	>50	>50	>50	>50
1A9	Propofol	>50	>50	>50	>50
2B4	1'-Hydroxymidazolam	>50	>50	>50	>50
2B7	Tarenflurbil	>50	>50	>50	>50

a = not applicable

Test article: Finerenone

Table 16-32: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1a (FDA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$1+[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.047	13.7[d]	1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP1A2	Basic	0.047	>16.6[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2A6	Basic	0.047	>22.8[f]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2B6	Basic	0.047	>16.6[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C8	Basic	0.047	>22.8[f]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C9	Basic	0.047	11.4[g]	1.004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C19	Basic	0.047	>16.6[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2D6	Basic	0.047	>16.6[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2E1	Basic	0.047	>16.6[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/midazolam	Basic	0.047	>22.8[f]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/testosterone	Basic	0.047	>22.8[f]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A1	Basic	0.047	>21.2[h]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A4	Basic	0.047	>21.2[h]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A6	Basic	0.047	>22.8[f]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A9	Basic	0.047	>21.2[h]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B4	Basic	0.047	>21.2[h]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B7	Basic	0.047	>21.2[h]	<1.002	$1+[I]_{max,u}/K_i \geq 1.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020
b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition
c = M-1a was not dosed orally; therefore, only systemic DDIs are assessed
d = Unbound K_i for CYP1A1 (13.7 µM; K_i = 15 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.911))
e = Unbound K_i (>16.6 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.662; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.662))
f = Unbound K_i (>22.8 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.911)
g = Unbound K_i (11.4 µM; K_i = 12.5 µM; unbound fraction in 0.05 mg/mL microsomes = 0.911)
h = Unbound K_i (>21.2 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.848)
Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1a calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-1a total $[I]_{max}$ = 0.80 µM [302 µg/L] and unbound fraction = 0.0582); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase
Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

Test article: Finerenone

Table 16-33: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1a (EMA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.047	13.7[d]	0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP1A2	Basic	0.047	>16.6[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2A6	Basic	0.047	>22.8[f]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
CYP2B6	Basic	0.047	>16.6[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C8	Basic	0.047	>22.8[f]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
CYP2C9	Basic	0.047	11.4[g]	0.004	$[I]_{max,u}/K_i \geq 0.02$
CYP2C19	Basic	0.047	>16.6[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2D6	Basic	0.047	>16.6[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2E1	Basic	0.047	>16.6[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/midazolam	Basic	0.047	>22.8[f]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/testosterone	Basic	0.047	>22.8[f]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT1A1	Basic	0.047	>21.2[h]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT1A4	Basic	0.047	>21.2[h]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT1A6	Basic	0.047	>22.8[f]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT1A9	Basic	0.047	>21.2[h]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT2B4	Basic	0.047	>21.2[h]	<0.002	$[I]_{max,u}/K_i \geq 0.02$
UGT2B7	Basic	0.047	>21.2[h]	<0.002	$[I]_{max,u}/K_i \geq 0.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-1a was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i for CYP1A1 (13.7 µM; K_i = 15 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.911))

e = Unbound K_i (>16.6 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.662; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.662))

f = Unbound K_i (>22.8 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.911)

g = Unbound K_i (11.4 µM; K_i = 12.5 µM; unbound fraction in 0.05 mg/mL microsomes = 0.911)

h = Unbound K_i (>21.2 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.848)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1a calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-1a total $[I]_{max}$ = 0.80 µM [302 µg/L] and unbound fraction = 0.0582); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

Test article: Finerenone

Table 16-34: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1b (FDA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$1+[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.0063	12.9[d]	1.0005	$1+[I]_{max,u}/K_i \geq 1.02$
CYP1A2	Basic	0.0063	>14.5[e]	<1.0004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2A6	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2B6	Basic	0.0063	>14.5[e]	<1.0004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C8	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C9	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C19	Basic	0.0063	>14.5[e]	<1.0004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2D6	Basic	0.0063	>14.5[e]	<1.0004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2E1	Basic	0.0063	>14.5[e]	<1.0004	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/midazolam	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/testosterone	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A1	Basic	0.0063	>21.1[g]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A4	Basic	0.0063	>21.1[g]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A6	Basic	0.0063	>22.3[f]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A9	Basic	0.0063	>21.1[g]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B4	Basic	0.0063	>21.1[g]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B7	Basic	0.0063	>21.1[g]	<1.0003	$1+[I]_{max,u}/K_i \geq 1.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-1b was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i for CYP1A1 (12.9 µM; K_i = 14.5 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.891))

e = Unbound K_i (>14.5 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.580; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.580))

f = Unbound K_i (>22.3 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.891)

g = Unbound K_i (>21.1 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.842)

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1b in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1b calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-1b total $[I]_{max}$ = 0.16 µM [61.5 µg/L] and unbound fraction = 0.0388); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

Test article: Finerenone

Table 16-35: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1b (EMA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.0063	12.9[d]	0.0005	$[I]_{max,u}/K_i \geq 0.02$
CYP1A2	Basic	0.0063	>14.5[e]	<0.0004	$[I]_{max,u}/K_i \geq 0.02$
CYP2A6	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
CYP2B6	Basic	0.0063	>14.5[e]	<0.0004	$[I]_{max,u}/K_i \geq 0.02$
CYP2C8	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C9	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C19	Basic	0.0063	>14.5[e]	<0.0004	$[I]_{max,u}/K_i \geq 0.02$
CYP2D6	Basic	0.0063	>14.5[e]	<0.0004	$[I]_{max,u}/K_i \geq 0.02$
CYP2E1	Basic	0.0063	>14.5[e]	<0.0004	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/midazolam	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/testosterone	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A1	Basic	0.0063	>21.1[g]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A4	Basic	0.0063	>21.1[g]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A6	Basic	0.0063	>22.3[f]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A9	Basic	0.0063	>21.1[g]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT2B4	Basic	0.0063	>21.1[g]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$
UGT2B7	Basic	0.0063	>21.1[g]	<0.0003	$[I]_{max,u}/K_i \geq 0.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-1b was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i for CYP1A1 (12.9 µM; K_i = 14.5 µM; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.891))

e = Unbound K_i (>14.5 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.580; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.580))

f = Unbound K_i (>22.3 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.891)

g = Unbound K_i (>21.1 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.842)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1b in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1b calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-1b total $[I]_{max}$ = 0.16 µM [61.5 µg/L] and unbound fraction = 0.0388); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

Test article: Finerenone

Table 16-36: Pharmacokinetics: Drug-drug Interaction, enzyme inhibition by M-2a (FDA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$1+[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP1A2	Basic	0.067	>20.7[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2A6	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2B6	Basic	0.067	>20.7[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C8	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C9	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C19	Basic	0.067	>20.7[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2D6	Basic	0.067	>20.7[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2E1	Basic	0.067	>20.7[e]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/midazolam	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/testosterone	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A1	Basic	0.067	>22.9[f]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A4	Basic	0.067	>22.9[f]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A6	Basic	0.067	>23.2[d]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A9	Basic	0.067	>22.9[f]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B4	Basic	0.067	>22.9[f]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B7	Basic	0.067	>22.9[f]	<1.003	$1+[I]_{max,u}/K_i \geq 1.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020
b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition
c = M-2a was not dosed orally; therefore, only systemic DDIs are assessed
d = Unbound K_i (>23.2 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.929; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.929))
e = Unbound K_i (>20.7 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.828; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.828))
f = Unbound K_i (>22.9 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.915)
Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-2a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-2a calculated under assumption of dose-linearity from exposures of M-2 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-2a:M-2b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-2a total $[I]_{max}$ = 0.39 µM [152 µg/L] and unbound fraction = 0.174); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase
Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

Test article: Finerenone

Table 16-37: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-2a (EMA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP1A2	Basic	0.067	>20.7[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2A6	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2B6	Basic	0.067	>20.7[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C8	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C9	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2C19	Basic	0.067	>20.7[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2D6	Basic	0.067	>20.7[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP2E1	Basic	0.067	>20.7[e]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/midazolam	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/testosterone	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A1	Basic	0.067	>22.9[f]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A4	Basic	0.067	>22.9[f]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A6	Basic	0.067	>23.2[d]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT1A9	Basic	0.067	>22.9[f]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT2B4	Basic	0.067	>22.9[f]	<0.003	$[I]_{max,u}/K_i \geq 0.02$
UGT2B7	Basic	0.067	>22.9[f]	<0.003	$[I]_{max,u}/K_i \geq 0.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-2a was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i (>23.2 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.929; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.929))

e = Unbound K_i (>20.7 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.828; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.828))

f = Unbound K_i (>22.9 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.915)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-2a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-2a calculated under assumption of dose-linearity from exposures of M-2 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-2a:M-2b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-2a total $[I]_{max}$ = 0.39 µM [152 µg/L] and unbound fraction = 0.174); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

Test article: Finerenone

Table 16-38: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-3a (FDA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$1+[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
CYP1A2	Basic	0.12	>21.0[e]	<1.006	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2A6	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2B6	Basic	0.12	>21.0[e]	<1.006	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C8	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C9	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2C19	Basic	0.12	>21.0[e]	<1.006	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2D6	Basic	0.12	>21.0[e]	<1.006	$1+[I]_{max,u}/K_i \geq 1.02$
CYP2E1	Basic	0.12	>21.0[e]	<1.006	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/midazolam	Basic	0.12	14.0[f]	1.009	$1+[I]_{max,u}/K_i \geq 1.02$
CYP3A4/testosterone	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A1	Basic	0.12	>23.2[g]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A4	Basic	0.12	>23.2[g]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A6	Basic	0.12	>23.4[d]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT1A9	Basic	0.12	>23.2[g]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B4	Basic	0.12	>23.2[g]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$
UGT2B7	Basic	0.12	>23.2[g]	<1.005	$1+[I]_{max,u}/K_i \geq 1.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a and co-administered substrates of various enzymes, based on the FDA guidance (2020)[a]

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-3a was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i (>23.4 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.934; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.934))

e = Unbound K_i (>21.0 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.838; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.838))

f = Unbound K_i (14.0 µM; K_i = 15 µM; unbound fraction in 0.05 mg/mL microsomes = 0.934)

g = Unbound K_i (>23.2 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.928)

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-3a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-3a calculated under assumption of dose-linearity from exposures of M-3 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-3a:M-3b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-3a total $[I]_{max}$ = 0.17 µM [69.6 µg/L] and unbound fraction = 0.678); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a

Test article: Finerenone

Table 16-39: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-3a (EMA)

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

Enzyme	Model	$[I]_{max,u}$ [µM]	K_i[b] [µM]	$[I]_{max,u}/K_i$	Threshold cutoff for potential DDI
			Systemic[c]		
CYP1A1	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
CYP1A2	Basic	0.12	>21.0[e]	<0.006	$[I]_{max,u}/K_i \geq 0.02$
CYP2A6	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
CYP2B6	Basic	0.12	>21.0[e]	<0.006	$[I]_{max,u}/K_i \geq 0.02$
CYP2C8	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
CYP2C9	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
CYP2C19	Basic	0.12	>21.0[e]	<0.006	$[I]_{max,u}/K_i \geq 0.02$
CYP2D6	Basic	0.12	>21.0[e]	<0.006	$[I]_{max,u}/K_i \geq 0.02$
CYP2E1	Basic	0.12	>21.0[e]	<0.006	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/midazolam	Basic	0.12	14.0[f]	0.009	$[I]_{max,u}/K_i \geq 0.02$
CYP3A4/testosterone	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT1A1	Basic	0.12	>23.2[g]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT1A4	Basic	0.12	>23.2[g]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT1A6	Basic	0.12	>23.4[d]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT1A9	Basic	0.12	>23.2[g]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT2B4	Basic	0.12	>23.2[g]	<0.005	$[I]_{max,u}/K_i \geq 0.02$
UGT2B7	Basic	0.12	>23.2[g]	<0.005	$[I]_{max,u}/K_i \geq 0.02$

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a and co-administered substrates of various enzymes, based on the EMA guidance (2012)[a]

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = Calculated $K_i = IC_{50}/2$ assuming competitive inhibition

c = M-3a was not dosed orally; therefore, only systemic DDIs are assessed

d = Unbound K_i (>23.4 µM; K_i > 25 µM; unbound fraction in 0.05 mg/mL microsomes = 0.934; unbound fraction in 1 pmol/mL recombinant CYP1A1 was not measured, but was assumed as the same in 0.05 mg/mL microsomes (0.934))

e = Unbound K_i (>21.0 µM; K_i > 25 µM; unbound fraction in 0.5 mg/mL microsomes = 0.838; unbound fraction in 124 pmol/mL recombinant CYP2E1 was not measured, but was assumed as the same in 0.5 mg/mL microsomes (0.838))

f = Unbound K_i (14.0 µM; K_i = 15 µM; unbound fraction in 0.05 mg/mL microsomes = 0.934)

g = Unbound K_i (>23.2 µM; K_i > 25 µM; unbound fraction in 0.1 mg/mL microsomes = 0.928)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-3a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-3a calculated under assumption of dose-linearity from exposures of M-3 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-3a:M-3b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19 PH-40388) (M-3a total $[I]_{max}$ = 0.17 µM [69.6 µg/L] and unbound fraction = 0.678); K_i = inhibition constant; IC_{50} = concentration required for 50% inhibition; CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase

Additional information: Unbound K_i value for each CYP or UGT isoform was calculated based on the unbound fraction in the incubations containing various concentrations of microsomal protein; conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a

Test article: Finerenone

Table 16-40: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 mRNA: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on CYP1A2 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1a	0.014	1.3	1.4	1.4
	0.041	1.1	1.1	1.3
	0.123	1.1	1.0	1.3
	0.370	1.1	1.1	1.2
	1.1	1.2	1.0	1.5
	3.3	1.2	1.4	1.4
	10	1.5	2.0	1.7
	30	2.1	2.8	2.5
Omeprazole	16.7/16.7/50	13.2	15.7	9.5

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-41: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 activity: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on the rate of phenacetin O-dealkylase activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	37.7	1.0	47.0	1.0	51.0
M-1a	0.014	0.9	34.6	1.1	53.7	0.9	45.8
	0.041	0.9	34.9	0.9	43.4	1.0	50.5
	0.123	0.9	34.1	0.9	42.4	0.8	40.8
	0.370	1.0	37.2	1.0	47.3	0.9	44.7
	1.1	1.2	46.2	1.0	49.1	1.0	52.0
	3.3	1.5	56.0	1.1	51.6	1.3	68.2
	10	2.3	87.6	1.8	85.2	2.0	102.2
	30	3.6	135.9	2.4	115.5	2.5	127.5
Omeprazole	16.7/5.6/16.7	10.2	382.3	9.9	467.4	14.3	727.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol acetaminophen/min/10^6 cells

Test article: Finerenone

Table 16-42: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 mRNA: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on CYP2B6 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1a	0.014	1.1	1.4	1.3
	0.041	1.0	1.0	1.1
	0.123	1.0	0.9	1.1
	0.370	1.0	1.1	1.2
	1.1	1.4	0.9	1.4
	3.3	1.8	1.4	2.2
	10	3.3	5.7	2.9
	30	7.2	10.1	5.9
Rifampicin	30/10/30	8.3	10.2	8.3
Phenobarbital	333/333/333	10.5	7.6	8.1

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-43: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 activity: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on the rate of S-mephenytoin N-demethylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	7.1	1.0	4.3	1.0	5.8
M-1a	0.014	0.9	6.6	0.9	4.1	1.0	5.6
	0.041	0.8	6.0	0.9	4.0	0.9	5.3
	0.123	0.9	6.1	0.9	4.0	1.0	5.6
	0.370	0.9	6.7	1.0	4.1	0.9	5.5
	1.1	1.1	8.0	1.0	4.2	1.1	6.5
	3.3	1.2	8.7	1.1	4.6	1.2	6.8
	10	1.7	12.1	1.3	5.7	1.4	8.0
	30	2.6	18.2	2.0	8.6	1.9	10.7
Rifampicin	10/3.3/3.3	4.8	34.1	4.1	17.6	5.5	31.4
Phenobarbital	333/111/333	8.5	60.3	4.5	19.5	6.2	35.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol nirvanol/min/10^6 cells

Test article: Finerenone

Table 16-44: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 mRNA: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on CYP2C19 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1a	0.014	1.2	1.3	1.3
	0.041	1.2	1.2	1.1
	0.123	1.0	0.8	1.1
	0.370	1.0	0.9	1.0
	1.1	1.2	1.3	1.2
	3.3	1.2	1.3	1.1
	10	1.7	2.3	1.1
	30	4.4	5.3	1.3
Rifampicin	30/30/30	6.3	4.0	2.4
Phenobarbital	333/333/333	6.5	3.7	2.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-45: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 activity: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on the rate of S-mephenytoin 4'-hydroxylation activity

	Concentration [µg/mL]	Donor 1		Donor 2		Donor 3	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	14.37	1.0	12.71	1.0	0.81
M-1a	0.014	0.5	8.81	0.6	9.95	0.7	0.68
	0.041	0.6	10.49	0.7	11.22	0.7	0.66
	0.123	0.7	12.84	0.7	12.02	0.8	0.79
	0.370	0.8	15.48	0.8	13.34	0.9	0.85
	1.1	1.0	17.74	0.9	15.39	1.1	1.07
	3.3	0.9	16.61	0.9	14.29	1.2	1.20
	10	1.1	20.27	0.9	15.13	1.9	1.81
	30	2.4	43.63	1.4	23.33	5.3	5.19
Rifampicin	10/30/30	7.1	101.8	5.5	67.5	16.2	13.1
Phenobarbital	333/111/333	4.1	59.4	3.0	37.4	13.3	10.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 4'-OH mephenytoin/min/10^6 cells

Test article: Finerenone

Table 16-46: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4 mRNA: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on CYP3A4 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1a	0.014	1.0	1.1	1.3
	0.041	0.9	1.1	1.3
	0.123	0.9	0.9	1.2
	0.370	1.0	1.2	1.4
	1.1	1.6	1.7	2.1
	3.3	2.7	2.5	3.7
	10	5.1	8.1	7.4
	30	10.0	11.6	16.1
Rifampicin	1.1/10/30	16.0	13.7	22.8
Phenobarbital	111/333/333	13.9	10.5	18.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-47: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4/5 activity: The effect of treating cultured human hepatocytes with BAY 1117267 (M-1a) on the rate of testosterone 6β-hydroxylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	64.2	1.0	67.1	1.0	70.5
M-1a	0.014	0.8	51.6	1.2	80.3	1.0	74.0
	0.041	0.9	55.1	0.9	61.1	1.0	72.8
	0.123	0.9	55.0	1.0	64.9	0.9	65.3
	0.370	1.0	64.4	1.2	82.6	1.0	71.1
	1.1	1.4	89.7	1.4	96.5	1.3	92.6
	3.3	2.0	130.7	1.9	126.1	2.2	152.7
	10	3.5	227.8	2.9	197.3	3.8	269.5
	30	5.3	340.5	4.0	267.2	4.8	336.0
Rifampicin	30/3.3/3.3	8.6	550.6	11.5	753.9	12.2	858.9
Phenobarbital	333/111/333	10.1	650.0	10.2	686.6	12.5	881.0

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 6β-hydroxytestosterone/min/10^6 cells

Test article: Finerenone

Table 16-48: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 mRNA: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on CYP1A2 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1b	0.014	1.1	1.4	1.3
	0.041	1.1	1.0	1.2
	0.123	1.0	1.1	1.2
	0.370	1.1	1.2	1.2
	1.1	1.1	1.0	1.4
	3.3	1.2	1.2	1.5
	10	1.5	1.5	2.0
	30	1.5	1.6	2.1
Omeprazole	16.7/16.7/50	13.2	15.7	9.5

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-49: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 activity: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on the rate of phenacetin O-dealkylase activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	37.7	1.0	47.0	1.0	51.0
M-1b	0.014	1.0	37.5	1.2	57.9	1.0	52.2
	0.041	1.0	38.8	1.0	47.1	0.9	45.7
	0.123	0.8	31.6	0.9	41.9	0.9	48.0
	0.370	1.1	40.5	1.2	54.6	1.0	49.2
	1.1	1.2	46.6	1.0	48.0	1.2	63.4
	3.3	2.0	74.5	1.4	65.7	1.8	90.8
	10	2.7	103.1	0.6	28.8	2.0	102.2
	30	1.5	55.2	0.7	32.3	0.8	43.0
Omeprazole	16.7/5.6/16.7	10.2	382.3	9.9	467.4	14.3	727.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol acetaminophen/min/10^6 cells

Test article: Finerenone

Table 16-50: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 mRNA: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on CYP2B6 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1b	0.014	0.9	1.1	1.1
	0.041	1.0	0.9	1.0
	0.123	1.0	1.0	0.8
	0.370	1.0	1.2	1.1
	1.1	1.3	0.8	1.2
	3.3	1.5	1.6	2.0
	10	2.5	4.9	3.1
	30	5.6	6.8	5.9
Rifampicin	30/10/30	8.3	10.2	8.3
Phenobarbital	333/333/333	13.8	7.6	8.1

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-51: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 activity: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on the rate of S-mephenytoin N-demethylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	7.1	1.0	4.3	1.0	5.8
M-1b	0.014	0.9	6.5	0.9	4.1	1.1	5.6
	0.041	0.8	6.1	0.9	3.9	1.1	5.5
	0.123	0.9	6.4	1.0	4.1	1.1	5.7
	0.370	0.9	6.3	0.8	3.3	1.1	5.8
	1.1	1.1	7.8	1.1	4.7	1.3	7.3
	3.3	1.4	9.9	1.1	4.8	1.3	7.8
	10	1.7	12.1	1.4	6.0	1.6	9.1
	30	1.8	12.6	1.8	7.6	1.6	9.3
Rifampicin	10/3.3/3.3	4.8	34.1	4.1	17.6	5.5	31.4
Phenobarbital	333/111/333	8.5	60.3	4.5	19.5	6.2	35.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol nirvanol/min/10^6 cells

Test article: Finerenone

Table 16-52: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 mRNA: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on CYP2C19 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1b	0.014	1.2	1.2	1.2
	0.041	1.1	0.9	1.1
	0.123	1.0	1.0	1.1
	0.370	1.0	0.9	1.0
	1.1	1.2	1.2	1.1
	3.3	1.4	2.1	1.1
	10	2.3	2.4	1.2
	30	5.9	3.4	1.8
Rifampicin	3.3/30/30	6.3	4.0	2.4
Phenobarbital	333/333/333	6.5	3.7	2.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-53: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 activity: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on the rate of S-mephenytoin 4'-hydroxylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	14.37	1.0	12.71	1.0	0.81
M-1b	0.014	0.5	10.04	0.7	11.69	0.8	0.79
	0.041	0.6	11.01	0.8	12.87	0.8	0.77
	0.123	0.8	15.36	0.8	13.86	0.8	0.87
	0.370	0.9	16.89	0.8	13.72	0.9	0.88
	1.1	1.0	19.07	1.1	18.20	1.5	1.50
	3.3	1.3	24.06	1.0	16.24	1.7	1.70
	10	1.7	30.71	1.3	20.96	3.6	3.69
	30	2.8	51.50	1.7	28.28	7.8	8.07
Rifampicin	10/30/30	7.1	101.8	5.5	67.5	16.2	13.1
Phenobarbital	333/111/333	4.1	59.4	3.0	37.4	13.3	10.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 4'-OH mephenytoin/min/10^6 cells

Test article: Finerenone

Table 16-54: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4 mRNA: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on CYP3A4 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-1b	0.014	0.9	1.1	1.3
	0.041	1.1	1.3	1.3
	0.123	1.1	1.6	1.2
	0.370	1.2	3.1	1.8
	1.1	2.2	2.3	3.2
	3.3	4.0	4.4	6.1
	10	8.3	8.5	13.2
	30	11.0	9.5	18.3
Rifampicin	1.1/10/30	16.0	13.7	22.8
Phenobarbital	111/333/333	13.9	10.5	18.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-55: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4/5 activity: The effect of treating cultured human hepatocytes with BAY 1117266 (M-1b) on the rate of testosterone 6β-hydroxylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	64.2	1.0	67.1	1.0	70.5
M-1b	0.014	0.9	59.5	1.3	85.9	1.1	74.5
	0.041	1.0	65.1	1.1	71.3	1.0	69.4
	0.123	0.8	53.2	1.0	66.3	1.1	74.5
	0.370	1.2	75.1	1.7	116.2	1.2	83.0
	1.1	1.6	101.5	1.9	125.7	1.8	130.2
	3.3	3.0	190.8	2.9	197.2	3.2	226.4
	10	4.8	309.3	0.9	58.9	4.2	293.5
	30	2.2	139.1	0.8	54.3	1.1	79.7
Rifampicin	30/3.3/3.3	8.6	550.6	11.2	753.9	12.3	871.1
Phenobarbital	333/111/333	10.1	650.0	10.2	686.6	12.5	881.0

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 6β-hydroxytestosterone/min/10^6 cells

Test article: Finerenone

Table 16-56: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 mRNA: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on CYP1A2 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-2a	0.005	1.0	1.2	1.1
	0.014	1.0	1.0	1.1
	0.041	1.0	0.9	1.0
	0.123	1.0	0.9	1.2
	0.370	1.2	1.0	1.3
	1.1	0.9	1.1	1.2
	3.3	1.1	1.3	1.3
	10	1.5	1.6	1.7
Omeprazole	16.7/16.7/50	13.2	15.7	9.5

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-57: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 activity: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on the rate of phenacetin O-dealkylase activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	37.7	1.0	47.0	1.0	51.0
M-2a	0.005	1.0	37.3	1.1	50.9	1.0	51.6
	0.014	1.0	36.0	1.0	44.8	1.0	49.8
	0.041	1.0	38.0	0.9	43.4	0.9	44.9
	0.123	1.0	39.1	1.1	50.4	0.9	45.1
	0.370	1.0	37.6	0.8	38.4	0.9	43.7
	1.1	1.2	43.3	1.1	50.9	1.0	52.1
	3.3	1.3	49.4	1.4	64.7	1.3	66.9
	10	2.3	86.6	2.3	108.5	2.1	105.9
Omeprazole	16.7/5.6/16.7	10.2	382.3	9.9	467.4	14.3	727.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol acetaminophen/min/10^6 cells

Test article: Finerenone

Table 16-58: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 mRNA: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on CYP2B6 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-2a	0.005	1.0	1.1	1.0
	0.014	0.8	0.9	1.0
	0.041	0.9	0.9	0.8
	0.123	0.9	0.8	1.1
	0.370	1.1	1.0	0.9
	1.1	1.0	1.3	1.2
	3.3	1.4	1.2	1.6
	10	2.1	2.0	2.2
Rifampicin	30/10/30	8.3	10.2	8.3
Phenobarbital	333/333/333	13.8	7.6	8.1

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-59: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 activity: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on the rate of S-mephenytoin N-demethylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	7.1	1.0	4.3	1.0	5.8
M-2a	0.005	1.1	7.5	1.0	4.1	1.0	6.0
	0.014	0.9	6.4	1.0	4.2	0.9	5.2
	0.041	0.8	5.9	1.0	4.1	1.0	6.0
	0.123	0.9	6.1	0.9	4.0	1.0	5.5
	0.370	1.0	7.4	1.0	4.2	1.0	5.9
	1.1	1.0	7.1	0.9	4.1	1.1	6.3
	3.3	1.1	8.1	1.0	4.4	1.2	6.8
	10	1.5	10.9	1.9	8.2	1.7	10.0
Rifampicin	10/3.3/3.3	4.8	34.1	4.1	17.6	5.5	5.1
Phenobarbital	333/111/333	8.5	60.3	4.5	19.5	6.2	5.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol nirvanol/min/10^6 cells

Test article: Finerenone

Table 16-60: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 mRNA: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on CYP2C19 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-2a	0.005	1.1	1.2	1.1
	0.014	0.9	0.8	1.0
	0.041	1.0	0.9	0.9
	0.123	1.0	0.7	1.0
	0.370	1.0	1.0	1.2
	1.1	1.1	1.2	1.0
	3.3	1.2	1.1	1.1
	10	1.3	2.0	1.1
Rifampicin	30/30/30	6.3	4.0	2.4
Phenobarbital	333/333/333	6.5	3.7	2.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-61: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 activity: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on the rate of S-mephenytoin 4'-hydroxylation activity

	Concentration [µg/mL]	Donor 1		Donor 2		Donor 3	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	17.6	1.0	16.7 / 12.3[c]	1.0	0.81
M-2a	0.005	0.9	15.3	0.8	13.8	1.0	0.85
	0.014	0.8	14.6	0.9	15.2	0.8	0.66
	0.041	0.9	15.2	0.9	14.7	1.1	0.90
	0.123	1.0	16.9	1.0	15.9	0.9	0.75
	0.370	1.2	20.3	1.0	16.9	1.1	0.86
	1.1	1.0	18.4	0.8	14.2	1.1	0.92
	3.3	0.9	16.1	0.8	13.1	1.2	1.00
	10	1.3	23.0	1.6	25.9	2.6	2.08
Rifampicin	10/30/30	5.8	101.8	5.5[c]	67.5	16.2	13.1
Phenobarbital	333/111/333	3.4	59.4	3.0[c]	37.4	13.3	10.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 4'-OH mephenytoin/min/10^6 cells
c = control rate used for fold change calculation

Test article: Finerenone

Table 16-62: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4 mRNA: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on CYP3A4 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-2a	0.005	1.0	1.1	0.9
	0.014	1.0	1.0	1.1
	0.041	1.0	0.8	0.9
	0.123	1.0	1.0	1.1
	0.370	1.2	1.0	1.3
	1.1	1.2	1.6	1.5
	3.3	2.4	2.8	2.7
	10	6.0	5.6	8.5
Rifampicin	1.1/10/30	16.0	13.7	22.8
Phenobarbital	111/333/333	13.9	10.5	18.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-63: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4/5 activity: The effect of treating cultured human hepatocytes with BAY 1117268 (M-2a) on the rate of testosterone 6β-hydroxylation activity

	Concentration [µg/mL]	Donor 1		Donor 2		Donor 3	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	64.2	1.0	67.1	1.0	70.5
M-2a	0.005	0.9	54.9	1.0	64.8	1.0	67.4
	0.014	1.0	61.8	0.9	59.7	0.9	66.3
	0.041	1.0	66.8	1.0	65.1	0.9	63.4
	0.123	1.1	69.9	1.2	81.9	0.9	62.7
	0.370	1.2	75.0	1.0	66.1	0.8	58.8
	1.1	1.2	77.5	1.4	95.1	1.2	82.8
	3.3	1.5	97.6	2.3	151.0	1.9	131.8
	10	3.3	210.0	4.3	290.5	3.8	269.1
Rifampicin	30/3.3/10	8.6	550.6	11.2	753.9	12.3	871.1
Phenobarbital	333/111/333	10.1	650.0	10.2	686.6	12.5	881.0

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 6β-hydroxytestosterone/min/10^6 cells

Test article: Finerenone

Table 16-64: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 mRNA: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on CYP1A2 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-3a	0.014	1.1	1.1	1.1
	0.041	1.0	1.0	0.9
	0.123	1.0	1.0	1.0
	0.370	0.9	0.9	1.0
	1.1	0.9	0.8	1.1
	3.3	0.9	0.8	1.0
	10	1.2	1.0	1.1
	30	1.4	1.1	1.4
Omeprazole	16.7/16.7/50	13.2	15.7	9.5

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-65: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP1A2 activity: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on the rate of phenacetin O-dealkylase activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	37.7	1.0	47.0	1.0	51.0
M-3a	0.014	1.0	39.1	1.2	58.0	1.1	55.2
	0.041	0.9	35.3	1.1	51.9	1.0	52.1
	0.123	0.9	35.1	1.0	46.5	0.8	42.3
	0.370	1.0	38.7	1.1	52.7	0.8	42.6
	1.1	1.0	37.5	0.9	42.7	0.9	45.0
	3.3	1.1	40.5	1.0	46.8	1.1	54.1
	10	1.1	39.7	1.0	48.5	1.1	54.6
	30	1.3	50.2	1.4	64.8	1.4	68.9
Omeprazole	16.7/5.6/16.7	10.2	382.3	9.9	467.4	14.3	727.8

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol acetaminophen/min/10^6 cells

Test article: Finerenone

Table 16-66: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 mRNA: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on CYP2B6 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-3a	0.014	0.9	0.9	1.0
	0.041	1.0	1.0	0.6
	0.123	0.8	1.1	0.8
	0.370	1.0	0.8	0.9
	1.1	1.1	0.9	0.9
	3.3	1.0	0.9	0.9
	10	0.9	1.2	1.1
	30	1.0	1.3	1.3
Rifampicin	30/10/30	8.3	10.2	8.3
Phenobarbital	333/333/333	13.8	7.6	8.1

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-67: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2B6 activity: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on the rate of S-mephenytoin N-demethylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	7.1	1.0	4.3	1.0	5.8
M-3a	0.014	1.0	7.2	1.2	5.0	1.2	6.8
	0.041	0.9	6.5	1.0	4.5	1.1	6.2
	0.123	0.8	5.7	1.0	4.1	1.0	5.5
	0.370	1.0	6.8	1.0	4.2	0.8	4.8
	1.1	1.1	7.6	1.1	4.8	1.0	5.9
	3.3	1.0	7.0	1.0	4.2	0.9	5.0
	10	1.0	7.0	1.0	4.4	1.1	6.6
	30	1.1	7.8	1.3	5.4	1.2	7.0
Rifampicin	10/3.3/3.3	4.8	34.1	4.1	17.6	5.5	31.4
Phenobarbital	333/111/333	8.5	60.2	4.5	19.5	6.2	35.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol nirvanol/min/10^6 cells

Test article: Finerenone

Table 16-68: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 mRNA: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on CYP2C19 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-3a	0.014	1.1	0.8	1.0
	0.041	1.0	0.9	0.8
	0.123	0.9	1.0	1.0
	0.370	1.0	0.8	1.1
	1.1	1.2	1.0	0.8
	3.3	0.9	1.0	1.0
	10	0.9	1.7	1.1
	30	0.8	1.7	1.0
Rifampicin	30/30/30	6.3	4.0	2.4
Phenobarbital	333/333/333	6.5	3.7	2.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-69: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP2C19 activity: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on the rate of S-mephenytoin 4'-hydroxylation activity

	Concentration [µg/mL]	**Donor 1**		**Donor 2**		**Donor 3**	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	14.37	1.0	12.71	1.0	0.81
M-3a	0.014	0.9	15.90	1.1	18.94	1.0	1.01
	0.041	0.8	15.37	1.0	16.50	1.0	0.94
	0.123	0.7	13.46	0.9	15.76	0.9	0.90
	0.370	1.1	19.74	0.9	15.67	0.8	0.78
	1.1	1.1	20.64	1.1	18.95	0.9	0.84
	3.3	1.0	17.48	0.8	13.73	0.6	0.60
	10	0.8	14.54	0.7	11.62	0.9	0.91
	30	0.7	12.88	0.8	12.71	1.0	0.95
Rifampicin	10/30/30	7.1	101.8	5.5	67.5	16.2	13.1
Phenobarbital	333/111/333	4.1	59.4	3.0	37.4	13.3	10.7

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 4'-OH mephenytoin/min/10^6 cells

Test article: Finerenone

Table 16-70: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	Quantitative real time PCR
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4 mRNA: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on CYP3A4 mRNA levels

	Concentration [µg/mL]	**Donor 1** Fold change[a]	**Donor 2** Fold change[a]	**Donor 3** Fold change[a]
Vehicle control		1.0	1.0	1.0
M-3a	0.014	0.9	0.9	0.9
	0.041	1.0	1.0	0.9
	0.123	1.0	1.0	0.9
	0.370	1.0	1.1	1.0
	1.1	1.0	0.8	1.0
	3.3	1.0	0.8	1.0
	10	1.0	1.2	1.1
	30	1.0	1.0	1.6
Rifampicin	1.1/10/30	16.0	13.7	22.8
Phenobarbital	111/333/333	13.9	10.5	18.0

a = fold change values are relative to vehicle control, normalized to β-actin/β-tubulin

Test article: Finerenone

Table 16-71: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS
Table:	Evaluation of the CYP induction potential of metabolites *in vitro* in cultured human hepatocytes		

CYP3A4/5 activity: The effect of treating cultured human hepatocytes with BAY 1117271 (M-3a) on the rate of testosterone 6β-hydroxylation activity

	Concentration [µg/mL]	Donor 1		Donor 2		Donor 3	
		Fold change[a]	Rate[b]	Fold change[a]	Rate[b]	Fold change[a]	Rate[b]
Vehicle control		1.0	64.2	1.0	67.1	1.0	70.5
M-3a	0.014	0.9	58.6	1.3	90.2	1.0	72.9
	0.041	0.9	58.4	1.2	78.4	1.0	67.3
	0.123	0.9	60.1	1.0	69.5	0.8	53.3
	0.370	1.1	67.4	1.3	86.1	0.9	61.2
	1.1	1.0	65.2	0.9	63.5	0.8	59.3
	3.3	1.2	75.0	1.1	73.7	1.1	77.1
	10	0.9	58.9	1.1	75.1	1.1	77.0
	30	1.1	72.2	1.5	98.3	1.5	102.3
Rifampicin	30/3.3/10	8.6	550.6	11.2	753.9	12.3	871.1
Phenobarbital	333/111/333	10.1	650.0	10.2	686.6	12.5	881.0

a = fold change: activity of test article treated cells / activity of vehicle control
b = rate is expressed in pmol 6β-hydroxytestosterone/min/10^6 cells

Test article: Finerenone

Table 16-72: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	Quantitative real time PCR
Table:	BAY 1117267 (M-1a): Parameters generated *in vitro* (CYP3A4mRNA) and prediction of CYP3A4 induction effects *in vivo* based on different models		

Test compound M-1a		**Donor 1**	**Donor 2**	**Donor 3**	**CYP induction assessment**
E_{max}	[fold induction]	11.4	14.1	16.9	
EC_{50}	[µg/L]	14637	11994	11599	
Dose[a]	[mg]	20	20	20	
Total $C_{max,ss}$[a]	[µg/L]	302	302	302	
Unbound $C_{max,ss}$	[µg/L]	17.6	17.6	17.6	
PXR regulation					yes
RIS model					
RIS score *in vitro*		0.014	0.021	0.026	
% Decrease in AUC of midazolam predicted		39	40	40	weak

a = median $C_{max,ss}$ for M-1a calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388)

Test article: Finerenone

Table 16-73: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	Quantitative real time PCR
Table:	BAY 1117266 (M-1b): Parameters generated *in vitro* (CYP3A4mRNA) and prediction of CYP3A4 induction effects *in vivo* based on different models		

Test compound M-1b		**Donor 1**	**Donor 2**	**Donor 3**	**CYP induction assessment**
E_{max}	[fold induction]	16.2	9.8	21.3	
EC_{50}	[µg/L]	12599	4602	7657	
Dose[a]	[mg]	20	20	20	
Total $C_{max,ss}$[a]	[µg/L]	61.5	61.5	61.5	
Unbound $C_{max,ss}$	[µg/L]	2.39	2.39	2.39	
PXR regulation					yes
RIS model					
RIS score *in vitro*		0.003	0.005	0.007	
% Decrease in AUC of midazolam predicted		19	18	16	no

a = median $C_{max,ss}$ for M-1b calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388)

Test article: Finerenone

Table 16-74: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms

Location: 4.2.2.4.7
Report no.: PH-39130

Species / strain:	Human / Caucasian, African-American	Route:	*in vitro*
Material:	Cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	Quantitation by real time PCR
Table:	BAY 1117268 (M-2a): Parameters generated *in vitro* (CYP3A4mRNA) and prediction of CYP3A4 induction effects *in vivo* based on different models		

Test compound M-2a		**Donor 1**	**Donor 2**	**Donor 3**	**CYP induction assessment**
E_{max}	[fold induction]	8.0	11.0	8.5	
EC_{50}	[µg/L]	6911	11322	4178	
Dose[a]	[mg]	20	20	20	
Total $C_{max,ss}$[a]	[µg/L]	152	152	152	
Unbound $C_{max,ss}$	[µg/L]	26.5	26.5	26.5	
PXR regulation					yes
RIS model					
RIS score *in vitro*		0.031	0.026	0.054	
% Decrease in AUC of midazolam predicted		50	45	54	weak to moderate

a = median $C_{max,ss}$ for M-2a calculated under assumption of dose-linearity from exposures of M-2 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-2a:M-2b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388)

Test article: Finerenone

Table 16-75: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter P-gp

Location: 4.2.2.7.3
Report no.: PH-40886

Species:	Human	Route:	*in vitro*
Material:	L-MDR1 cells	Nuclide:	-
Test compound:	BAY 1117267 (M-1a)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio		
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.	% of control
Dipyridamole[a]	2	Control	0	14.1	1.1	681.9	73.7	48.4	6.46	100 ± S.D.
Dipyridamole[a]	2	BAY 1117267	0.1	15.1	2.3	628.4	15.8	41.7	6.48	86.0
Dipyridamole[a]	2	BAY 1117267	1	15.8	0.2	652.2	79.9	41.4	5.09	85.4
Dipyridamole[a]	2	BAY 1117267	3	16.5	3.2	574.6	37.2	34.8	7.08	71.7
Dipyridamole[a]	2	BAY 1117267	10	16.7	1.1	619.2	85.0	37.0	5.66	76.4
Dipyridamole[a]	2	BAY 1117267	30	17.6	2.8	580.0	102.2	32.9	7.81	68.0
Dipyridamole[a]	2	BAY 1117267	100	21.9	2.5	552.4	35.4	25.2	3.29	52.0
Digoxin[b]	20	Control	0	7.8	0.7	111.7	2.0	14.3	1.25	100 ± S.D.
Digoxin[b]	20	BAY 1117267	0.1	8.7	0.3	92.9	9.6	10.7	1.15	74.6
Digoxin[b]	20	BAY 1117267	1	8.4	0.6	107.2	3.9	12.8	1.07	89.4
Digoxin[b]	20	BAY 1117267	3	9.1	0.2	96.8	16.1	10.6	1.77	73.8
Digoxin[b]	20	BAY 1117267	10	8.3	0.5	96.2	9.4	11.7	1.37	81.3
Digoxin[b]	20	BAY 1117267	30	8.5	0.4	102.1	18.5	12.0	2.25	83.4
Digoxin[b]	20	BAY 1117267	100	9.7	0.8	103.6	5.8	10.7	1.06	74.3

a = IC_{50} of BAY 1117267 (M-1a) against this probe substrate = 70 µM
b = IC_{50} of BAY 1117267 (M-1a) against this probe substrate not reached in the investigated concentration range (IC_{50} >100 µM)

Test article: Finerenone

Table 16-76: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter P-gp

Location: 4.2.2.7.3
Report no.: PH-40886

Species:	Human	Route:	*in vitro*
Material:	L-MDR1 cells	Nuclide:	-
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio		
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.	% of control
Dipyridamole[a]	2	Control	0	9.7	0.2	714.2	63.1	73.5	6.70	100 ± S.D.
Dipyridamole[a]	2	BAY 1117266	0.1	9.5	0.2	585.6	50.4	61.9	5.44	84.2
Dipyridamole[a]	2	BAY 1117266	0.3	10.8	0.4	667.4	53.6	62.0	5.42	84.3
Dipyridamole[a]	2	BAY 1117266	1	10.2	0.3	633.0	24.2	61.9	2.93	84.2
Dipyridamole[a]	2	BAY 1117266	3	11.9	0.5	685.7	6.1	57.6	2.48	78.4
Dipyridamole[a]	2	BAY 1117266	10	12.1	0.2	659.8	7.7	54.6	1.13	74.2
Dipyridamole[a]	2	BAY 1117266	30	16.2	2.2	542.2	18.0	33.5	4.77	45.6
Digoxin[b]	20	Control	0	6.6	0.4	114.9	9.7	17.3	1.75	100 ± S.D.
Digoxin[b]	20	BAY 1117266	0.1	6.4	0.4	101.9	14.4	15.9	2.45	91.9
Digoxin[b]	20	BAY 1117266	0.3	6.8	0.2	105.8	6.3	15.6	1.00	90.1
Digoxin[b]	20	BAY 1117266	1	6.3	0.7	102.0	0.1	16.1	1.79	93.1
Digoxin[b]	20	BAY 1117266	3	6.5	0.3	105.2	3.3	16.3	0.96	94.0
Digoxin[b]	20	BAY 1117266	10	7.3	0.3	110.1	2.3	15.1	0.73	87.5
Digoxin[b]	20	BAY 1117266	30	7.8	0.9	102.6	10.4	13.1	2.03	75.8

a = IC_{50} of BAY 1117266 (M-1b) against this probe substrate = 31 µM
b = IC_{50} of BAY 1117266 (M-1b) against this probe substrate not reached in the investigated concentration range (IC_{50} >30 µM)

Test article: Finerenone

Table 16-77: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter P-gp

Location: 4.2.2.7.3
Report no.: PH-40886

Species:	Human	Route:	*in vitro*
Material:	L-MDR1 cells	Nuclide:	-
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean	Efflux ratio S.D.	Efflux ratio % of control
Dipyridamole[a]	2	Control	0	14.4	0.8	631.3	18.3	43.9	2.71	100 ± S.D.
Dipyridamole[a]	2	BAY 1117268	0.1	17.1	1.0	562.0	26.3	32.9	2.42	74.9
Dipyridamole[a]	2	BAY 1117268	0.3	19.0	0.8	612.7	9.6	32.3	1.50	73.6
Dipyridamole[a]	2	BAY 1117268	1	17.0	2.8	604.3	4.9	35.5	5.83	81.0
Dipyridamole[a]	2	BAY 1117268	3	15.5	2.9	615.5	62.1	39.8	8.55	90.7
Dipyridamole[a]	2	BAY 1117268	10	16.6	0.9	622.9	73.1	37.6	4.89	85.6
Dipyridamole[a]	2	BAY 1117268	30	17.2	3.2	557.2	48.3	32.3	6.55	73.6
Digoxin[a]	20	Control	0	8.9	1.8	107.0	3.3	12.0	2.48	100 ± S.D.
Digoxin[a]	20	BAY 1117268	0.1	8.9	0.3	112.3	3.3	12.6	0.61	105.3
Digoxin[a]	20	BAY 1117268	0.3	8.8	0.2	108.0	1.4	12.3	0.31	102.3
Digoxin[a]	20	BAY 1117268	1	9.5	0.9	104.3	7.3	10.9	1.32	91.3
Digoxin[a]	20	BAY 1117268	3	8.5	0.8	107.0	12.6	12.6	1.88	105.4
Digoxin[a]	20	BAY 1117268	10	9.1	0.2	112.3	12.2	12.4	1.37	103.3
Digoxin[a]	20	BAY 1117268	30	9.1	0.0	115.2	2.0	12.6	0.22	105.4

a = IC_{50} of BAY 1117268 (M-2a) against these probe substrates not reached in the investigated concentration range (IC_{50} >30 µM)

Test article: Finerenone

Table 16-78: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter P-gp

Location: 4.2.2.7.3
Report no.: PH-40886

Species:	Human	Route:	*in vitro*
Material:	L-MDR1 cells	Nuclide:	-
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B Mean [nm/s]	P_{app} A-B S.D. [nm/s]	P_{app} B-A Mean [nm/s]	P_{app} B-A S.D. [nm/s]	Efflux ratio Mean	Efflux ratio S.D.	Efflux ratio % of control
Dipyridamole[a]	2	Control	0	13.6	0.0	578.6	10.8	42.5	0.80	100 ± S.D.
Dipyridamole[a]	2	BAY 1117271	0.1	14.0	0.2	594.9	49.5	42.6	3.61	100.2
Dipyridamole[a]	2	BAY 1117271	0.3	12.9	0.3	536.9	52.2	41.5	4.17	97.6
Dipyridamole[a]	2	BAY 1117271	1	14.2	3.3	600.2	63.5	42.3	10.77	99.6
Dipyridamole[a]	2	BAY 1117271	3	14.8	1.9	608.8	24.2	41.3	5.43	97.1
Dipyridamole[a]	2	BAY 1117271	10	14.5	1.1	634.2	179.8	43.8	12.85	103.0
Dipyridamole[a]	2	BAY 1117271	30	13.1	1.0	593.0	28.1	45.4	4.10	106.9
Digoxin[a]	20	Control	0	9.5	1.0	95.8	15.3	10.1	1.90	100 ± S.D.
Digoxin[a]	20	BAY 1117271	0.1	10.5	0.8	102.5	9.8	9.7	1.19	96.6
Digoxin[a]	20	BAY 1117271	0.3	9.9	0.5	97.6	6.1	9.9	0.80	98.2
Digoxin[a]	20	BAY 1117271	1	11.2	0.2	98.5	4.6	8.8	0.45	87.8
Digoxin[a]	20	BAY 1117271	3	9.5	1.3	98.7	15.2	10.4	2.16	103.4
Digoxin[a]	20	BAY 1117271	10	10.4	0.1	95.4	5.2	9.2	0.50	91.4
Digoxin[a]	20	BAY 1117271	30	11.2	0.1	103.2	3.0	9.2	0.28	91.8

a = IC_{50} of BAY 1117271 (M-3a) against these probe substrates not reached in the investigated concentration range (IC_{50} >30 µM)

Test article: Finerenone

Table 16-79: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter BCRP

Location: 4.2.2.7.5
Report no.: PH-40885

Species:	Human	Route:	*in vitro*
Material:	MDCKII-BCRP cells	Nuclide:	-
Test compounds:	BAY 1117267 (M-1a) BAY 1117268 (M-2a) BAY 1117271 (M-3a)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio		
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.	% of control
Topotecan[a]	2	Control	0	8.1	0.5	254.1	9.7	31.2	2.10	100 ± S.D.
Topotecan[a]	2	BAY 1117267	20	9.9	1.4	182.1	26.9	18.4	3.80	59.0
Topotecan[a]	2	BAY 1117268	20	7.9	0.3	210.0	10.2	26.6	1.68	85.2
Topotecan[a]	2	BAY 1117271	20	6.2	0.6	248.5	28.0	40.1	5.80	128.5
PhIP[a,b]	2	Control	0	65.3	11.5	612.7	6.7	9.4	1.65	100 ± S.D.
PhIP[a,b]	2	BAY 1117267	20	90.2	14.7	591.7	45.6	6.6	1.18	69.9
PhIP[a,b]	2	BAY 1117268	20	71.3	15.3	503.5	4.3	7.1	1.51	75.2
PhIP[a,b]	2	BAY 1117271	20	85.9	12.5	671.9	55.0	7.8	1.31	83.3

a = IC_{50} of BAY 1117267 (M-1a), BAY 1117268 (M-2a) and BAY 1117271 (M-3a) against these probe substrates not reached in the investigated concentration range (IC_{50} >20 µM)
b = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

Test article: Finerenone

Table 16-80: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter BCRP

Location: 4.2.2.7.5
Report no.: PH-40885

Species:	Human	Route:	*in vitro*
Material:	MDCKII-BCRP cells	Nuclide:	-
Test compound:	BAY1117266 (M-1b)	Assay:	LC-MS/MS

Probe substrate	Probe substrate concentration [µM]	Inhibitor	Inhibitor concentration [µM]	P_{app} A-B		P_{app} B-A		Efflux ratio		
				Mean [nm/s]	S.D. [nm/s]	Mean [nm/s]	S.D. [nm/s]	Mean	S.D.	% of control
Topotecan[a]	2	Control	0	5.2	0.1	143.2	21.2	27.5	4.12	100 ± S.D.
Topotecan[a]	2	BAY 1117266	0.1	5.7	0.4	138.7	0.2	24.3	1.79	88.5
Topotecan[a]	2	BAY 1117266	0.3	5.7	0.5	126.8	14.9	22.1	3.27	80.5
Topotecan[a]	2	BAY 1117266	1	6.0	0.1	125.9	4.5	21.1	0.82	76.8
Topotecan[a]	2	BAY 1117266	3	6.5	0.5	132.5	10.4	20.3	2.33	73.8
Topotecan[a]	2	BAY 1117266	10	6.0	0.4	123.9	9.4	20.6	2.04	75.1
Topotecan[a]	2	BAY 1117266	30	6.7	0.2	127.8	10.2	19.2	1.66	69.8

a = IC_{50} of BAY1117266 (M-1b) against this probe substrate not reached in the investigated concentration range (IC_{50} >30 µM)

Test article: Finerenone

Table 16-81: Pharmacokinetics: In vitro studies to evaluate the inhibitory potential of metabolites towards human efflux transporter BSEP using B- CLEAR®

Location: 4.2.2.7.22
Report no.: R-11130

Species:	Human	Route:	*in vitro*
Material:	Sandwich-cultured human hepatocytes	Nuclide:	-
Test compound:	BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)	Assay:	LC-MS/MS

Inhibitor	Inhibitor concentration	$CL_{Biliary}$[a]				BEI[b]			
	[µM]	[mL/min/kg]	S.D.	% control	S.D.	[%]	S.D.	% control	S.D.
MeOH control (0.1%)		2.56	0.70	100	27	82.1	29	100	35
Cyclosporine[c]	0.78	2.08	0.56	81.3	22	82.6	29	101	35
Cyclosporine[c]	1.56	1.61	0.30	62.9	12	79.0	18	96.2	22
Cyclosporine[c]	3.16	0.710	0.18	27.7	7.0	61.6	18	75.0	22
Cyclosporine[c]	6.25	0.407	0.09	15.9	3.4	50.8	12	61.9	15
Cyclosporine[c]	12.5	0.198	0.07	7.73	2.8	37.5	14	45.7	17
Cyclosporine[c]	25	0.020	0.13	0.80	5.1	5.75	36	7.00	44
Cyclosporine[c]	50	0.123	0.04	4.80	1.6	30.2	11	36.8	13
DMSO control (0.1%)		2.62	0.23	100	8.8	81.4	8.5	100	10
BAY 1117267[d]	0.03	2.50	0.37	95.4	14	84.0	16	103	20
BAY 1117267[d]	0.1	2.88	0.39	110	15	84.9	14	104	17
BAY 1117267[d]	0.3	2.99	0.27	114	10	85.8	9.7	105	12
BAY 1117267[d]	1	2.91	0.24	111	9.2	85.2	9.0	105	11
BAY 1117267[d]	3	2.91	0.37	111	14	82.9	13	102	16
BAY 1117267[d]	10	2.94	0.56	112	21	80.4	19	98.8	23
BAY 1117267[d]	30	2.64	0.31	101	12	75.7	11	93.0	14
DMSO control (0.1%)		2.30	0.45	100	20	78.2	19	100	24
BAY 1117266[d]	0.03	2.74	0.21	119	9.1	82.1	8.2	105	10
BAY 1117266[d]	0.1	2.56	0.29	111	13	82.3	12	105	15
BAY 1117266[d]	0.3	2.77	0.14	120	6.1	80.8	5.2	103	6.6
BAY 1117266[d]	1	2.84	0.21	123	9.1	81.5	7.5	104	9.6

Inhibitor	Inhibitor concentration	$CL_{Biliary}$[a]				BEI[b]			
	[µM]	[mL/min/kg]	S.D.	% control	S.D.	[%]	S.D.	% control	S.D.
BAY 1117266[d]	3	2.61	0.43	113	19	79.8	17	102	22
BAY 1117266[d]	10	2.79	0.16	121	7.0	79.7	5.5	102	7.0
BAY 1117266[d]	30	2.25	0.29	97.8	13	73.7	12	94.2	15
DMSO control (0.1%)		2.92	0.41	100	14	83.3	15	100	18
BAY 1117268[d]	0.03	2.60	0.44	89.0	15	81.7	18	98.1	22
BAY 1117268[d]	0.1	2.84	0.39	97.3	13	83.9	15	101	18
BAY 1117268[d]	0.3	2.61	0.67	89.4	23	82.0	27	98.4	32
BAY 1117268[d]	1	2.47	0.37	84.6	13	80.5	15	96.6	18
BAY 1117268[d]	3	2.50	0.38	85.6	13	80.7	15	96.9	18
BAY 1117268[d]	10	3.03	0.47	104	16	82.4	16	98.9	19
BAY 1117268[d]	30	2.99	0.20	102	6.8	80.9	6.5	97.1	7.8
DMSO control (0.1%)		3.80	0.46	100	12	88.0	14	100	16
BAY 1117271[d]	0.03	3.50	0.45	92.1	12	86.0	14	97.7	16
BAY 1117271[d]	0.1	3.52	0.47	92.6	12	84.4	13	95.9	15
BAY 1117271[d]	0.3	3.47	0.42	91.3	11	86.1	14	97.8	16
BAY 1117271[d]	1	3.52	0.46	92.6	12	87.6	15	99.5	17
BAY 1117271[d]	3	3.51	0.33	92.4	8.7	85.6	10	97.3	11
BAY 1117271[d]	10	3.63	0.52	95.5	14	85.3	15	96.9	17
BAY 1117271[d]	30	3.91	0.65	103	17	88.0	20	100	23

a = of probe substrate d8-taurocholic acid (d8-TCA) at a concentration of 5 µM
b = BEI = biliary excretion index [100 x Bile Accumulation / Total Accumulation (where, Bile Accumulation = Total Accumulation - Cellular Accumulation)]
c = IC_{50} of cyclosporine against d8-TCA as probe substrate = 0.866 µM
d = IC_{50} of M-1a, M-1b, M-2a and M-3a against d8-TCA as probe substrate not reached in the investigated concentration range (IC_{50} >30 µM)

Test article: Finerenone

Table 16-82: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter MATE1

Location: 4.2.2.7.23
Report no.: R-11820

Species: Human
Material: hMATE1 transfected HEK-cells, vector-HEK cells
Test compound: BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)

Route: *in vitro*
Assay: LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of metformin mediated by MATE1 [pmol/mg protein/min]							
					Vector-HEK		hMATE1-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Metformin[a]	50	10 min	BAY 1117267	0.5	5.18	0.19	468	16	463	16	-15.2[b]	8.8
Metformin[a]	50	10 min	BAY 1117267	5	4.94	0.60	418	24	414	24	-2.95[b]	9.1
Metformin	50	10 min	-	-	5.59	0.30	407	27	402	27	-	-
Metformin	50	10 min	Cimetidine	100	4.52	0.65	11.1	0.6	6.58	0.90	98.4	0.2
Metformin[a]	50	10 min	BAY 1117266	0.5	6.18	0.09	844	41	837	41	-66.1[b]	10.7
Metformin[a]	50	10 min	BAY 1117266	5	6.16	0.16	847	27	841	27	-66.8[b]	8.7
Metformin	50	10 min	-	-	5.74	0.42	510	21	504	21	-	-
Metformin	50	10 min	Cimetidine	100	5.09	0.20	10.5	1.2	5.39	1.2	98.9	0.3
Metformin[a]	50	10 min	BAY 1117268	0.5	6.11	0.39	537	50	531	50	-4.41[b]	12.3
Metformin[a]	50	10 min	BAY 1117268	5	7.49	1.76	470	23	462	23	9.09	7.9
Metformin	50	10 min	-	-	5.88	0.90	514	36	508	36	-	-
Metformin	50	10 min	Cimetidine	100	6.74	1.91	10.6	0.2	3.90	1.93	99.2	0.4
Metformin[a]	50	10 min	BAY 1117271	0.5	5.31	0.55	726	43	721	43	11.2	6.3
Metformin[a]	50	10 min	BAY 1117271	5	5.67	0.31	675	26	669	26	17.6	4.4
Metformin	50	10 min	-	-	6.14	0.73	818	30	812	30	-	-
Metformin	50	10 min	Cimetidine	100	5.84	0.95	13.1	0.7	7.26	1.2	99.1	0.2

a = IC_{50} of finerenone metabolites against this probe substrate not reached in the investigated concentration range (IC_{50} >5 µM)
b = negative percentage inhibition indicates no inhibition

Test article: Finerenone

Table 16-83: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human efflux transporter MATE2K

Location: 4.2.2.7.23
Report no.: R-11820

Species: Human
Material: hMATE2K transfected HEK-cells, vector-HEK cells
Test compound: BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)

Route: *in vitro*
Assay: LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of metformin mediated by MATE2K [pmol/mg protein/min]							
					Vector-HEK		hMATE2K-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Metformin[a]	50	10 min	BAY 1117267	0.5	5.18	0.38	48.4	0.2	43.3	0.4	17.4	2.4
Metformin[a]	50	10 min	BAY 1117267	5	5.76	0.37	46.4	0.8	40.6	0.9	22.5	2.7
Metformin	50	10 min	-	-	8.22	0.63	60.6	1.3	52.4	1.4	-	-
Metformin	50	10 min	Pyrimethamine	1	6.08	2.09	10.5	0.9	4.40	2.3	91.6	4.4
Metformin[a]	50	10 min	BAY 1117266	0.5	6.34	0.36	47.9	1.8	41.6	1.9	20.6	4.2
Metformin[a]	50	10 min	BAY 1117266	5	6.86	0.50	46.1	0.7	39.2	0.9	25.1	2.6
Metformin[a]	50	10 min	BAY 1117268	0.5	6.62	0.65	60.4	1.9	53.8	2.0	-2.63[b]	4.7
Metformin[a]	50	10 min	BAY 1117268	5	6.71	0.34	61.1	0.9	54.3	1.0	-3.73[b]	3.3
Metformin[a]	50	10 min	BAY 1117271	0.5	3.81	0.13	29.3	2.5	25.5	2.5	4.59	10.9
Metformin[a]	50	10 min	BAY 1117271	5	4.52	0.50	32.6	1.3	28.1	1.4	-4.92[b]	8.3
Metformin	50	10 min	-	-	4.71	0.39	31.4	1.6	26.7	1.6	-	-
Metformin	50	10 min	Pyrimethamine	1	4.10	0.38	5.43	0.15	1.34	0.4	95.0	1.6

a = IC_{50} of finerenone metabolites against this probe substrate not reached in the investigated concentration range (IC_{50} >5 µM)
b = negative percentage inhibition indicates no inhibition

Test article: Finerenone

Table 16-84: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OATP1B1 and OATP1B3 in a preincubation assay

Location: 4.2.2.7.9
Report no.: PH-40952

Species:	Human		Route:	*in vitro*	
Material:	hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells				
Test compound:	BAY1117267 (M-1a)		Assay:	LC-MS/MS	

Inhibitor	Inhibitor concentration [µM]	Vector-HEK cells [pmol/mg/min]		hOATP1B1 cells [pmol/mg/min]		Net uptake [pmol/mg/min]		Uptake ratio		% of net uptake [%]
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Uptake of pravastatin mediated by OATP1B1										
BAY 1117267[a]	0	1.02	0.03	15.90	1.67	14.88	1.67	15.63	1.71	100
BAY 1117267[a]	0.2	1.08	0.08	16.45	0.94	15.37	0.94	15.19	1.47	103.3
BAY 1117267[a]	0.5	0.80	0.06	13.45	1.21	12.65	1.21	16.86	2.03	85.0
BAY 1117267[a]	2	0.90	0.24	10.60	1.45	9.70	1.47	11.81	3.51	65.2
BAY 1117267[a]	5	0.87	0.12	6.91	0.64	6.04	0.65	7.95	1.33	40.6
BAY 1117267[a]	10	0.91	0.03	4.93	0.78	4.02	0.79	5.43	0.88	27.0
Uptake of pravastatin mediated by OATP1B3										
BAY 1117267[b]	0	1.21	0.07	36.22	2.03	35.02	2.03	30.02	2.45	100
BAY 1117267[b]	0.2	1.34	0.06	39.07	0.89	37.73	0.89	29.21	1.50	107.7
BAY 1117267[b]	0.5	0.94	0.12	29.95	2.17	29.01	2.17	31.86	4.82	82.8
BAY 1117267[b]	2	0.86	0.06	25.15	1.01	24.29	1.01	29.35	2.24	69.4
BAY 1117267[b]	5	1.23	0.06	22.81	2.51	21.58	2.51	18.50	2.20	61.6
BAY 1117267[b]	10	1.12	0.05	16.60	1.85	15.48	1.85	14.83	1.77	44.2

a = IC_{50} of BAY1117267 (M-1a) against pravastatin (5 µM) as probe substrate = 3.8 µM
b = IC_{50} of BAY1117267 (M-1a) against pravastatin (5 µM) as probe substrate = 7.6 µM

Test article: Finerenone

Table 16-85: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OATP1B1 and OATP1B3 in a preincubation assay

Location: 4.2.2.7.9
Report no.: PH-40952

Species:	Human	Route:	*in vitro*
Material:	hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells		
Test compound:	BAY 1117266 (M-1b)	Assay:	LC-MS/MS

Uptake of pravastatin mediated by OATP1B1										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B1 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117266[a]	0	0.69	0.17	7.96	0.30	7.27	0.34	11.55	2.80	100
BAY 1117266[a]	0.2	0.97	0.15	7.67	0.51	6.70	0.53	7.93	1.35	92.2
BAY 1117266[a]	0.5	0.59	0.34	6.38	0.14	5.79	0.37	10.86	6.32	79.6
BAY 1117266[a]	2	0.76	0.20	5.15	0.64	4.39	0.67	6.76	1.94	60.4
BAY 1117266[a]	5	0.81	0.04	4.13	0.18	3.32	0.18	5.11	0.34	45.7
BAY 1117266[a]	10	0.84	0.09	2.66	0.13	1.82	0.16	3.16	0.39	25.0
Uptake of pravastatin mediated by OATP1B3										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B3 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117266[b]	0	1.41	0.18	35.53	1.24	34.11	1.25	25.15	3.28	100
BAY 1117266[b]	0.2	1.38	0.09	32.70	0.96	31.32	0.97	23.64	1.66	91.8
BAY 1117266[b]	0.5	0.94	0.07	31.65	0.87	30.71	0.88	33.60	2.79	90.0
BAY 1117266[b]	2	1.15	0.19	24.98	0.01	23.83	0.19	21.79	3.52	69.9
BAY 1117266[b]	5	1.26	0.12	20.04	0.49	18.78	0.51	15.89	1.61	55.1
BAY 1117266[b]	10	1.27	0.14	16.19	2.85	14.92	2.85	12.79	2.67	43.7

a = IC_{50} of BAY 1117266 (M-1b) against pravastatin (5 µM) as probe substrate = 3.9 µM
b = IC_{50} of BAY 1117266 (M-1b) against pravastatin (5 µM) as probe substrate = 7.3 µM

Test article: Finerenone

Table 16-86: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OATP1B1 and OATP1B3 in a preincubation assay

Location: 4.2.2.7.9
Report no.: PH-40952

Species:	Human	Route:	*in vitro*
Material:	hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells		
Test compound:	BAY 1117268 (M-2a)	Assay:	LC-MS/MS

Uptake of pravastatin mediated by OATP1B1										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B1 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117268[a]	0	0.77	0.25	16.81	0.48	16.04	0.54	21.75	6.99	100
BAY 1117268[a]	0.2	1.22	0.30	16.48	0.70	15.26	0.76	13.46	3.33	95.1
BAY 1117268[a]	0.5	0.79	0.46	13.84	0.36	13.04	0.58	17.45	10.11	81.3
BAY 1117268[a]	2	1.13	0.54	14.15	0.96	13.02	1.10	12.50	6.02	81.2
BAY 1117268[a]	5	1.03	0.27	11.96	1.02	10.93	1.06	11.65	3.22	68.1
BAY 1117268[a]	10	1.33	0.07	10.53	0.41	9.20	0.41	7.94	0.54	57.4

Uptake of pravastatin mediated by OATP1B3										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B3 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117268[a]	0	1.18	0.50	22.37	3.91	21.19	3.94	18.96	8.69	100
BAY 1117268[a]	0.2	1.44	0.25	30.31	1.58	28.87	1.60	21.05	3.82	136.2
BAY 1117268[a]	0.5	0.91	0.14	23.99	1.16	23.08	1.17	26.36	4.25	108.9
BAY 1117268[a]	2	1.65	0.33	23.10	1.97	21.45	2.00	14.00	3.04	101.2
BAY 1117268[a]	5	1.38	0.36	20.04	0.66	18.66	0.75	14.52	3.82	88.1
BAY 1117268[a]	10	1.34	0.35	17.71	0.68	16.37	0.76	13.22	3.49	77.3

a = IC_{50} of BAY 1117268 (M-2a) against pravastatin (5 µM) as probe substrate not reached in the investigated concentration range (IC_{50} >10 µM)

Test article: Finerenone

Table 16-87: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OATP1B1 and OATP1B3 in a preincubation assay

Location: 4.2.2.7.9
Report no.: PH-40952

Species:	Human	Route:	*in vitro*
Material:	hOATP1B1, hOATP1B3 transfected cells, vector-HEK cells		
Test compound:	BAY 1117271 (M-3a)	Assay:	LC-MS/MS

Uptake of pravastatin mediated by OATP1B1										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B1 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117271[a]	0	3.91	0.47	20.89	0.75	16.99	0.88	5.35	0.67	100
BAY 1117271[a]	0.2	3.90	0.40	18.04	0.74	14.15	0.84	4.63	0.52	83.3
BAY 1117271[a]	0.5	4.40	0.26	18.12	0.31	13.72	0.40	4.12	0.25	80.8
BAY 1117271[a]	2	4.82	0.49	16.45	0.15	11.64	0.51	3.42	0.35	68.5
BAY 1117271[a]	5	4.16	0.22	14.13	0.44	9.98	0.49	3.40	0.21	58.7
BAY 1117271[a]	10	3.27	0.95	11.89	0.85	8.62	1.28	3.63	1.08	50.7

Uptake of pravastatin mediated by OATP1B3										
Inhibitor	**Inhibitor concentration [µM]**	**Vector-HEK cells [pmol/mg/min]**		**hOATP1B3 cells [pmol/mg/min]**		**Net uptake [pmol/mg/min]**		**Uptake ratio**		**% of net uptake [%]**
		Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
BAY 1117271[b]	0	1.36	0.01	33.11	5.37	31.76	5.37	24.37	3.95	100
BAY 1117271[b]	0.2	1.43	0.04	32.42	2.69	30.99	2.69	22.67	1.97	97.6
BAY 1117271[b]	0.5	1.21	0.15	26.54	2.08	25.34	2.09	22.02	3.29	79.8
BAY 1117271[b]	2	1.45	0.28	21.04	2.35	19.59	2.37	14.52	3.28	61.7
BAY 1117271[b]	5	1.29	0.12	14.04	1.43	12.75	1.44	10.87	1.52	40.1
BAY 1117271[b]	10	1.44	0.16	9.50	0.97	8.05	0.98	6.58	1.00	25.3

a = IC_{50} of BAY 1117271 (M-3a) against pravastatin (5 µM) as probe substrate not reached in the investigated concentration range (IC_{50} >10 µM)
b = IC_{50} of BAY 1117271 (M-3a) against pravastatin (5 µM) as probe substrate = 3.4 µM

Test article: Finerenone

Table 16-88: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OAT1 and OAT3

Location: 4.2.2.7.24
Report no.: R-9702

Species: Human
Material: hOAT1, hOAT3 transfected HEK-cells, vector-HEK cells
Test compound: BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)
Route: *in vitro*
Assay: LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of PAH mediated by OAT1 [pmol/mg protein/min]							
					Vector-HEK		hOAT1-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
PAH[a,b]	10	5 min	BAY 1117267	0.25	0.303	0.027	306	10	306	10	-11.2[c]	4.6
PAH[a,b]	10	5 min	BAY 1117267	2.47	0.738	0.234	332	10	331	10	-20.4[c]	4.9
PAH[a,b]	10	5 min	BAY 1117266	0.52	2.07	0.73	304	7	302	7	-9.79[c]	3.93
PAH[a,b]	10	5 min	BAY 1117266	5.16	1.83	0.30	276	8	274	8	0.418	3.97
PAH[a,b]	10	5 min	BAY 1117268	0.31	1.24	0.30	314	17	313	17	-13.8[c]	7.0
PAH[a,b]	10	5 min	BAY 1117268	3.10	1.34	0.25	339	13	338	13	-23.0[c]	5.7
PAH[a,b]	10	5 min	BAY 1117271	0.43	1.95	0.36	305	7	303	7	-10.2[c]	3.8
PAH[a,b]	10	5 min	BAY 1117271	4.25	2.85	0.66	317	14	315	14	-14.4[c]	6.0
PAH[a]	10	5 min	-	-	0.919	0.194	276	7	275	7	-	-
PAH[a]	10	5 min	Probenecid	100	2.29	0.34	12.2	1.2	9.91	1.29	96.4	0.5

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of Furosemide mediated by OAT3 [pmol/mg protein/min]							
					Vector-HEK		hOAT3-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Furosemide[b]	5	5 min	BAY 1117267	0.25	1.90	0.33	140	10	138	10	3.40	7.56
Furosemide[b]	5	5 min	BAY 1117267	2.47	2.64	0.14	134	3	132	3	7.63	3.76
Furosemide[b]	5	5 min	BAY 1117266	0.52	3.09	0.71	132	6	129	6	9.69	5.42
Furosemide[b]	5	5 min	BAY 1117266	5.16	4.41	0.58	112	5	108	5	24.3	4.3
Furosemide[b]	5	5 min	BAY 1117268	0.31	1.74	0.22	113	12	111	12	22.2	8.9
Furosemide[b]	5	5 min	BAY 1117268	3.10	2.80	0.28	115	4	112	4	21.4	4.2
Furosemide[b]	5	5 min	BAY 1117271	0.43	3.10	0.34	108	10	105	10	26.4	7.7
Furosemide[b]	5	5 min	BAY 1117271	4.25	4.51	0.49	117	6	113	6	20.9	5.3
Furosemide	5	5 min	-	-	2.36	0.37	145	5	142	5	-	-
Furosemide	5	5 min	Probenecid	100	3.17	0.61	2.52	0.59	-0.65	0.85	100[d]	

a = p-aminohippuric acid
b = IC_{50} of finerenone metabolites against these probe substrates not reached in the investigated concentration range (M-1a: IC_{50} >2.5 µM; M-1b: IC_{50} >5.2 µM; M-2a: IC_{50} >3.1 µM; M-3a: IC_{50} >4.3 µM)
c = negative values idicate no inhibition
d = the calculated percentage inhibition was greater than 100, but the value of 100 is reported as the maximal value

Test article: Finerenone

Table 16-89: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential of metabolites towards human uptake transporters OCT1 and OCT2

Location: 4.2.2.7.25
Report no.: R-9701

Species:	Human	Route:	*in vitro*
Material:	hOCT1, hOCT2 transfected HEK-cells, vector-HEK cells		
Test compound:	BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117271 (M-3a)	Assay:	LC-MS/MS

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of MPP^+ [a] mediated by OCT1 [pmol/mg protein/min]							
					Vector-HEK		hOCT1-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
MPP^+ [a,b]	5	2 min	BAY 1117267	0.85	13.7	1.8	219	15	205	15	-30.8[c]	16.4
MPP^+ [a,b]	5	2 min	BAY 1117267	8.50	13.1	2.6	202	9	189	9	-20.7[c]	13.6
MPP^+ [a,b]	5	2 min	BAY 1117266	0.72	13.3	1.1	199	10	186	10	-18.6[c]	13.6
MPP^+ [a,b]	5	2 min	BAY 1117266	7.17	13.6	1.6	204	17	190	18	-21.2[c]	16.6
MPP^+ [a,b]	5	2 min	BAY 1117268	0.36	9.88	1.79	182	15	172	15	-9.78[c]	14.8
MPP^+ [a,b]	5	2 min	BAY 1117268	3.57	9.72	1.39	173	9	164	9	-4.52[c]	12.1
MPP^+ [a,b]	5	2 min	BAY 1117271	0.43	10.3	1.0	175	16	165	16	-5.30[c]	14.9
MPP^+ [a,b]	5	2 min	BAY 1117271	4.25	10.8	1.4	185	11	175	11	-11.4[c]	13.4
MPP^+ [a]	5	2 min	-	-	14.0	6.4	171	15	157	16	-	-
MPP^+ [a]	5	2 min	Repaglinide	600	4.50	0.59	30.3	1.9	25.8	2.0	83.6	2.1

Probe substrate	Probe substrate conc. [µM]	Incubation time	Inhibitor	Inhibitor conc. [µM]	Uptake of MPP+ a mediated by OCT2 [pmol/mg protein/min]							
					Vector-HEK		hOCT2-HEK		Net uptake		Inhibition [%]	
					Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
MPP+ a,d	5	2 min	BAY 1117267	0.25	13.1	2.9	197	12	184	12	0.45	9.61
MPP+ a,d	5	2 min	BAY 1117267	2.47	12.4	0.9	184	14	172	14	7.06	9.94
MPP+ a,d	5	2 min	BAY 1117266	0.52	12.3	0.8	165	11	153	11	17.4	8.5
MPP+ a,d	5	2 min	BAY 1117266	5.16	12.1	0.7	192	15	180	15	2.54	10.48
MPP+ a,d	5	2 min	BAY 1117268	0.31	14.6	1.7	236	14	221	14	-19.6c	11.4
MPP+ a,d	5	2 min	BAY 1117268	3.10	15.1	1.2	226	9	210	9	-13.9c	9.4
MPP+ a,d	5	2 min	BAY 1117271	0.43	14.3	1.1	216	6	201	6	-8.95c	8.44
MPP+ a,d	5	2 min	BAY 1117271	4.25	15.0	1.0	224	16	209	16	-13.0c	11.9
MPP+ a	5	2 min	-	-	14.7	3.2	199	13	185	13	-	-
MPP+ a	5	2 min	Imipramine	300	5.55	1.46	30.6	1.0	25.0	1.8	86.5	1.4

a = 1-methyl-4-phenylpyridinium
b = IC_{50} of finerenone metabolites against this probe substrate not reached in the investigated concentration range (M-1a: IC_{50} >8.5 µM; M-1b: IC_{50} >7.2 µM; M-2a: IC_{50} >3.6 µM; M-3a: IC_{50} >4.3 µM)
c = negative values idicate no inhibition
d = IC_{50} of finerenone metabolites against this probe substrate not reached in the investigated concentration range (M-1a: IC_{50} >2.5 µM; M-1b: IC_{50} >5.2 µM; M-2a: IC_{50} >3.1 µM; M-3a: IC_{50} >4.3 µM)

Test article: Finerenone

Table 16-90: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by finerenone

Type of study: Inhibition potential on transporter proteins
Methods: LC-MS/MS
Table: *In vitro* evaluation of finerenone as an inhibitor of human P-gp, BCRP, BSEP, MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters

Transporter	Cell line	Probe substrate	Finerenone IC_{50} [µM]	Inhibition at highest concentration tested	Estimated *in vivo* DDI risk (Yes/No)	Location, report number
P-gp	LLC-PK1-MDR1	Dipyridamole (2 µM)	47	96% at 600 µM	No	4.2.2.7.3, PH-40886
P-gp	LLC-PK1-MDR1	Digoxin (20 µM)	121	96% at 600 µM	No	4.2.2.7.3, PH-40886
BCRP	MDCKII-BCRP	Topotecan (2 µM)	18.1	90% at 200 µM	Yes	4.2.2.7.5, PH-40885
BCRP	MDCKII-BCRP	PhIP (2 µM)	17.4	90% at 300 µM	Yes	4.2.2.7.5, PH-40885
BSEP	SCHH (BEI)	d8-TCA (5 µM)	>100	0% at 100 µM	No	4.2.2.7.6, R-11129
NTCP/BSEP	SCHH ($CL_{Biliary}$)	d8-TCA (5 µM)	>100	0% at 100 µM	No	4.2.2.7.6, R-11129
MATE1	HEK293-MATE1	Metformin (50 µM)	>5	10% at 5 µM	No	4.2.2.7.7, R-11196
MATE2K	HEK293-MATE2K	Metformin (50 µM)	>5	35% at 5 µM	No	4.2.2.7.7, R-11196
OATP1B1	HEK293-OATP1B1	Pravastatin (5 µM)	3.2	79% at 10 µM	Yes	4.2.2.7.9, PH-40952
OATP1B3	HEK293-OATP1B3	Pravastatin (5 µM)	>10	47% at 10 µM	No	4.2.2.7.9, PH-40952
OAT1	HEK293-OAT1	PAH (10 µM)	>3	-5% at 3 µM	No	4.2.2.7.10, R-9494
OAT3	HEK293-OAT3	Furosemide (5 µM)	>3	-13% at 3 µM	No	4.2.2.7.10, R-9494
OCT1	HEK293-OCT1	MPP^+ (5 µM)	>5	-27% at 5 µM	No	4.2.2.7.11, R-9495
OCT2	HEK293-OCT2	MPP^+ (5 µM)	>3	1.1% at 3 µM	No	4.2.2.7.12, R-9440

An assessment of DDI risk between finerenone and co-administered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, is provided in [2.6.5.16 Table 16-91] and [2.6.5.16 Table 16-92], respectively

Abbreviations: LC-MS/MS = liquid chromatography-tandem mass spectrometry; IC_{50} = concentration required for 50% inhibition; DDI = drug-drug interaction; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; NTCP = sodium-taurocholate cotransporting polypeptide; MATE1 = multidrug and toxin extrusion protein 1; MATE2K = multidrug and toxin extrusion protein 2K; OATP1B1 = organic anion transporting polypeptide 1B1; OATP1B3 = organic anion transporting polypeptide 1B3; OAT1 = organic anion transporter 1; OAT3 = organic anion transporter 3; OCT1 = organic cation transporter 1; OCT2 = organic cation transporter 2; LLC-PK1 = Lilly Laboratories cell - porcine kidney 1; MDR1 = multidrug resistance protein 1; MDCKII = Madin-Darby canine kidney cells; SCHH = sandwich-cultured human hepatocytes; BEI = biliary excretion index; $CL_{Biliary}$ = *in vitro* biliary clearance; HEK293 = human embryonic kidney 293 cells; d8-TCA = d8-taurocholic acid; PAH = p-aminohippuric acid; MPP^+ = 1-methyl-4-phenylpyridinium; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

Additional information: IC_{50} values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

Test article: Finerenone

Table 16-91: Pharmacokinetics: Drug-drug interaction, transporter inhibition by finerenone (FDA)

Table: Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

Transporter	Location, report number	$[I]_{max,u}$ [µM]	$[I]_{in,max,u}$ [µM]	$[I]_{gut}$ [µM]	IC_{50} [µM]	$[I]/IC_{50}$	Threshold cutoff for potential DDI
			Intestinal				
P-gp	4.2.2.7.3, PH-40886	-	-	211	47	4.5	$[I]/IC_{50} \geq 10$
BCRP	4.2.2.7.5, PH-40885	-	-	211	17.4	12.1	$[I]/IC_{50} \geq 10$
			Systemic				
BSEP	4.2.2.7.6, R-11129	0.035		-	>100	<0.0004	$[I]/IC_{50} \geq 0.1$
MATE1	4.2.2.7.7, R-11196	0.035	-	-	>5	<0.007	$[I]/IC_{50} \geq 0.1$
MATE2K	4.2.2.7.7, R-11196	0.035	-	-	>5	<0.007	$[I]/IC_{50} \geq 0.1$
OATP1B1	4.2.2.7.9, PH-40952	-	0.292	-	3.2	0.091	$[I]/IC_{50} \geq 0.1$
OATP1B3	4.2.2.7.9, PH-40952	-	0.292	-	>10	<0.029	$[I]/IC_{50} \geq 0.1$
OAT1	4.2.2.7.10, R-9494	0.035	-	-	>3	<0.01	$[I]/IC_{50} \geq 0.1$
OAT3	4.2.2.7.10, R-9494	0.035	-	-	>3	<0.01	$[I]/IC_{50} \geq 0.1$
OCT1	4.2.2.7.11, R-9495	-	0.292	-	>5	<0.058	$[I]/IC_{50} \geq 0.1$
OCT2	4.2.2.7.12, R-9440	0.035	-	-	>3	<0.01	$[I]/IC_{50} \geq 0.1$

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for finerenone calculated under assumption of dose-linearity from exposures of finerenone at steady state observed in patients receiving 10 mg finerenone (5.3.3.5.3 R-9543) (finerenone total $[I]_{max}$ = 0.43 µM [161 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.292 µM ($I_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/R_B)$, where fraction absorbed (F_a) = 1, fraction escaping gut metabolism (F_g) = 0.575 [Heinig R et al., Eur J Drug Metab Pharmacokinet 2018:43:715–727 (4.3.48)], observed absorption rate constant (k_a) = 0.153 min^{-1} (5.3.3.5.2 PH-36697), hepatic blood flow (Q_h) = 1617 mL/min, R_B (blood-to-plasma ratio) = 0.935; unbound fraction = 0.0833); $[I]_{gut}$ = theoretical maximum gastrointestinal drug concentration, calculated as the highest clinical dose on a molar basis in a volume of 250 mL; [I] = $[I]_{max,u}$ or $[I]_{in,max,u}$ or $[I]_{gut}$ used for IC_{50} ratio formation depending on specific guideline requirement; IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

Test article: Finerenone

Table 16-92: Pharmacokinetics: Drug-drug interaction, transporter inhibition by finerenone (EMA)

Table: Assessment of risk for *in vivo* DDI between finerenone and co-administered substrates of various transporters, based on the EMA guidance (2012)[a]

Transporter	Location, report number	K_i[b] [µM]	50 × $[I]_{max,u}$ [µM]	25 × $[I]_{in,max,u}$ [µM]	0.1 × Dose/250 [µM]	Threshold cutoff for potential DDI
			Intestinal			
P-gp	4.2.2.7.3, PH-40886	47	-	-	21.14	$K_i \leq (0.1 \times Dose/250)$
BCRP	4.2.2.7.5, PH-40885	17.4	-	-	21.14	$K_i \leq (0.1 \times Dose/250)$
			Systemic			
P-gp	4.2.2.7.3, PH-40886	47	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
BCRP	4.2.2.7.5, PH-40885	17.4	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
BSEP	4.2.2.7.6, R-11129	>100	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
MATE1	4.2.2.7.7, R-11196	>5	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
MATE2K	4.2.2.7.7, R-11196	>5	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
OATP1B1	4.2.2.7.9, PH-40952	3.2	-	7.29	-	$K_i \leq (25 \times [I]_{in,max,u})$
OATP1B3	4.2.2.7.9, PH-40952	>10	-	7.29	-	$K_i \leq (25 \times [I]_{in,max,u})$
OAT1	4.2.2.7.10, R-9494	>3	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
OAT3	4.2.2.7.10, R-9494	>3	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$
OCT1	4.2.2.7.11, R-9495	>5[c]	-	7.29	-	$K_i \leq (25 \times [I]_{in,max,u})$
OCT2	4.2.2.7.12, R-9440	>3	1.77	-	-	$K_i \leq (50 \times [I]_{max,u})$

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = assuming $K_i = IC_{50}$: inhibition data obtained at substrate concentrations << K_m (Michaelis Menten constant)

c = OCT1 inhibition at a concentration of 5 µM = -26.9%

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for finerenone calculated under assumption of dose-linearity from exposures of finerenone at steady state observed in patients receiving 10 mg finerenone (5.3.3.5.3 R-9543) (finerenone total $[I]_{max}$ = 0.43 µM [161 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.292 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/R_B)$, where fraction absorbed (F_a) = 1, fraction escaping gut metabolism (F_g) = 0.575 [Heinig R et al., Eur J Drug Metab Pharmacokinet 2018:43:715–727 (4.3.48)], observed absorption rate constant (k_a) = 0.153 min^{-1} (5.3.3.5.2 PH-36697), hepatic blood flow (Q_h) = 1617 mL/min, R_B (blood-to-plasma ratio) = 0.935; unbound fraction = 0.0833); K_i = inhibition constant (reversible); IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

Test article: Finerenone

Table 16-93: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117267 (M-1a)

Type of study: Inhibition potential on transporter proteins
Methods: LC-MS/MS
Table: *In vitro* evaluation of BAY 1117267 (M-1a) as an inhibitor of human P-gp, BCRP, BSEP, MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters

Transporter	Cell line	Probe substrate	M-1a IC_{50} [µM]	Inhibition at highest concentration tested	Estimated *in vivo* DDI risk (Yes/No)	Location, report number
P-gp	LLC-PK1-MDR1	Dipyridamole (2 µM)	70	48.0% at 100 µM	No	4.2.2.7.3, PH-40886
P-gp	LLC-PK1-MDR1	Digoxin (20 µM)	>100	25.7% at 100 µM	No	4.2.2.7.3, PH-40886
BCRP	MDCKII-BCRP	Topotecan (2 µM)	>20	41.0% at 20 µM	No	4.2.2.7.5, PH-40885
BCRP	MDCKII-BCRP	PhIP (2 µM)	>20	30.1% at 20 µM	No	4.2.2.7.5, PH-40885
BSEP	SCHH (BEI)	d8-TCA (5 µM)	>30	7.0% at 30 µM	No	4.2.2.7.22, R-11130
NTCP/BSEP	SCHH ($CL_{Biliary}$)	d8-TCA (5 µM)	>30	0% at 30 µM	No	4.2.2.7.22, R-11130
MATE1	HEK293-MATE1	Metformin (50 µM)	>5	-3.0% at 5 µM	No	4.2.2.7.23, R-11820
MATE2K	HEK293-MATE2K	Metformin (50 µM)	>5	22.5% at 5 µM	No	4.2.2.7.23, R-11820
OATP1B1	HEK293-OATP1B1	Pravastatin (5 µM)	3.8	73.0% at 10 µM	No	4.2.2.7.9, PH-40952
OATP1B3	HEK293-OATP1B3	Pravastatin (5 µM)	7.6	55.8% at 10 µM	No	4.2.2.7.9, PH-40952
OAT1	HEK293-OAT1	PAH (10 µM)	>2.5	-20.4% at 2.5 µM	No	4.2.2.7.24, R-9702
OAT3	HEK293-OAT3	Furosemide (5 µM)	>2.5	7.6% at 2.5 µM	No	4.2.2.7.24, R-9702
OCT1	HEK293-OCT1	MPP^+ (5 µM)	>8.5	-20.7% at 8.5 µM	No	4.2.2.7.25, R-9701
OCT2	HEK293-OCT2	MPP^+ (5 µM)	>2.5	7.1% at 2.5 µM	No	4.2.2.7.25, R-9701

An assessment of DDI risk between BAY 1117267 (M-1a) and co-administered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, is provided in [2.6.5.16 Table 16-94] and [2.6.5.16 Table 16-95], respectively

Abbreviations: LC-MS/MS = liquid chromatography-tandem mass spectrometry; IC_{50} = concentration required for 50% inhibition; DDI = drug-drug interaction; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; NTCP = sodium-taurocholate cotransporting polypeptide; MATE1 = multidrug and toxin extrusion protein 1; MATE2K = multidrug and toxin extrusion protein 2K; OATP1B1 = organic anion transporting polypeptide 1B1; OATP1B3 = organic anion transporting polypeptide 1B3; OAT1 = organic anion transporter 1; OAT3 = organic anion transporter 3; OCT1 = organic cation transporter 1; OCT2 = organic cation transporter 2; LLC-PK1 = Lilly Laboratories cell - porcine kidney 1; MDR1 = multidrug resistance protein 1; MDCKII = Madin-Darby canine kidney cells; SCHH = sandwich-cultured human hepatocytes; BEI = biliary excretion index; $CL_{Biliary}$ = *in vitro* biliary clearance; HEK293 = human embryonic kidney 293 cells; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; d8-TCA = d8-taurocholic acid; PAH = p-aminohippuric acid; MPP^+ = 1-methyl-4-phenylpyridinium

Additional information: IC_{50} values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

Test article: Finerenone

Table 16-94: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117267 (M-1a) (FDA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117267 (M-1a) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

Transporter	Location, report number	$[I]_{max,u}$ [µM]	IC_{50} [µM]	$[I]_{max,u}/IC_{50}$	Threshold cutoff for potential DDI
			Systemic		
BSEP	4.2.2.7.22, R-11130	0.047	>30	<0.002	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE1	4.2.2.7.23, R-11820	0.047	>5	<0.009	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE2K	4.2.2.7.23, R-11820	0.047	>5	<0.009	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B1	4.2.2.7.9, PH-40952	0.047	3.8	0.012	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B3	4.2.2.7.9, PH-40952	0.047	7.6	0.006	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT1	4.2.2.7.24, R-9702	0.047	>2.5	<0.019	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT3	4.2.2.7.24, R-9702	0.047	>2.5	<0.019	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT1	4.2.2.7.25, R-9701	0.047	>8.5	<0.006	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT2	4.2.2.7.25, R-9701	0.047	>2.5	<0.019	$[I]_{max,u}/IC_{50} \geq 0.1$

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1a calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-1a total $[I]_{max}$ = 0.80 µM [302 µg/L] and unbound fraction = 0.0582); IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

Test article: Finerenone

Table 16-95: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117267 (M-1a) (EMA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117267 (M-1a) and co-administered substrates of various transporters, based on the EMA guidance (2012)[a]

Transporter	Location, report number	K_i[b] [µM]	50 × $[I]_{max,u}$ [µM]	Threshold cutoff for potential DDI
		Systemic		
P-gp	4.2.2.7.3, PH-40886	70	2.33	$K_i \leq (50 \times [I]_{max,u})$
BCRP	4.2.2.7.5, PH-40885	>20	2.33	$K_i \leq (50 \times [I]_{max,u})$
BSEP	4.2.2.7.22, R-11130	>30	2.33	$Ki \leq (50 \times [I]_{max,u})$
MATE1	4.2.2.7.23, R-11820	>5	2.33	$K_i \leq (50 \times [I]_{max,u})$
MATE2K	4.2.2.7.23, R-11820	>5	2.33	$K_i \leq (50 \times [I]_{max,u})$
OATP1B1	4.2.2.7.9, PH-40952	3.8	2.33	$K_i \leq (50 \times [I]_{max,u})$
OATP1B3	4.2.2.7.9, PH-40952	7.6	2.33	$K_i \leq (50 \times [I]_{max,u})$
OAT1	4.2.2.7.24, R-9702	>2.5	2.33	$K_i \leq (50 \times [I]_{max,u})$
OAT3	4.2.2.7.24, R-9702	>2.5	2.33	$K_i \leq (50 \times [I]_{max,u})$
OCT1	4.2.2.7.25, R-9701	>8.5	2.33	$K_i \leq (50 \times [I]_{max,u})$
OCT2	4.2.2.7.25, R-9701	>2.5	2.33	$K_i \leq (50 \times [I]_{max,u})$

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = assuming $K_i = IC_{50}$: inhibition data obtained at substrate concentrations << K_m (Michaelis-Menten constant)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1a calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-1a total $[I]_{max}$ = 0.80 µM [302 µg/L] and unbound fraction = 0.0582); K_i = inhibition constant (reversible)

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

Test article: Finerenone

Table 16-96: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117266 (M-1b)

Type of study: Inhibition potential on transporter proteins
Methods: LC-MS/MS
Table: *In vitro* evaluation of BAY 1117266 (M-1b) as an inhibitor of human P-gp, BCRP, BSEP, MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters

Transporter	Cell line	Probe substrate	M-1b IC_{50} [µM]	Inhibition at highest concentration tested	Estimated *in vivo* DDI risk (Yes/No)	Location, report number
P-gp	LLC-PK1-MDR1	Dipyridamole (2 µM)	31	54.4% at 30 µM	No	4.2.2.7.3, PH-40886
P-gp	LLC-PK1-MDR1	Digoxin (20 µM)	>30	24.2% at 30 µM	No	4.2.2.7.3, PH-40886
BCRP	MDCKII-BCRP	Topotecan (2 µM)	>30	30.2% at 30 µM	No	4.2.2.7.5, PH-40885
BSEP	SCHH (BEI)	d8-TCA (5 µM)	>30	5.8% at 30 µM	No	4.2.2.7.22, R-11130
NTCP/BSEP	SCHH ($CL_{Biliary}$)	d8-TCA (5 µM)	>30	2.2% at 30 µM	No	4.2.2.7.22, R-11130
MATE1	HEK293-MATE1	Metformin (50 µM)	>5	-66.8% at 5 µM	No	4.2.2.7.23, R-11820
MATE2K	HEK293-MATE2K	Metformin (50 µM)	>5	25.1% at 5 µM	No	4.2.2.7.23, R-11820
OATP1B1	HEK293-OATP1B1	Pravastatin (5 µM)	3.9	75.0% at 10 µM	No	4.2.2.7.9, PH-40952
OATP1B3	HEK293-OATP1B3	Pravastatin (5 µM)	7.3	56.3% at 10 µM	No	4.2.2.7.9, PH-40952
OAT1	HEK293-OAT1	PAH (10 µM)	>5.2	0.4% at 5.2 µM	No	4.2.2.7.24, R-9702
OAT3	HEK293-OAT3	Furosemide (5 µM)	>5.2	24.3% at 5.2 µM	No	4.2.2.7.24, R-9702
OCT1	HEK293-OCT1	MPP^+ (5 µM)	>7.2	-21.2% at 7.2 µM	No	4.2.2.7.25, R-9701
OCT2	HEK293-OCT2	MPP^+ (5 µM)	>5.2	2.5% at 5.2 µM	No	4.2.2.7.25, R-9701

An assessment of DDI risk between BAY 1117266 (M-1b) and co-administered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, is provided in [2.6.5.16 Table 16-97] and [2.6.5.16 Table 16-98], respectively

Abbreviations: LC-MS/MS = liquid chromatography-tandem mass spectrometry; IC_{50} = concentration required for 50% inhibition; DDI = drug-drug interaction; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; NTCP = sodium-taurocholate cotransporting polypeptide; MATE1 = multidrug and toxin extrusion protein 1; MATE2K = multidrug and toxin extrusion protein 2K; OATP1B1 = organic anion transporting polypeptide 1B1; OATP1B3 = organic anion transporting polypeptide1B3; OAT1 = organic anion transporter 1; OAT3 = organic anion transporter 3; OCT1 = organic cation transporter 1; OCT2 = organic cation transporter 2; LLC-PK1 = Lilly Laboratories cell - porcine kidney 1; MDR1 = multidrug resistance protein 1; MDCKII = Madin-Darby canine kidney cells; SCHH = sandwich-cultured human hepatocytes; BEI = biliary excretion index; $CL_{Biliary}$ = *in vitro* biliary clearance; HEK293 = human embryonic kidney 293 cells; d8-TCA = d8-taurocholic acid; PAH = p-aminohippuric acid; MPP^+ = 1-methyl-4-phenylpyridinium

Additional information: IC_{50} values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

Test article: Finerenone

Table 16-97: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117266 (M-1b) (FDA)

Table: Assessment of risk for *in vivo* DDI between BAY 111726 (M-1b) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

Transporter	Location, report number	$[I]_{max,u}$ [µM]	IC_{50} [µM]	$[I]_{max,u}/IC_{50}$	Threshold cutoff for potential DDI
			Systemic		
BSEP	4.2.2.7.22, R-11130	0.006	>30	<0.0002	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE1	4.2.2.7.23, R-11820	0.006	>5	<0.001	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE2K	4.2.2.7.23, R-11820	0.006	>5	<0.001	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B1	4.2.2.7.9, PH-40952	0.006	3.9	0.002	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B3	4.2.2.7.9, PH-40952	0.006	7.3	0.0008	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT1	4.2.2.7.24, R-9702	0.006	>5.2	<0.001	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT3	4.2.2.7.24, R-9702	0.006	>5.2	<0.001	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT1	4.2.2.7.25, R-9701	0.006	>7.2	<0.0008	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT2	4.2.2.7.25, R-9701	0.006	>5.2	<0.001	$[I]_{max,u}/IC_{50} \geq 0.1$

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1b in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1b calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-1b total $[I]_{max}$ = 0.16 µM [61.5 µg/L] and unbound fraction = 0.0388); IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

Test article: Finerenone

Table 16-98: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117266 (M-1b) (EMA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117266 (M-1b) and co-administered substrates of various transporters, based on the EMA guidance (2012)[a]

Transporter	Location, report number	K_i[b] [µM]	50 × $[I]_{max,u}$ [µM]	Threshold cutoff for potential DDI
		Systemic		
P-gp	4.2.2.7.3, PH-40886	31	0.32	$K_i \leq (50 \times [I]_{max,u})$
BCRP	4.2.2.7.5, PH-40885	>30	0.32	$K_i \leq (50 \times [I]_{max,u})$
BSEP	4.2.2.7.22, R-11130	>30	0.32	$K_i \leq (50 \times [I]_{max,u})$
MATE1	4.2.2.7.23, R-11820	>5	0.32	$K_i \leq (50 \times [I]_{max,u})$
MATE2K	4.2.2.7.23, R-11820	>5	0.32	$K_i \leq (50 \times [I]_{max,u})$
OATP1B1	4.2.2.7.9, PH-40952	3.9	0.32	$K_i \leq (50 \times [I]_{max,u})$
OATP1B3	4.2.2.7.9, PH-40952	7.3	0.32	$K_i \leq (50 \times [I]_{max,u})$
OAT1	4.2.2.7.24, R-9702	>5.2	0.32	$K_i \leq (50 \times [I]_{max,u})$
OAT3	4.2.2.7.24, R-9702	>5.2	0.32	$K_i \leq (50 \times [I]_{max,u})$
OCT1	4.2.2.7.25, R-9701	>7.2	0.32	$K_i \leq (50 \times [I]_{max,u})$
OCT2	4.2.2.7.25, R-9701	>5.2	0.32	$K_i \leq (50 \times [I]_{max,u})$

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = assuming $K_i = IC_{50}$: inhibition data obtained at substrate concentrations << K_m (Michaelis-Menten constant)

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-1b in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-1b calculated under assumption of dose-linearity from exposures of M-1 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-1a:M-1b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-1b total $[I]_{max}$ = 0.16 µM [61.5 µg/L] and unbound fraction = 0.0388); K_i = inhibition constant (reversible)

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

Test article: Finerenone

Table 16-99: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117268 (M-2a)

Type of study: Inhibition potential on transporter proteins
Methods: LC-MS/MS
Table: *In vitro* evaluation of BAY 1117268 (M-2a) as an inhibitor of human P-gp, BCRP, BSEP, MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters

Transporter	Cell line	Probe substrate	M-2a IC_{50} [µM]	Inhibition at highest concentration tested	Estimated *in vivo* DDI risk (Yes/No)	Location, report number
P-gp	LLC-PK1-MDR1	Dipyridamole (2 µM)	>30	26.4% at 30 µM	No	4.2.2.7.3, PH-40886
P-gp	LLC-PK1-MDR1	Digoxin (20 µM)	>30	-5.4% at 30 µM	No	4.2.2.7.3, PH-40886
BCRP	MDCKII-BCRP	Topotecan (2 µM)	>20	14.8% at 20 µM	No	4.2.2.7.5, PH-40885
BCRP	MDCKII-BCRP	PhIP (2 µM)	>20	24.8% at 20 µM	No	4.2.2.7.5, PH-40885
BSEP	SCHH (BEI)	d8-TCA (5 µM)	>30	2.9% at 30 µM	No	4.2.2.7.22, R-11130
NTCP/BSEP	SCHH ($CL_{Biliary}$)	d8-TCA (5 µM)	>30	0% at 30 µM	No	4.2.2.7.22, R-11130
MATE1	HEK293-MATE1	Metformin (50 µM)	>5	9.1% at 5 µM	No	4.2.2.7.23, R-11820
MATE2K	HEK293-MATE2K	Metformin (50 µM)	>5	-3.7% at 5 µM	No	4.2.2.7.23, R-11820
OATP1B1	HEK293-OATP1B1	Pravastatin (5 µM)	>10	42.6% at 10 µM	No	4.2.2.7.9, PH-40952
OATP1B3	HEK293-OATP1B3	Pravastatin (5 µM)	>10	22.7% at 10 µM	No	4.2.2.7.9, PH-40952
OAT1	HEK293-OAT1	PAH (10 µM)	>3.1	-23% at 3.1 µM	No	4.2.2.7.24, R-9702
OAT3	HEK293-OAT3	Furosemide (5 µM)	>3.1	21.4% at 3.1 µM	No	4.2.2.7.24, R-9702
OCT1	HEK293-OCT1	MPP^+ (5 µM)	>3.6	-4.5% at 3.6 µM	No	4.2.2.7.25, R-9701
OCT2	HEK293-OCT2	MPP^+ (5 µM)	>3.1	-13.0% at 3.1 µM	No	4.2.2.7.25, R-9701

An assessment of DDI risk between BAY 1117268 (M-2a) and co-administered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, is provided in [2.6.5.16 Table 16-100] and [2.6.5.16 Table 16-101], respectively

Abbreviations: LC-MS/MS = liquid chromatography-tandem mass spectrometry; IC_{50} = concentration required for 50% inhibition; DDI = drug-drug interaction; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; NTCP = sodium-taurocholate cotransporting polypeptide; MATE1 = multidrug and toxin extrusion protein 1; MATE2K = multidrug and toxin extrusion protein 2K; OATP1B1 = organic anion transporting polypeptide 1B1; OATP1B3 = organic anion transporting polypeptide 1B3; OAT1 = organic anion transporter 1; OAT3 = organic anion transporter 3; OCT1 = organic cation transporter 1; OCT2 = organic cation transporter 2; LLC-PK1 = Lilly Laboratories cell - porcine kidney 1; MDR1 = multidrug resistance protein 1; MDCKII = Madin-Darby canine kidney cells; SCHH = sandwich-cultured human hepatocytes; BEI = biliary excretion index; $CL_{Biliary}$ = *in vitro* biliary clearance; HEK293 = human embryonic kidney 293 cells; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; PAH = p-aminohippuric acid; MPP^+ = 1-methyl-4-phenylpyridinium; d8-TCA = d8-taurocholic acid

Additional information: IC_{50} values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

Test article: Finerenone

Table 16-100: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117268 (M-2a) (FDA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117268 (M-2a) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

Transporter	Location, report number	$[I]_{max,u}$ [µM]	IC_{50} [µM]	$[I]_{max,u}/IC_{50}$	Threshold cutoff for potential DDI
			Systemic		
BSEP	4.2.2.7.22, R-11130	0.07	>30	<0.002	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE1	4.2.2.7.23, R-11820	0.07	>5	<0.014	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE2K	4.2.2.7.23, R-11820	0.07	>5	<0.014	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B1	4.2.2.7.9, PH-40952	0.07	>10	<0.007	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B3	4.2.2.7.9, PH-40952	0.07	>10	<0.007	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT1	4.2.2.7.24, R-9702	0.07	>3.1	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT3	4.2.2.7.24, R-9702	0.07	>3.1	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT1	4.2.2.7.25, R-9701	0.07	>3.6	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT2	4.2.2.7.25, R-9701	0.07	>3.1	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-2a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-2a calculated under assumption of dose-linearity from exposures of M-2 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-2a:M-2b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-2a total $[I]_{max}$ = 0.39 µM [152 µg/L] and unbound fraction = 0.174); IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

Test article: Finerenone

Table 16-101: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117268 (M-2a) (EMA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117268 (M-2a) and co-administered substrates of various transporters, based on the EMA guidance (2012)[a]

Transporter	Location, report number	K_i[b] [µM]	50 × $[I]_{max,u}$ [µM]	Threshold cutoff for potential DDI
		Systemic		
P-gp	4.2.2.7.3, PH-40886	>30	3.37	$K_i \leq (50 \times [I]_{max,u})$
BCRP	4.2.2.7.5, PH-40885	>20	3.37	$K_i \leq (50 \times [I]_{max,u})$
BSEP	4.2.2.7.22, R-11130	>30	3.37	$K_i \leq (50 \times [I]_{max,u})$
MATE1	4.2.2.7.23, R-11820	>5	3.37	$K_i \leq (50 \times [I]_{max,u})$
MATE2K	4.2.2.7.23, R-11820	>5	3.37	$K_i \leq (50 \times [I]_{max,u})$
OATP1B1	4.2.2.7.9, PH-40952	>10	3.37	$K_i \leq (50 \times [I]_{max,u})$
OATP1B3	4.2.2.7.9, PH-40952	>10	3.37	$K_i \leq (50 \times [I]_{max,u})$
OAT1	4.2.2.7.24, R-9702	>3.1[c]	3.37	$K_i \leq (50 \times [I]_{max,u})$
OAT3	4.2.2.7.24, R-9702	>3.1[c]	3.37	$K_i \leq (50 \times [I]_{max,u})$
OCT1	4.2.2.7.25, R-9701	>3.6	3.37	$K_i \leq (50 \times [I]_{max,u})$
OCT2	4.2.2.7.25, R-9701	>3.1[c]	3.37	$K_i \leq (50 \times [I]_{max,u})$

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = assuming $K_i = IC_{50}$: inhibition data obtained at substrate concentrations << K_m (Michaelis-Menten constant)

c = inhibition at a concentration of 3.1 µM: OAT1 = -23.0%; OAT3 = 21.4%; OCT2 = -13.9%

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-2a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-2a calculated under assumption of dose-linearity from exposures of M-2 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-2a:M-2b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-2a total $[I]_{max}$ = 0.39 µM [152 µg/L] and unbound fraction = 0.174); K_i = inhibition constant (reversible)

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

Test article: Finerenone

Table 16-102: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117271 (M-3a)

Type of study: Inhibition potential on transporter proteins
Methods: LC-MS/MS
Table: *In vitro* evaluation of BAY 1117271 (M-3a) as an inhibitor of human P-gp, BCRP, BSEP, MATE1, MATE2K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters

Transporter	Cell line	Probe substrate	M-3a IC_{50} [µM]	Inhibition at highest concentration tested	Estimated *in vivo* DDI risk (Yes/No)	Location, report number
P-gp	LLC-PK1-MDR1	Dipyridamole (2 µM)	>30	-6.9% at 30 µM	No	4.2.2.7.3, PH-40886
P-gp	LLC-PK1-MDR1	Digoxin (20 µM)	>30	8.2% at 30 µM	No	4.2.2.7.3, PH-40886
BCRP	MDCKII-BCRP	Topotecan (2 µM)	>20	-28.5% at 20 µM	No	4.2.2.7.5, PH-40885
BCRP	MDCKII-BCRP	PhIP (2 µM)	>20	16.7% at 20 µM	No	4.2.2.7.5, PH-40885
BSEP	SCHH (BEI)	d8-TCA (5 µM)	>30	0.0% at 30 µM	No	4.2.2.7.22, R-11130
NTCP/BSEP	SCHH ($CL_{Biliary}$)	d8-TCA (5 µM)	>30	0% at 30 µM	No	4.2.2.7.22, R-11130
MATE1	HEK293-MATE1	Metformin (50 µM)	>5	17.6% at 5 µM	No	4.2.2.7.23, R-11820
MATE2K	HEK293-MATE2K	Metformin (50 µM)	>5	-4.9% at 5 µM	No	4.2.2.7.23, R-11820
OATP1B1	HEK293-OATP1B1	Pravastatin (5 µM)	>10	49.3% at 10 µM	No	4.2.2.7.9, PH-40952
OATP1B3	HEK293-OATP1B3	Pravastatin (5 µM)	3.4	74.7% at 10 µM	Yes	4.2.2.7.9, PH-40952
OAT1	HEK293-OAT1	PAH (10 µM)	>4.3	-14.4% at 4.3 µM	No	4.2.2.7.24, R-9702
OAT3	HEK293-OAT3	Furosemide (5 µM)	>4.3	20.9% at 4.3 µM	No	4.2.2.7.24, R-9702
OCT1	HEK293-OCT1	MPP^+ (5 µM)	>4.3	-11.4% at 4.3 µM	No	4.2.2.7.25, R-9701
OCT2	HEK293-OCT2	MPP^+ (5 µM)	>4.3	-13% at 4.3 µM	No	4.2.2.7.25, R-9701

An assessment of DDI risk between BAY 1117271 (M-3a) and co-administered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, is provided in [2.6.5.16 Table 16-103] and [2.6.5.16 Table 16-104], respectively

Abbreviations: LC-MS/MS = liquid chromatography-tandem mass spectrometry; IC_{50} = concentration required for 50% inhibition; DDI = drug-drug interaction; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; BSEP = bile salt export pump; NTCP = sodium-taurocholate cotransporting polypeptide; MATE1 = multidrug and toxin extrusion protein 1; MATE2K = multidrug and toxin extrusion protein 2K; OATP1B1 = organic anion transporting polypeptide 1B1; OATP1B3 = organic anion transporting polypeptide 1B3; OAT1 = organic anion transporter 1; OAT3 = organic anion transporter 3; OCT1 = organic cation transporter 1; OCT2 = organic cation transporter 2; LLC-PK1 = Lilly Laboratories cell - porcine kidney 1; MDR1 = multidrug resistance protein 1; MDCKII = Madin-Darby canine kidney cells; SCHH = sandwich-cultured human hepatocytes; BEI = biliary excretion index; $CL_{Biliary}$ = *in vitro* biliary clearance; HEK293 = human embryonic kidney 293 cells; d8-TCA = d8-taurocholic acid; PAH = p-aminohippuric acid; MPP^+ = 1-methyl-4-phenylpyridinium; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

Additional information: IC_{50} values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

Test article: Finerenone

Table 16-103: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117271 (M-3a) (FDA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117271 (M-3a) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

Transporter	Location, report number	$[I]_{max,u}$ [µM]	IC_{50} [µM]	$[I]_{max,u}/IC_{50}$	Threshold cutoff for potential DDI
			Systemic		
BSEP	4.2.2.7.22, R-11130	0.12	>30	<0.004	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE1	4.2.2.7.23, R-11820	0.12	>5	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$
MATE2K	4.2.2.7.23, R-11820	0.12	>5	<0.02	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B1	4.2.2.7.9, PH-40952	0.12	>10	<0.012	$[I]_{max,u}/IC_{50} \geq 0.1$
OATP1B3	4.2.2.7.9, PH-40952	0.12	3.4	0.035	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT1	4.2.2.7.24, R-9702	0.12	>4.3	<0.03	$[I]_{max,u}/IC_{50} \geq 0.1$
OAT3	4.2.2.7.24, R-9702	0.12	>4.3	<0.03	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT1	4.2.2.7.25, R-9701	0.12	>4.3	<0.03	$[I]_{max,u}/IC_{50} \geq 0.1$
OCT2	4.2.2.7.25, R-9701	0.12	>4.3	<0.03	$[I]_{max,u}/IC_{50} \geq 0.1$

a = *In Vitro* Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Guidance for Industry. Issued by: U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Jan 2020

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-3a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-3a calculated under assumption of dose-linearity from exposures of M-3 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-3a:M-3b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-3a total $[I]_{max}$ = 0.17 µM [69.6 µg/L] and unbound fraction = 0.678); IC_{50} = concentration required for 50% inhibition

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a

Test article: Finerenone

Table 16-104: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117271 (M-3a) (EMA)

Table: Assessment of risk for *in vivo* DDI between BAY 1117271 (M-3a) and co-administered substrates of various transporters, based on the EMA guidance (2012)[a]

Transporter	Location, report number	K_i[b] [µM]	50 × $[I]_{max,u}$ [µM]	Threshold cutoff for potential DDI
		Systemic		
P-gp	4.2.2.7.3, PH-40886	>30	5.81	$K_i \leq (50 \times [I]_{max,u})$
BCRP	4.2.2.7.5, PH-40885	>20	5.81	$K_i \leq (50 \times [I]_{max,u})$
BSEP	4.2.2.7.22, R-11130	>30	5.81	$K_i \leq (50 \times [I]_{max,u})$
MATE1	4.2.2.7.23, R-11820	>5[c]	5.81	$K_i \leq (50 \times [I]_{max,u})$
MATE2K	4.2.2.7.23, R-11820	>5[c]	5.81	$K_i \leq (50 \times [I]_{max,u})$
OATP1B1	4.2.2.7.9, PH-40952	>10	5.81	$K_i \leq (50 \times [I]_{max,u})$
OATP1B3	4.2.2.7.9, PH-40952	3.4	5.81	$K_i \leq (50 \times [I]_{max,u})$
OAT1	4.2.2.7.24, R-9702	>4.3[d]	5.81	$K_i \leq (50 \times [I]_{max,u})$
OAT3	4.2.2.7.24, R-9702	>4.3[d]	5.81	$K_i \leq (50 \times [I]_{max,u})$
OCT1	4.2.2.7.25, R-9701	>4.3[d]	5.81	$K_i \leq (50 \times [I]_{max,u})$
OCT2	4.2.2.7.25, R-9701	>4.3[d]	5.81	$K_i \leq (50 \times [I]_{max,u})$

a = Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. In: CPMP/EWP/560/95/Rev. 1 Corr. 2. London, England: European Medicines Agency; 2012

b = assuming $K_i = IC_{50}$: inhibition data obtained at substrate concentrations << K_m (Michaelis-Menten constant)

c = inhibition at a concentration of 5 µM: MATE1 = 17.6%, MATE2K = -4.9%

d = inhibition at a concentration of 4.3 µM: OAT1 = -14.4%; OAT3 = 20.9%; OCT1 = -11.4%; OCT2 = -13.0%

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration of M-3a in humans treated with 20 mg finerenone, based on median $C_{max,ss}$ for M-3a calculated under assumption of dose-linearity from exposures of M-3 at steady state observed in patients receiving 10 mg finerenone (2.7.2.2.5.2.2) as well as the atropisomer ratio of M-3a:M-3b obtained in healthy volunteers at steady state receiving 40 mg finerenone (4.2.2.7.19, PH-40388) (M-3a total $[I]_{max}$ = 0.17 µM [69.6 µg/L] and unbound fraction = 0.678); K_i = inhibition constant (reversible)

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a