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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（BAY 94-8862）は 2022 年 3 月に「2 型糖尿病を合併する慢性腎臓病」の効能・効果で承認されている。フィネレノン及びヒト血漿中主代謝物（M-1a、M-1b、M-2a 及び M-3a）の薬物動態特性を明らかにするための試験は実施済みであり、初回承認申請時に試験成績を提出済みである〔「2 型糖尿病を合併する慢性腎臓病」の承認時申請資料（以下、CTD-CKD）〕。

今回の「慢性心不全」の効能・効果を追加する承認事項一部変更承認申請においては、臨床最高用量が既承認の 20mg から 40mg に増量され、臨床曝露量が増加する。一方、既提出の *in vitro* 試験ではフィネレノン又は主代謝物の添加濃度は、臨床における 20mg 投与後の最高血漿中濃度に基づき設定された。そのため、40mg 投与後の最高血漿中濃度を考慮すると、一部のトランスポーターに対する阻害試験では検討濃度が低く、ガイドラインで推奨されるカットオフ基準によって相互作用の可能性を否定することができなかった。本申請では、一部のトランスポーター〔有機アニオントランスポーター（OAT）1/3、有機カチオントランスポーター（OCT）1/2、多剤排出トランスポーター（MATE）1/2K〕に対する阻害作用について、フィネレノン又はその主代謝物を高濃度で添加した *in vitro* 試験を新たに実施し、薬物動態学的薬物相互作用の可能性を再評価した。

更に、P-糖タンパク（P-gp）に対する *in vitro* 阻害試験では、試験系により阻害剤の影響にばらつきが報告[1、2]されている。そのため、新たに Caco-2 細胞を用いた試験系にて、フィネレノンの P-gp に対する阻害試験を実施した。その結果、50%阻害濃度（$IC_{50}$）として 7.74μM が得られ、初回承認申請時に提出した、P-gp をトランスフェクトした LLC-PK1（L-MDR1）細胞における $IC_{50}$（47μM）と比較して強い阻害作用がみられた。

上記の追加試験及び既提出の試験を含めた *in vitro* 試験成績、更に、フィネレノン 40mg を反復経口投与後のフィネレノン及び主代謝物の曝露量に基づき、主要な薬物代謝酵素に対する誘導及び阻害作用、並びにトランスポーターに対する阻害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を再評価した（2.6.5.12 及び 2.6.5.16）。新たに Caco-2 細胞から得た、P-gp に対するフィネレノンの阻害作用の試験成績によると、フィネレノン 20 及び 40mg のいずれの用量でも、P-gp の阻害を介した臨床的に問題となる相互作用を引き起こす可能性が示唆された。しかしながら、フィネレノン 20mg を、P-gp の典型基質薬ジゴキシンと併用した臨床薬物相互作用試験において、フィネレノン併用の影響は認められなかった（CTD-CKD 2.7.2.2.3.2.5）。また、フィネレノン 40mg 投与が P-gp 基質薬に及ぼす影響について生理学的薬物速度論モデルを用いて検討した結果、40mg の用量でもフィネレノンは P-gp を阻害しないと考えられた（2.7.2.2.5.3.1）。そのほかに *in vitro* 試験で示唆された相互作用の可能性は、フィネレノン 40mg を投与した臨床薬物相互作用試験によって確認又は否定された（2.7.2.2.3.2）。

### 2.6.4.2　分析法

臨床試験試料の分析法に関連する新たな報告書については2.6.5.1及び2.6.5.2に記載する。

既提出の分析法に関してはCTD-CKD 2.6.4.2を参照。

### 2.6.4.3　吸収

CTD-CKD 2.6.4.3を参照。

### 2.6.4.4　分布

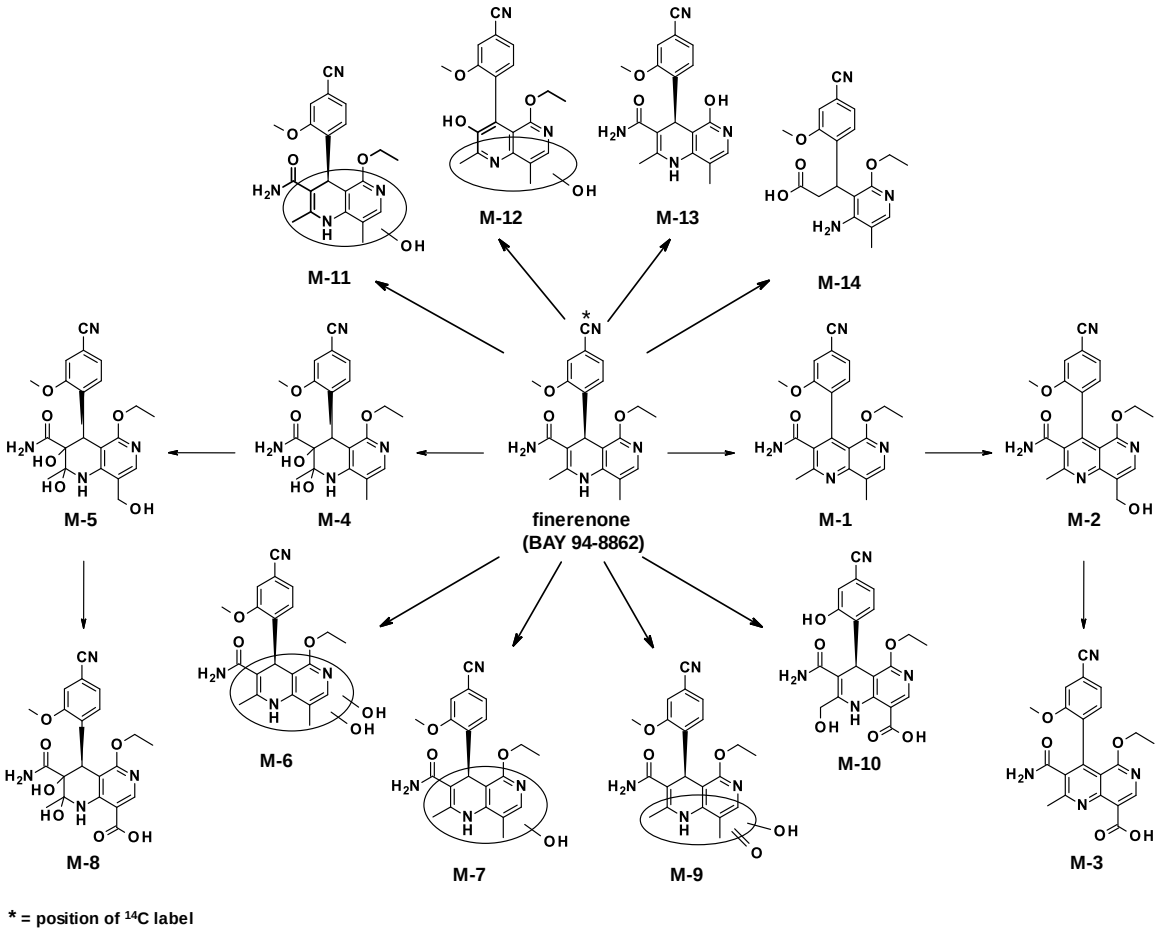
CTD-CKD 2.6.4.4を参照。

### 2.6.4.5　代謝

代謝に関する新たな試験は実施していない。*In vitro*及び*in vivo*におけるフィネレノンの代謝試験成績はCTD-CKD 2.6.4.5を参照。これらの試験成績より推定される代謝経路を図2.6.4.5-1に再掲する。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。単回又は反復投与後のヒト血漿中の異性体の存在比及びヒトでのマスバランス試験又は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（CTD-CKD 2.6.4.8.6.1）。

フィネレノンの代謝に関わる酵素分子種の同定、代謝酵素に対する阻害作用並びに誘導作用の試験成績はCTD-CKD 2.6.4.5を参照。フィネレノンの代謝酵素に対する阻害作用及び誘導作用、並びに本申請の最高用量であるフィネレノン40mgを1日1回反復経口投与後のヒトにおける曝露量を考慮した薬物相互作用の予測計算は、2.6.5.12 Table 12-1～Table 12-4（阻害作用）及び2.6.5.12 Table 12-5（誘導作用）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**




CTD-CKD 図 2.6.4.5-1 の再掲

## 2.6.4.5.1 *In vitro* 代謝

参照項目： 4.2.2.4.1 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、チトクローム P450（CYP）分子種に対するフィネレノンの誘導作用を評価した既提出の報告書に、用量の増加（40mg）を考慮した相対誘導スコア（RIS）及び静的薬物速度論モデルによる評価を追記した（4.2.2.4.1 PH-39130、Appendix 7）。試験成績は 2.6.5.12 Table 12-5 に示す。

そのほかの試験成績については CTD-CKD 2.6.4.5 を参照。

## 2.6.4.6 排泄

CTD-CKD 2.6.4.6 を参照。

## 2.6.4.7 薬物動態学的薬物相互作用

CTD-CKD 2.6.4.7 を参照。

## 2.6.4.8 その他の薬物動態試験

膜透過性に関する試験成績は CTD-CKD 2.6.4.8.1 を参照。

フィネレノンの P-gp に対する阻害作用を、既提出の L-MDR1 細胞とは異なる Caco-2 細胞を用いて検討した。また、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、有機アニオン輸送ポリペプチド（OATP）1B1 及び OATP1B3 に対するフィネレノンの基質特性を低濃度（臨床濃度）で新たに検討した。また、一部のトランスポーターに対するフィネレノンの阻害作用について、フィネレノン 40mg を 1 日 1 回反復投与時の曝露量に基づき、既提出の試験よりも高濃度を用いた *in vitro* 試験を実施した。

フィネレノンのトランスポーターに対する基質特性及び阻害作用の既提出の試験成績は CTD-CKD 2.6.4.8.2～CTD-CKD 2.6.4.8.5 を参照。フィネレノンのトランスポーターに対する阻害作用、並びに本申請の最高用量であるフィネレノン 40mg を 1 日 1 回反復経口投与後のヒトにおける曝露量を考慮した薬物相互作用の可能性の評価については、2.6.5.16 Table 16-18～Table 16-20 に示す。

### 2.6.4.8.1 排泄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 B003719

Caco-2 細胞を使用して、フィネレノンの P-gp に対する阻害作用を検討した。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 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* assays, inhibitory potential towards P-gp |
|---|---|
| Bayer reference | 4.2.2.7.3, B003719 |
| Test system | Caco-2 cells: P-gp |
| Probe Substrates | Digoxin |
| Reference Inhibitors | Ivermectin |
| Test compound | Finerenone:<br>0.3 – 100 µM (114 – 37842 µg/L) |

**表 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阻害作用**

| **Transporter** | **Probe substrate** | **$IC_{50}$ [µM]** |
|---|---|---|
| P-gp (LLC-PK1 cells) | Digoxin | 121[a] |
| P-gp (LLC-PK1 cells) | Dipyridamole | 47[a] |
| BCRP | Topotecan | 18.1[a] |
| BCRP | 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) | 17.4[a] |
| BSEP | d8-taurocholic acid (d8-TCA) | >100[a] |
| MATE1 | Metformin | >5[a] |
| MATE2K | Metformin | >5[a] |
| **P-gp (Caco-2 cells)** | **Digoxin** | **7.74** |

**Source: 4.2.2.7.3 B003719**
a: CTD-CKD 2.6.4.8.4 表 2.6.4.8-6 のデータの再掲

典型基質としてジゴキシンを使用した場合、フィネレノンの P-gp に対する $IC_{50}$ は 7.74μM（2929μg/L）であった。

### 2.6.4.8.2　　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： 4.2.2.7.1　 R-13843

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 及び OATP1B3 に対するフィネレノンの基質特性を検討した。これらの細胞において、フィネレノンの取込みを測定した。陽性対照は典型基質薬を用いた。

既提出の試験（CTD-CKD 2.6.4.8.3）ではフィネレノン濃度 0.5 及び 5μM において、OATP1B1 及び OATP1B3 を介する能動的な取込みは認められなかった。今回、欧州医薬品庁（EMA）の薬物相互作用ガイドライン[2)]の付録Ⅲに従って、より低濃度の 0.01、0.05、0.10 及び 0.15μM において検討しても、いずれのトランスポーターにおいてもフィネレノンの能動的な取込みはみられなかった。（取込み比＜2、範囲：OATP1B1 は 0.849～1.03、OATP1B3 は 0.668～0.968）。フィネレノンを 1 日 1 回 20 及び 40mg の用量で反復経口投与後の非結合型最高血漿濃度〔$C_{max,u}$＝0.043μM（20mg）、0.083μM（40mg）〕及び肝臓入り口における非結合型最高濃度〔$[I]_{in,max,u}$＝0.299μM（20mg）、0.596μM（40mg）〕は検討した濃度範囲に含まれる。結果として、フィネレノンは臨床濃度においても OATP1B1 及び OATP1B3 の基質特性を示さず、新たに実施した *in vitro* 試験成績は、既提出の試験成績と矛盾しなかった。

**表 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検討試験の概要**

| Study type | *In vitro* assay, substrate characteristics for uptake transporters |
|---|---|
| Bayer reference | 4.2.2.7.1 R-13843 |
| Test system | Control cells and transfected HEK cells: OATP1B1, OATP1B3 |
| Probe substrate | Atorvastatin (OATPs) |
| Test compound | Finerenone: 0.01 – 0.15 µM (3.78 – 56.8 µg/L for OATPs) |

### 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阻害作用

参照項目：4.2.2.7.2 R-14427

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、OCT1 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。試験の概要を表 2.6.4.8- 4 に、試験成績を表 2.6.4.8- 5 に示す。

**表 2.6.4.8- 4　取込みトランスポーターOCT1 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 | 4.2.2.7.2 R-14427 |
| Test system | Transfected HEK cells: OCT1 |
| Probe substrates | $MPP^+$ |
| Reference inhibitor | Repaglinide |
| Test compound | Finerenone: 15 µM (5676 µg/L) |

表 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

| Transporter | Probe substrate | $IC_{50}$ [μM] |
|---|---|---|
| OATP1B1 | Pravastatin | 3.2[a] |
| OATP1B3 | Pravastatin | >10[a] |
| OAT1 | p-aminohippuric acid (PAH) | >3[a] |
| OAT3 | Furosemide | >3[a] |
| **OCT1** | **$MPP^+$** | **>15** |
| OCT2 | $MPP^+$ | >3[a] |

**Source: 4.2.2.7.2 R-14427 (OCT1)**
a: CTD-CKD 2.6.4.8.5 表 2.6.4.8-8 のデータの再掲

フィネレノンは、本申請における最高用量 40mg を考慮した濃度範囲で、OCT1 に対して阻害作用を示さなかった。米国食品医薬品局（FDA）[3]及び EMA の薬物相互作用ガイダンスに基づく薬物相互作用の可能性の評価については、2.6.5.16 Table 16-18～Table 16-20 に示す。

### 2.6.4.8.4 ヒト血漿中主代謝物に関する検討

主代謝物の代謝酵素に対する阻害及び誘導作用に関する新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.4.8.6.3～CTD-CKD 2.6.4.8.6.5 を参照。主代謝物の代謝酵素に対する阻害作用及び誘導作用、並びに本申請の最高用量であるフィネレノン 40mg を 1 日 1 回反復経口投与後のヒトにおける主代謝物の曝露量を考慮した薬物相互作用の予測計算は、2.6.5.16 Table 16-7～Table 16-14（阻害作用）及び 2.6.5.16 Table 16-15～Table 16-17（誘導作用）に示す。

一部のトランスポーターに対するフィネレノン主代謝物の阻害作用について、ガイドラインでのカットオフ基準により本申請用量での相互作用を否定できるように高濃度を用いて検討した。主代謝物のトランスポーターに対する基質特性及び阻害作用の既提出の試験成績は CTD-CKD 2.6.4.8.6.6～CTD-CKD 2.6.4.8.6.7 を参照。フィネレノン主代謝物のトランスポーターに対する阻害作用、並びに本申請の最高用量であるフィネレノン 40mg を 1 日 1 回反復経口投与後のヒトにおける主代謝物の曝露量を考慮した薬物相互作用の可能性の評価については、2.6.5.16 Table 16-21～Table 16-32 に示す。

#### 2.6.4.8.4.1 CYP 分子種に対する代謝物の誘導作用

参照項目： 4.2.2.4.1 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 M-1a、M-1b、M-2a 及び M-3a の誘導作用を評価した。既提出の報告書に、用量の増加を考慮した RIS モデル及び静的薬物動態速度論モデルによる誘導の予測を追記した。試験成績は 2.6.5.16 Table 16-15～Table 16-17 に示す。そのほかの試験成績については CTD-CKD 2.6.4.8.6.5 を参照。

#### 2.6.4.8.4.2 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： 4.2.2.7.2 R-14427

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を用いて、MATE1 及び MATE2K を介した典型基質の輸送に対する 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- 6 に、試験成績を表 2.6.4.8- 7 に示す。

表 2.6.4.8- 6 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 | 4.2.2.7.2 R-42271 |
| Test system | Transfected HEK cells: MATE1 and MATE2K |
| Probe substrates | Metformin (MATE1 and MATE2K) |
| Reference Inhibitors | Cimetidine (MATE1); pyrimethamine (MATE2K) |
| Test compound | M-2a (BAY 1117268): 0.3 – 50 µM (118 – 19621 µg/L) for MATE1, 7 µM (2747 µg/L) for MATE2K<br>M-3a (BAY 1117271): 0.3 – 50 µM (122 - 20320 µg/L) for MATE1, 29 µM (11785 µg/L) for MATE2K |

表 2.6.4.8- 7 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 [b] | >30 [b] | >30 [b] | >30 [b] |
| P-gp | Dipyridamole | 70 [b] | 31 [b] | >30 [b] | >30 [b] |
| BCRP | Topotecan | >20 [b] | >30 [b] | >20 [b] | >20 [b] |
| BCRP | PhIP | >20 [b] | n.d. [b, c] | >20 [b] | >20 [b] |
| BSEP | d8-TCA | >30 [b] | >30 [b] | >30 [b] | >30 [b] |
| **MATE1** | **Metformin** | >5 [b] | >5 [b] | **>50** | **>50** |
| **MATE2K** | **Metformin** | >5 [b] | >5 [b] | **>7** | **>29** |

**Source: 4.2.2.7.2 R-14427**
a = values in µg/L:
M-1a: >5 µM = >1882 µg/L, >20 µM = >7528 µg/L, >30 µM = >11292 µg/L, 70 µM = 26349 µg/L, >100 µM = >37641 µg/L
M-1b: >5 µM = >1882 µg/L, >30 µM = >11292 µg/L, 31 µM = 11669 µg/L
M-2a: >7 µM = >2747 µg/L, >20 µM = >7848 µg/L, >30 µM = >11772 µg/L, >50 µM = >19621 µg/L
M-3a: >20 µM = >8128 µg/L, >29 µM = >11785 µg/L, >30 µM = >12192 µg/L, >50 µM = >20320 µg/L
b: CTD-CKD 2.6.4.8.6 表 2.6.4.8-29 のデータの再掲
c: not applicable

M-2a 及び M-3a は、本申請における最高用量 40mg を考慮した濃度範囲で MATE1 及び MATE2K に対して阻害作用を示さなかった（表 2.6.4.8- 7）。FDA 及び EMA の薬物相互作用ガイダンスに基づく薬物相互作用の可能性の評価については、2.6.5.16 Table 16-21～Table 16-32 に示す。

## 2.6.4.8.4.3 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：4.2.2.7.2 R-14427

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、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（OCT1 を除く）、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- 8 に、試験成績を表 2.6.4.8- 9 に示す。

表 2.6.4.8- 8 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 | 4.2.2.7.2 R-14427 | |
| Test system | Transfected HEK cells: OAT1, OAT3, OCT1, OCT2 | |
| Probe substrates | PAH (OAT1); furosemide (OAT3); $MPP^+$ (OCTs) | |
| Reference inhibitors | probenecid (OATs); repaglinide (OCT1); imipramine (OCT2) | |
| Test compound | M-1a (BAY 1117267): | 0.3 – 50 µM (113 – 18821 µg/L) for OCT2/OAT3,<br>5 µM (1882 µg/L) for OAT1<br>0.3 – 50 µM (118 – 19621 µg/L) for OCT1/OAT3 |
| | M-2a (BAY 1117268): | 7 µM (2747 µg/L) for OCT2/OAT1<br>29 µM (11785 µg/L) for OCTs/OAT1 |
| | M-3a (BAY 1117271): | 0.3 – 50 µM (122 – 20320 µg/L) for OAT3 |

表 2.6.4.8- 9 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[b] | 3.9[b] | >10[b] | >10[b] |
| OATP1B3 | Pravastatin | 7.6[b] | 7.3[b] | >10[b] | 3.4[b] |
| **OAT1** | **PAH** | **>5** | >5.2[b] | **>7** | **>29** |
| **OAT3** | **Furosemide** | **>50** | >5.2[b] | **>50** | **>50** |
| **OCT1** | **$MPP^+$** | >8.5[b] | >7.2[b] | **>50** | **>29** |
| **OCT2** | **$MPP^+$** | **>50** | >5.2[b] | **>7** | **>29** |

**Source: 4.2.2.7.2 R-14427**
a: values in µg/L:
M-1a/b: 3.8 µM = 1430 µg/L, 3.9 µM = 1468 µg/L, >5 µM = >1882 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: >7 µM = >2747 µg/L, >10 µM = >3924 µg/L, 50 µM = 19621 µg/L,
M-3a: >10 µM = >4064 µg/L, 29 µM = 11785 µg/L, >50 µM = >20320 µg/L,
b: CTD-CKD 2.6.4.8.6 表 2.6.4.8-31 のデータの再掲

代謝物 M-1a、M-2a 及び M-3a は、本申請における最高用量 40mg を考慮した濃度範囲で OAT1、OAT3、OCT1（M-1a は検討していない）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- 9）。FDA 及び EMA の薬物相互作用ガイダンスに基づく薬物相互作用の可能性の再評価については、2.6.5.16 Table 16-21～Table 16-32 に示す。

## 2.6.4.9 考察及び結論

既提出の非臨床薬物動態試験成績については CTD-CKD 2.6.4 及び 2.6.5 を、フィネレノンの 1 日 1 回 20mg の反復経口投与を支持する考察及び結論については CTD-CKD 2.6.4.9 をそれぞれ参照。

本申請に際して、フィネレノン 1 日 1 回 40mg の反復経口投与が薬物相互作用を引き起こす可能性を評価するため、一部、薬物トランスポーターに対する *in vitro* 阻害試験を追加で実施した。追加試験では、フィネレノン並びにヒト血漿中の主代謝物 M-1a、M-2a 及び M-3a を既提出の試験よりも高濃度で添加した。また、フィネレノンの取込みトランスポーターOATP1B1/1B3 に対する基質特性の検討を臨床濃度で実施した。

新たな検討結果を既提出の検討結果と合わせ、フィネレノン 40mg 投与時の薬物相互作用の可能性を以下に記載する。

フィネレノンは、*in vitro* における検討において、主要な CYP 及びウリジン二リン酸グルクロン酸転移酵素（UGT）分子種のうち、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、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〔最大不活性化速度定数（$k_{inact}$）：0.012$min^{-1}$、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〕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 40mg 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[3]及び EMA[2]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評価した。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 AUC 比（AUCR：時間依存性阻害の basic model で算出）及び CYP2C8 基質薬の AUCR〔静的薬物速度論モデル（mechanistic static model）で算出〕は 1.25 を超えた。これは、フィネレノンが CYP3A4 及び CYP2C8 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するものであった。CYP1A1 の最高血漿中非結合型濃度（$C_{max,u}$=$I_{max,u}$）/$K_i$ は 0.029 となり、ガイドラインのカットオフ基準（0.02、basic model）をわずかに上回ったが、静的薬物速度論モデル（基質薬の $f_m$=1 を仮定）を使用した場合には、CYP1A1 の可逆的阻害による薬物相互作用の可能性は示唆されなかった。更に、フィネレノンは、組換え CYP1A1 とのプレインキュベーションによりわずかな不可逆的阻害を示した。しかしながら、現在知られる CYP1A1 の基質薬物は限られており、フィネレノンにより不可逆的な CYP1A1 阻害を介する薬物相互作用が臨床的に問題となる可能性は低いと考えられる。CYP3A4、CYP2C8 及び CYP1A1 を除くほかのすべての CYP 並びに UGT 分子種に対しては、可逆的阻害の basic model を用いた評価により、フィネレノンが *in vivo* で酵素阻害剤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 40mg を 1 日 1 回反復経口投与後の最高血漿中濃度（$C_{max}$=$I_{max}$）：1.00μM（379μg/L）、最高血漿中非結合型濃度（$I_{max,u}$）：0.0834μM（31.6μg/L）、臨床試験で得られた吸収速度定数（$k_a$）：0.153 $min^{-1}$ 及び吸収率×消化管アベイラビリティ（Fa×Fg）：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（$I_{in,max,u}$）：0.596μM 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 40mg を 1 日 1 回反復経口投与後の定常状態における代謝物の曝露量〔M-1a：1.61μM（604μg/L）、M-1b：0.327μM（123μg/L）、M-2a：0.775μM（304μg/L）、M-3a：0.343μM（139μg/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は低いことが示された（2.6.5.16 Table 16-7～Table 16-14）。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（CTD-CKD 2.7.2.2.5,2.2 及び CTD-CKD 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、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 69%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 が中程度（2.6.5.12 Table 12-5 及び 2.6.5.16 Table 16-17）、M-1a が弱い～中程度（2.6.5.16 Table 16-15）、M-1b が弱い CYP3A4 誘導作用（2.6.5.16 Table 16-16）を示す可能性が示唆された。フィネレノン及び主代謝物の *in vitro* 誘導試験成績及び臨床曝露量を用い、共調節される CYP2B6 及び CYP2C19 誘導の可能性を静的薬物速度論モデルに基づき評価した。その結果、このモデルに基づくと、フィネレノン及び主代謝物は、*in vivo* で CYP2B6 及び CYP2C19 を誘導する可能性は低いことが予測された（4.2.2.4.1 PH-39130、Appendix 7）。

上記の *in vitro* において示唆された代謝酵素を介する相互作用の可能性を検討するために、臨床薬物相互作用試験において、フィネレノン 40mg の投与が CYP3A4 及び CYP2C8 の酵素阻害剤として薬物相互作用を引き起こす可能性を検討した。フィネレノン 40mg を 1 日 1 回 10 日間反復経口投与後の定常状態において、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は AUC として意味のある増加（AUCR：1.31）を示したが、$C_{max}$ は臨床的に意味のある増加を示さなかった（$C_{max}$R：1.15）（2.7.2.2.3.2.2）。ミダゾラムの代謝物である 1'-ヒドロキシミダゾラムの親化合物に対する比（AUC 及び AUC(0-$t_{last}$)）は、フィネレノン併用時にはミダゾラム単独投与時と比較してわずかに低く、フィネレノンによるミダゾラムの AUC 増加を反映するものであった。更に、フィネレノン 40mg を 1 日 1 回 10 日間反復経口投与後の定常状態において、CYP2C8 の典型基質薬であるレパグリニド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、臨床的に意味のあるレパグリニドの曝露量増加が認められた（AUCR：1.59、2.7.2.2.3.2.2）。結論として、フィネレノン 40mg の 1 日 1 回投与は CYP3A4 及び CYP2C8 に対する弱い阻害作用を示した。

フィネレノンは *in vitro* において、検討した濃度範囲で胆汁酸塩排出ポンプ（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 P-gp 及び BCRP のトランスフェクト細胞において、両トランスポーターを阻害し、それらに対する $IC_{50}$ は 47/121μM（P-gp）及び 17.4/18.1μM（BCRP）であった。また、代謝物 M-1a 及び M-1b はいずれも P-gp に対してわずかな阻害作用を示した（$IC_{50}$≧31μM）。P-gp に対する阻害作用は *in vitro* 試験系により阻害剤の影響にばらつきが報告[1、2)]されていることから、新たに Caco-2 細胞にて、ジゴキシンを典型基質として P-gp に対するフィネレノンの阻害作用を検討したところ、$IC_{50}$ は、トランスフェクト細胞を用いた場合よりも低く 7.74μM であった。新たに得られた P-gp に対する $IC_{50}$ については、消化管内最高薬物濃度と $IC_{50}$ との比（$I_{gut}/IC_{50}$）はフィネレノン 1 日 1 回 20 及び 40mg 投与時にそれぞれ 27.3 及び 54.6 であり、関連ガイドライン[2、3)]のカットオフ基準である 10 を超えていた。また、40mg 投与時の $C_{max}/K_i$ は 0.129 であり、FDA ガイドラインのカットオフ基準である 0.1 をわずかに超えていたが、$C_{max,u}/K_i$ は 0.0108 であり、EMA ガイドラインのカットオフ基準の 0.02 を超えなかった。MDRI（P-gp）をトランスフェクトした L-MDR1 細胞における $IC_{50}$ に基づく評価では、フィネレノンによる臨床的に問題となる P-gp の阻害作用の可能性は低いと考えられたが、Caco-2 を使用した評価では、フィネレノン 20 及び 40mg 投与時に P-gp 阻害を介する臨床的に問題となる相互作用が引き起こされる可能性を否定できなかった（2.6.5.16 Table 16-19 及び Table 16-20）。

加えて、フィネレノン、代謝物 M-1a 及び M-1b は OATP1B1 を阻害し、$IC_{50}$ はそれぞれ 3.2、3.8 及び 3.9μM であった。また、代謝物 M-1a、M-1b 及び M-3a は OATP1B3 を阻害し、それぞれの $IC_{50}$ は 7.6、7.3 及び 3.4μM であった。フィネレノン 40mg を 1 日 1 回反復経口投与後の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、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 0.182 となり、FDA ガイドライン[3)]によるカットオフ基準（$I_{in,max,u}/IC_{50}$≧0.1）及び、EMA ガイドライン[2)]によるカットオフ基準（$I_{in,max,u}/K_i$≧0.04）を上回った（2.6.5.16 Table 16-19 及び Table 16-20）。主代謝物に関してはフィネレノン 40mg を 1 日 1 回反復経口投与後の主代謝物の曝露量に基づき、FDA 及び EMA ガイドラインにより推奨されている $I_{max,u}/IC_{50}$ 又は $I_{max,u}/K_i$ によって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 16-22、Table 16-25、Table 16-28 及び Table 16-31 並びに EMA ガイドラインに基づく評価：2.6.5.16 Table 16-23、Table 16-26、Table 16-29 及び Table 16-32）。その結果、M-1a 及び M-3a については、OATP1B1 及び／又は OATP1B3 の基質薬に対するカットオフ基準をわずかに超えていた。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た。

フィネレノンが P-gp、BCRP、OATP1B1 及び OATP1B3 のトランスポーターに対する阻害作用を介して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臨床試験及びモデルによる評価により示唆されなかった。

すなわち、P-gp については、臨床薬物相互作用試験で、フィネレノン 20mg を 1 日 1 回反復経口投与後に、P-gp の基質薬ジゴキシンに対して臨床的に意味のある影響を示さなかった（AUCR=1.02、CTD-CKD 2.7.2.2.3.2.5）。更に、フィネレノン及びジゴキシンの生理学的薬物速度論モデルを組み合わせたモデルでは、臨床薬物相互作用試験で得られたジゴキシンに対するフィネレノン 20mg の影響を再現することが可能であったが、このモデルをフィネレノン 40mg に外挿した場合にもジゴキシンの薬物動態に臨床的に問題となる影響を及ぼす可能性は示されなかった（2.7.2.2.5.3.1）。

また、BCRP 及び OATP については、フィネレノン 40mg を 1 日 1 回反復経口投与後の定常状態において BCRP/OATP の基質薬ロスバスタチンを前投与及び同時投与したとき、フィネレノンがロスバスタチンの曝露量（AUC 及び $C_{max}$）に及ぼす明らかな影響は認められなかった（2.7.2.2.3.2.1）。

結論として、フィネレノン 40mg 反復投与後に、トランスポーターの阻害作用を介して基質薬に臨床的に問題となる相互作用を引き起こす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。

## 引用文献一覧

1) Bentz J et al., Drug Metab Dispos 2013:41:1347–1366 (4.3.3)

2) EMA, Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev. 1 Corr. 2. Jun 2012

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

## 2.6.5.1 薬物動態試験： 一覧表

Test article: Finerenone

**Table 1-1: Overview on new pharmacokinetic studies for support of a 40 mg OD dose of finerenone in HF**

| Type of study | Test system / Species / strain | Route of administration / method | Test compound | Report no. | Location |
|---|---|---|---|---|---|
| **Analytical methods** | | | | | |
| Synthesis | | | [$^2H_5$]BAY 1088090 ([$^2H_5$]M-3) [a] | PH-42128 | 4.2.2.1.1 |
| Analytical methods | Rat brain homogenate | - / LC-MS/MS | Finerenone | B003813[b] | 4.2.2.1.4 |
| Analytical methods | Human plasma | - / LC-MS/MS | Finerenone | R-13819[c, d] | 4.2.2.1.2 |
| Analytical methods | Human plasma | - / LC-MS/MS | Finerenone / Gemfibrozil, Verapamil | R-13997[b, e] | 4.2.2.1.3 |
| **Pharmacokinetics** | | | | | |
| No additional studies performed | | | | | |
| **Distribution** | | | | | |
| No additional studies performed | | | | | |
| **Metabolism** | | | | | |
| CYP Induction | Human hepatocytes | *in vitro* / LC-MS/MS, qRT-PCR | Finerenone<br>BAY 1117267 (M-1a)<br>BAY 1117266 (M-1b)<br>BAY 1117268 (M-2a)<br>BAY 1117271 (M-3a) | PH-39130[f] | 4.2.2.4.1 |
| **Excretion** | | | | | |
| No additional studies performed | | | | | |
| **Pharmacokinetic drug interactions** | | | | | |
| No additional studies performed | | | | | |
| **Other PK studies** | | | | | |
| OATP1B1, OATP1B3 Supplementary substrate characteristics | Transporter transfected HEK-cells | *in vitro* / LC-MS/MS | Finerenone | R-13843[g] | 4.2.2.7.1 |

| Type of study | Test system / Species / strain | Route of administration / method | Test compound | Report no. | Location |
|---|---|---|---|---|---|
| OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2K transporter inhibition | Transporter transfected HEK-cells | *in vitro* / LC-MS/MS | Finerenone<br>BAY 1117267 (M-1a)<br>BAY 1117268 (M-2a)<br>BAY 1117271 (M-3a) | R-14427[h] | 4.2.2.7.2 |
| P-gp transporter inhibition | Caco-2 cells | *in vitro* / LC-MS/MS | Finerenone | B003719 | 4.2.2.7.3 |

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

a = resynthesis report for deuterated major human plasma metabolite M-3 for application as internal standard for bioanalytics. For original synthesis report, see CTD-CKD 4.2.2.1.7 PH-37324.

b = testing facility: [redacted] Switzerland

c = testing facility: [redacted] China

d = (cross)validation report of method BAY9HPP for the determination of finerenone in human plasma. The method was utilized in China for samples derived from the FINEARTS-HF Phase III study 20103 in China. For details, see 2.7.1.5.2.

e = Bioanalytical validation report towards interference of finerenone and its metabolites M-1, M-2, M-3 with gemfibrozil and verapamil. Note that interference of finerenone and (if applicable) metabolites M-1, M-2, M-3 with other co-medications applied in clinical Phase I studies has been described in the respective clinical study reports.

f = new version of previously submitted report, now containing relative induction score (RIS) assessment for 40 mg OD finerenone and assessment of induction potential towards co-regulated CYP enzymes

g = testing facility: [redacted] USA

h = 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: New analytical methods and validation reports**

Overview on Bioanalytical Methods

| Type of Study | Method | Analyte | Matrix | Testing Facility | Report no. | Location |
|---|---|---|---|---|---|---|
| Qualification of a method for the determination of BAY 94-8862 in rat brain by HPLC-MS/MS[a] | LC-MS/MS | BAY 94-8862 | Rat brain homogenate | [redacted] Switzerland | B003813 | 4.2.2.1.4 |
| Validation and cross validation of a method for the determination of BAY 94-8862 in human plasma by LC-MS/MS[b] | LC-MS/MS | BAY 94-8862 | Human plasma | [redacted] | R-13819 | 4.2.2.1.2 |

a: A new method for determination of finerenone in rat brain homogenate was qualified to support a juvenile toxicology study (4.2.3.5.4.1 R-14405).
b: A new method for determination of finerenone in human plasma was validated for analysis of samples generated in China at a new bioanalytical site in [redacted]. For method details refer to 2.7.1.5.2.

### 2.6.5.3 薬物動態試験： 単回投与後の吸収

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.3 を参照。

### 2.6.5.4 薬物動態試験： 反復投与後の吸収

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.4 を参照。

### 2.6.5.5 薬物動態試験： 分布

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.5 を参照。

### 2.6.5.6 薬物動態試験： タンパク結合

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.6 を参照。

### 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

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.7 を参照。

### 2.6.5.8 薬物動態試験： その他の分布試験

新たな試験は実施していない。既提出の試験成績は CTD-CKD 2.6.5.8 を参照。

## 2.6.5.9 薬物動態試験： In Vivoにおける代謝

新たな試験は実施していない。既提出の試験成績はCTD-CKD 2.6.5.9を参照。

## 2.6.5.10 薬物動態試験： In Vitro代謝

新たな試験は実施していない。既提出の試験成績はCTD-CKD 2.6.5.10を参照。

## 2.6.5.11 薬物動態試験： 推定代謝経路

既提出の推定代謝経路を2.6.4.5に再掲する。

## 2.6.5.12 薬物動態試験： 薬物代謝酵素の誘導／阻害

フィネレノンの薬物代謝酵素に対する新たな誘導／阻害試験は実施していない。既提出の誘導／阻害試験成績を再掲し、フィネレノン40mg投与時の曝露量を考慮して、相互作用の予測計算の記載を更新した。

CTD-CKD 2.6.5.12 Table 12-1 の再掲。

Test article: Finerenone

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

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

| | | | |
|---|---|---|---|
| Species / race: | 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 preincubation 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

CTD-CKD 2.6.5.12 Table 12-2 の再掲。

Test article: Finerenone

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

Location: CTD-CKD 4.2.2.4.6
Report no.: A50906

| | | | |
|---|---|---|---|
| Species / race: | 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

CTD-CKD 2.6.5.12 Table 12-3 のデータを、フィネレノン 40mg 投与時の曝露量を考慮して再計算した。

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 (40 mg OD) 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 | 0.0834 | - | - | 2.91[c] | 1.029 | $1+[I]/K_i \geq 1.02$ |
| CYP1A1 | Mechanistic static[d] | - | 0.596 | - | 2.91[c] | 1.21 | AUCR ≥ 1.25 |
| CYP1A2 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| CYP2A6 | Basic | 0.0834 | - | - | >21.7[f] | <1.004 | $1+[I]/K_i \geq 1.02$ |
| CYP2B6 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| CYP2C8 | Basic | 0.0834 | - | - | 1.65[g] | 1.051 | $1+[I]/K_i \geq 1.02$ |
| CYP2C8 | Mechanistic static[d] | - | 0.596 | - | 1.65[g] | 1.36 | AUCR ≥ 1.25 |
| CYP2C9 | Basic | 0.0834 | - | - | 13.9[h] | 1.006 | $1+[I]/K_i \geq 1.02$ |
| CYP2C19 | Basic | 0.0834 | - | - | 9.39[i] | 1.009 | $1+[I]/K_i \geq 1.02$ |
| CYP2D6 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| CYP2E1 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| CYP3A4/midazolam, reversible | Basic | 0.0834 | - | - | 7.70[j] | 1.011 | $1+[I]/K_i \geq 1.02$ |
| CYP3A4/testosterone, reversible | Basic | 0.0834 | - | - | 4.86[k] | 1.017 | $1+[I]/K_i \geq 1.02$ |
| CYP3A4, TDI | Basic | 0.0834 | - | - | 6.24[l] | 16.0[m] | $(k_{obs} + k_{deg}) / k_{deg} \geq 1.25$ |
| | | | | Intestinal | | | |
| CYP3A4/midazolam | Basic | - | - | 423 | 7.70[j] | 55.9 | $1+[I]/K_i \geq 11$ |
| CYP3A4/testosterone | Basic | - | - | 423 | 4.86[k] | 88.0 | $1+[I]/K_i \geq 11$ |
| | | | | Systemic | | | |
| UGT1A1 | Basic | 0.0834 | - | - | >20.3[n] | <1.004 | $1+[I]/K_i \geq 1.02$ |
| UGT1A4 | Basic | 0.0834 | - | - | >20.3[n] | <1.004 | $1+[I]/K_i \geq 1.02$ |

Table: Assessment of risk for *in vivo* DDI between finerenone (40 mg OD) 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 |
|---|---|---|---|---|---|---|---|
| UGT1A6 | Basic | 0.0834 | - | - | >20.3[n] | <1.004 | $1+[I]/K_i \geq 1.02$ |
| UGT1A9 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| UGT2B4 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |
| UGT2B7 | Basic | 0.0834 | - | - | >15.2[e] | <1.005 | $1+[I]/K_i \geq 1.02$ |

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 CYP1A1 and CYP2C8 inhibition assumed no enzyme inhibition in the gut and $f_m$ = 1 (worst-case scenario)

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 40 mg finerenone, based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1 B002563) (finerenone total $[I]_{max}$ = 1.00 µM [379 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.596 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 (CTD-CKD 4.3.48)], observed absorption rate constant ($k_a$) = 0.153 $min^{-1}$ (CTD-CKD 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

CTD-CKD 2.6.5.12 Table 12-4 のデータを、フィネレノン 40mg 投与時の曝露量を考慮して再計算した。

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 (40 mg OD) 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 | 0.0834 | - | - | 2.91[c] | 0.029 | $[I]/K_i \geq 0.02$ |
| CYP1A1 | Mechanistic static[d] | - | 0.596 | - | 2.91[c] | 1.21[o] | AUCR ≥ 1.25 |
| CYP1A2 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| CYP2A6 | Basic | 0.0834 | - | - | >21.7[f] | <0.004 | $[I]/K_i \geq 0.02$ |
| CYP2B6 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| CYP2C8 | Basic | 0.0834 | - | - | 1.65[g] | 0.051 | $[I]/K_i \geq 0.02$ |
| CYP2C8 | Mechanistic static[d] | - | 0.596 | - | 1.65[g] | 1.36[o] | AUCR ≥ 1.25 |
| CYP2C9 | Basic | 0.0834 | - | - | 13.9[h] | 0.006 | $[I]/K_i \geq 0.02$ |
| CYP2C19 | Basic | 0.0834 | - | - | 9.39[i] | 0.009 | $[I]/K_i \geq 0.02$ |
| CYP2D6 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| CYP2E1 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| CYP3A4/midazolam, reversible | Basic | 0.0834 | - | - | 7.70[j] | 0.011 | $[I]/K_i \geq 0.02$ |
| CYP3A4/testosterone, reversible | Basic | 0.0834 | - | - | 4.86[k] | 0.017 | $[I]/K_i \geq 0.02$ |
| CYP3A4, TDI | Basic | 0.0834 | - | - | 6.24[l] | 16.0[m] | $(k_{obs} + k_{deg}) / k_{deg} \geq 1.25$ |
| | | | | Intestinal | | | |
| CYP3A4/midazolam | Basic | - | - | 423 | 7.70[j] | 54.9 | $[I]/K_i \geq 10$ |
| CYP3A4/testosterone | Basic | - | - | 423 | 4.86[k] | 87.0 | $[I]/K_i \geq 10$ |
| | | | | Systemic | | | |
| UGT1A1 | Basic | 0.0834 | - | - | >20.3[n] | <0.004 | $[I]/K_i \geq 0.02$ |
| UGT1A4 | Basic | 0.0834 | - | - | >20.3[n] | <0.004 | $[I]/K_i \geq 0.02$ |

Table: Assessment of risk for *in vivo* DDI between finerenone (40 mg OD) 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 |
|---|---|---|---|---|---|---|---|
| UGT1A6 | Basic | 0.0834 | - | - | >20.3[n] | <0.004 | $[I]/K_i \geq 0.02$ |
| UGT1A9 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| UGT2B4 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |
| UGT2B7 | Basic | 0.0834 | - | - | >15.2[e] | <0.005 | $[I]/K_i \geq 0.02$ |

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 CYP1A1 and CYP2C8 inhibition assumed no enzyme inhibition in the gut and $f_m$ = 1 (worst-case scenario)
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)
o = 1+[I]/Ki
Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 40 mg finerenone, based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1 B002563) (finerenone total $[I]_{max}$ = 1.00 µM [379 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.596 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 (CTD-CKD 4.3.48)], observed absorption rate constant ($k_a$) = 0.153 $min^{-1}$ (CTD-CKD 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； OD = once daily
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

CTD-CKD 2.6.5.12 Table 12-13 のデータを、フィネレノン 40mg 投与時の曝露量を考慮して再計算した。

Test article: Finerenone

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

Location: 4.2.2.4.1
Report no.: PH-39130

| | | | |
|---|---|---|---|
| Species / race: | Human / Caucasian, African-American | Route: | *in vitro* |
| Material: | Cultured human hepatocytes | Nuclide: | - |

Table: Finerenone: Kinetic parameters generated *in vitro* (CYP3A4mRNA) and prediction of CYP3A4 induction effects *in vivo* for 40 mg OD finerenone dose 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 | [mg] | 40 | 40 | 40 | |
| Total $C_{max,ss}$[a] | [µg/L] | 379 | 379 | 379 | |
| Unbound $C_{max,ss}$ | [µg/L] | 31.6 | 31.6 | 31.6 | |
| **PXR regulation** | | | | | yes |
| **Mechanistic static model** | | | | | |
| $AUCR_{liver}$[b] | | 0.61 | 0.59 | 0.69 | |
| % Decrease in AUC of midazolam predicted | | 39 | 41 | 31 | weak inducer |
| **RIS model** | | | | | |
| RIS score *in vitro* | | 0.102 | 0.108 | 0.070 | |
| % Decrease in AUC of midazolam predicted | | 65 | 69 | 60 | Moderate inducer |

a = Median $C_{max,ss}$ based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1, B002563)

b = AUCR calculated based on mechanistic static model for induction of hepatic CYP3A4 using following calculation parameters: $f_m$ midazolam = 0.95; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 40 mg finerenone, based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1 B002563) (finerenone total $[I]_{max}$ = 1.00 µM [379 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.596 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, observed absorption rate constant ($K_a$) = 0.153 $min^{-1}$ (CTD-CKD 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)

### 2.6.5.13 薬物動態試験： 累積排泄

新たな試験は実施していない。既提出の試験成績はCTD-CKD 2.6.5.13を参照。

### 2.6.5.14 薬物動態試験： 胆汁中排泄

新たな試験は実施していない。既提出の試験成績はCTD-CKD 2.6.5.14を参照。

### 2.6.5.15 薬物動態試験： 薬物相互作用

新たな試験は実施していない。既提出の試験成績はCTD-CKD 2.6.5.15を参照。

### 2.6.5.16 薬物動態試験： その他

フィネレノンのOATP1B1及びOATP1B3に対する基質特性を追加で検討した試験成績は2.6.4.8.2を参照。Caco-2細胞を用いて追加で実施したフィネレノンのP-gpに対する阻害作用の試験成績はTable 16-1に示す。フィネレノンのOCT2に対する阻害作用を追加で検討した試験成績は2.6.4.8.3に示す。そのほかにフィネレノンのトランスポーターに対する基質特性及び阻害作用の検討に関する新たな試験は実施していない。既提出のトランスポーターに関する試験成績はCTD-CKD 2.6.5.16を参照。既提出及び追加実施した阻害試験成績に基づき、フィネレノン40mg投与時の曝露量を考慮して、相互作用の予測計算の記載を更新した（Table 16-18～Table 16-20）。

フィネレノン主代謝物の薬物代謝酵素に対する新たな誘導／阻害試験は実施していない。既提出の誘導／阻害試験成績を再掲し、フィネレノン40mg投与時の主代謝物の曝露量を考慮して、相互作用の予測計算の記載を更新した（Table 16-2～Table 16-17）。フィネレノン主代謝物の一部トランスポーターに対する阻害作用の検討を追加実施した（2.6.4.8.4.2及び2.6.4.8.4.3）。既提出のトランスポーターに関する試験成績はCTD-CKD 2.6.5.16を参照。既提出及び追加実施した阻害試験成績に基づき、フィネレノン40mg投与時の主代謝物の曝露量を考慮して、相互作用の予測計算の記載を更新した（Table 16-21～Table 16-32）。

Test article: Finerenone

**Table 16-1: Pharmacokinetics: *In vitro* studies to evaluate the inhibitory potential towards human efflux transporter P-gp**

Location: 4.2.2.7.3
Report no.: B003719

| | | | |
|---|---|---|---|
| Species: | Human | Route: | *in vitro* |
| Material: | Caco-2 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 |
| Digoxin[a] | 10 | Control | 0 | 7.72 | 0.975 | 330 | 13.9 | 42.8 | 5.69 | 100 |
| Digoxin | 10 | Ivermectin | 5 | 48.8 | 1.59 | 98.9 | 14.8 | 2.03 | 0.311 | 4.7 |
| Digoxin[a] | 10 | Finerenone | 0.3 | 8.10 | 0.762 | 358 | 30.9 | 44.2 | 5.64 | 103.3 |
| Digoxin[a] | 10 | Finerenone | 1 | 8.21 | 1.01 | 339 | 26.3 | 41.4 | 6.01 | 96.7 |
| Digoxin[a] | 10 | Finerenone | 3 | 9.10 | 1.22 | 315 | 32.3 | 34.6 | 5.85 | 80.9 |
| Digoxin[a] | 10 | Finerenone | 10 | 13.1 | 2.33 | 235 | 34.5 | 18.0 | 4.16 | 42.1 |
| Digoxin[a] | 10 | Finerenone | 30 | 25.2 | 3.61 | 162 | 21.6 | 6.45 | 1.26 | 15.1 |
| Digoxin[a] | 10 | Finerenone | 100 | 46.1 | 3.72 | 93.5 | 7.13 | 2.03 | 0.225 | 4.74 |

a = $IC_{50}$ of finerenone against this probe substrate in Caco-2 cells = 7.74 µM

CTD-CKD 2.6.5.16 Table 16-27 の再掲。

Test article: Finerenone

**Table 16-2 : Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms**

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

| | | | |
|---|---|---|---|
| Species / race: | 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

CTD-CKD 2.6.5.16 Table 16-28 の再掲。

Test article: Finerenone

**Table 16-3: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms**

Location: CTD-CKD4.2.2.7.20, CTD-CKD 4.2.2.4.4, CTD-CKD 4.2.2.4.5
Report no.: PH-37685, PH-40971, PH-40973

| | | | |
|---|---|---|---|
| Species / race: | 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

CTD-CKD 2.6.5.16 Table 16-29 の再掲。

Test article: Finerenone

**Table 16-4: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms**

Location: CTD-CKD 4.2.2.7.20, CTD-CKD 4.2.2.4.4, CTD-CKD 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

CTD-CKD 2.6.5.16 Table 16-30 の再掲。

Test article: Finerenone

**Table 16-5: Pharmacokinetics: Inhibitory potential of metabolites towards human CYP isoforms**

Location: CTD-CKD 4.2.2.7.20, CTD-CKD 4.2.2.4.4, CTD-CKD 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

CTD-CKD 2.6.5.16 Table 16-31 の再掲。

Test article: Finerenone

**Table 16-6: Pharmacokinetics: Inhibitory potential of metabolites towards human UGT isoforms**

Location: CTD-CKD 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

CTD-CKD 2.6.5.16 Table 16-32 のデータを、フィネレノン 40mg 投与時の M-1a の曝露量を考慮し FDA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-7: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1a following 40 mg OD finerenone (FDA)**

| Table: | Assessment of risk for *in vivo* DDI between metabolite M-1a (following 40 mg OD finerenone) 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 | 0.0934 | 13.7[d] | 1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP1A2 | Basic | 0.0934 | >16.6[e] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2A6 | Basic | 0.0934 | >22.8[f] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2B6 | Basic | 0.0934 | >16.6[e] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C8 | Basic | 0.0934 | >22.8[f] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C9 | Basic | 0.0934 | 11.4[g] | 1.008 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C19 | Basic | 0.0934 | >16.6[e] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2D6 | Basic | 0.0934 | >16.6[e] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2E1 | Basic | 0.0934 | >16.6[e] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/midazolam | Basic | 0.0934 | >22.8[f] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/testosterone | Basic | 0.0934 | >22.8[f] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A1 | Basic | 0.0934 | >21.2[h] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A4 | Basic | 0.0934 | >21.2[h] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A6 | Basic | 0.0934 | >22.8[f] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A9 | Basic | 0.0934 | >21.2[h] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B4 | Basic | 0.0934 | >21.2[h] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B7 | Basic | 0.0934 | >21.2[h] | <1.004 | $1+[I]_{max,u}/K_i \geq 1.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-1a total $[I]_{max}$ = 1.61 µM [604 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; OD = once daily
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

CTD-CKD 2.6.5.16 Table 16-33 のデータを、フィネレノン 40mg 投与時の M-1a の曝露量を考慮し EMA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-8: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1a following 40 mg OD finerenone (EMA)**

| Table: | Assessment of risk for *in vivo* DDI between metabolite M-1a (following 40 mg OD finerenone) 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 | 0.0934 | 13.7[d] | 0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP1A2 | Basic | 0.0934 | >16.6[e] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2A6 | Basic | 0.0934 | >22.8[f] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2B6 | Basic | 0.0934 | >16.6[e] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C8 | Basic | 0.0934 | >22.8[f] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C9 | Basic | 0.0934 | 11.4[g] | 0.008 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C19 | Basic | 0.0934 | >16.6[e] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2D6 | Basic | 0.0934 | >16.6[e] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2E1 | Basic | 0.0934 | >16.6[e] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/midazolam | Basic | 0.0934 | >22.8[f] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/testosterone | Basic | 0.0934 | >22.8[f] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A1 | Basic | 0.0934 | >21.2[h] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A4 | Basic | 0.0934 | >21.2[h] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A6 | Basic | 0.0934 | >22.8[f] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A9 | Basic | 0.0934 | >21.2[h] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B4 | Basic | 0.0934 | >21.2[h] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B7 | Basic | 0.0934 | >21.2[h] | <0.004 | $[I]_{max,u}/K_i \geq 0.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-1a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-1a total $[I]_{max}$ = 1.61 µM [604 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-34 のデータを、フィネレノン 40mg 投与時の M-1b の曝露量を考慮し FDA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-9: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1b following 40 mg OD finerenone (FDA)**

| Table: | Assessment of risk for *in vivo* DDI between metabolite M-1b (following 40 mg OD finerenone) 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 | 0.0127 | 12.9[d] | 1.0010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP1A2 | Basic | 0.0127 | >14.5[e] | <1.0009 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2A6 | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2B6 | Basic | 0.0127 | >14.5[e] | <1.0009 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C8 | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C9 | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C19 | Basic | 0.0127 | >14.5[e] | <1.0009 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2D6 | Basic | 0.0127 | >14.5[e] | <1.0009 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2E1 | Basic | 0.0127 | >14.5[e] | <1.0009 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/midazolam | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/testosterone | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A1 | Basic | 0.0127 | >21.1[g] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A4 | Basic | 0.0127 | >21.1[g] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A6 | Basic | 0.0127 | >22.3[f] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A9 | Basic | 0.0127 | >21.1[g] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B4 | Basic | 0.0127 | >21.1[g] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B7 | Basic | 0.0127 | >21.1[g] | <1.0006 | $1+[I]_{max,u}/K_i \geq 1.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-1b total $[I]_{max}$ = 0.327 µM [123 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-35 のデータを、フィネレノン 40mg 投与時の M-1b の曝露量を考慮し EMA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-10: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-1b following 40 mg OD finerenone (EMA)**

| Table: | Assessment of risk for *in vivo* DDI between metabolite M-1b (following 40 mg OD finerenone) 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 | 0.0127 | 12.9[d] | 0.0010 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP1A2 | Basic | 0.0127 | >14.5[e] | <0.0009 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2A6 | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2B6 | Basic | 0.0127 | >14.5[e] | <0.0009 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C8 | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C9 | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C19 | Basic | 0.0127 | >14.5[e] | <0.0009 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2D6 | Basic | 0.0127 | >14.5[e] | <0.0009 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2E1 | Basic | 0.0127 | >14.5[e] | <0.0009 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/midazolam | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/testosterone | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A1 | Basic | 0.0127 | >21.1[g] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A4 | Basic | 0.0127 | >21.1[g] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A6 | Basic | 0.0127 | >22.3[f] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A9 | Basic | 0.0127 | >21.1[g] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B4 | Basic | 0.0127 | >21.1[g] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B7 | Basic | 0.0127 | >21.1[g] | <0.0006 | $[I]_{max,u}/K_i \geq 0.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-1b (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-1b total $[I]_{max}$ = 0.327 µM [123 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-36 のデータを、フィネレノン 40mg 投与時の M-2a の曝露量を考慮し FDA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-11: Pharmacokinetics: Drug-drug Interaction, enzyme inhibition by M-2a following 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a (following 40 mg OD finerenone) 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 | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP1A2 | Basic | 0.1348 | >20.7[e] | <1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2A6 | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2B6 | Basic | 0.1348 | >20.7[e] | <1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C8 | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C9 | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C19 | Basic | 0.1348 | >20.7[e] | <1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2D6 | Basic | 0.1348 | >20.7[e] | <1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2E1 | Basic | 0.1348 | >20.7[e] | <1.007 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/midazolam | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/testosterone | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A1 | Basic | 0.1348 | >22.9[f] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A4 | Basic | 0.1348 | >22.9[f] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A6 | Basic | 0.1348 | >23.2[d] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A9 | Basic | 0.1348 | >22.9[f] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B4 | Basic | 0.1348 | >22.9[f] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B7 | Basic | 0.1348 | >22.9[f] | <1.006 | $1+[I]_{max,u}/K_i \geq 1.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-2a total $[I]_{max}$ = 0.775 µM [304 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-37 のデータを、フィネレノン 40mg 投与時の M-2a の曝露量を考慮し EMA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-12: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-2a following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a (following 40 mg OD finerenone) 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 | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP1A2 | Basic | 0.1348 | >20.7[e] | <0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2A6 | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2B6 | Basic | 0.1348 | >20.7[e] | <0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C8 | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C9 | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C19 | Basic | 0.1348 | >20.7[e] | <0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2D6 | Basic | 0.1348 | >20.7[e] | <0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2E1 | Basic | 0.1348 | >20.7[e] | <0.007 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/midazolam | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/testosterone | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A1 | Basic | 0.1348 | >22.9[f] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A4 | Basic | 0.1348 | >22.9[f] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A6 | Basic | 0.1348 | >23.2[d] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A9 | Basic | 0.1348 | >22.9[f] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B4 | Basic | 0.1348 | >22.9[f] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B7 | Basic | 0.1348 | >22.9[f] | <0.006 | $[I]_{max,u}/K_i \geq 0.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-2a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-2a total $[I]_{max}$ = 0.775 µM [304 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-38 のデータを、フィネレノン 40mg 投与時の M-3a の曝露量を考慮し FDA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-13: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-3a following 40 mg OD finerenone (FDA)**

| Table: | Assessment of risk for *in vivo* DDI between metabolite M-3a (following 40 mg OD finerenone) 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 | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP1A2 | Basic | 0.232 | >21.0[e] | <1.011 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2A6 | Basic | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2B6 | Basic | 0.232 | >21.0[e] | <1.011 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C8 | Basic | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C9 | Basic | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2C19 | Basic | 0.232 | >21.0[e] | <1.011 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2D6 | Basic | 0.232 | >21.0[e] | <1.011 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP2E1 | Basic | 0.232 | >21.0[e] | <1.011 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/midazolam | Basic | 0.232 | 14.0[f] | 1.017 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| CYP3A4/testosterone | Basic | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A1 | Basic | 0.232 | >23.2[g] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A4 | Basic | 0.232 | >23.2[g] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A6 | Basic | 0.232 | >23.4[d] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT1A9 | Basic | 0.232 | >23.2[g] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B4 | Basic | 0.232 | >23.2[g] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |
| UGT2B7 | Basic | 0.232 | >23.2[g] | <1.010 | $1+[I]_{max,u}/K_i \geq 1.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-3a total $[I]_{max}$ = 0.343 µM [139 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-39 のデータを、フィネレノン 40mg 投与時の M-3a の曝露量を考慮し EMA ガイドラインに基づき更新した。

Test article: Finerenone

**Table 16-14: Pharmacokinetics: Drug-drug interaction, enzyme inhibition by M-3a following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a (following 40 mg OD finerenone) 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 | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP1A2 | Basic | 0.232 | >21.0[e] | <0.011 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2A6 | Basic | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2B6 | Basic | 0.232 | >21.0[e] | <0.011 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C8 | Basic | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C9 | Basic | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2C19 | Basic | 0.232 | >21.0[e] | <0.011 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2D6 | Basic | 0.232 | >21.0[e] | <0.011 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP2E1 | Basic | 0.232 | >21.0[e] | <0.011 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/midazolam | Basic | 0.232 | 14.0[f] | 0.017 | $[I]_{max,u}/K_i \geq 0.02$ |
| CYP3A4/testosterone | Basic | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A1 | Basic | 0.232 | >23.2[g] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A4 | Basic | 0.232 | >23.2[g] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A6 | Basic | 0.232 | >23.4[d] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT1A9 | Basic | 0.232 | >23.2[g] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B4 | Basic | 0.232 | >23.2[g] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |
| UGT2B7 | Basic | 0.232 | >23.2[g] | <0.010 | $[I]_{max,u}/K_i \geq 0.02$ |

Table: Assessment of risk for *in vivo* DDI between metabolite M-3a (following 40 mg OD 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 = 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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19 PH-40388) (M-3a total $[I]_{max}$ = 0.343 µM [139 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; OD = once daily

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

CTD-CKD 2.6.5.16 Table 16-72 のデータを、フィネレノン 40mg 投与時の主代謝物 M-1a の全身曝露量を考慮して更新した。

Test article: Finerenone

**Table 16-15: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms**

Location: 4.2.2.4.1
Report no.: PH-39130

| | | | |
|---|---|---|---|
| Species / race: | 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 [mg] | - | - | - | |
| Total $C_{max,ss}$[a] [µg/L] | 604 | 604 | 604 | |
| Unbound $C_{max,ss}$ [µg/L] | 35.2 | 35.2 | 35.2 | |
| **PXR regulation** | | | | yes |
| **Mechanistic static model** | | | | |
| AUCRliver[b] | 0.97 | 0.96 | 0.95 | |
| % Decrease in AUC of midazolam predicted | 2.5 | 3.7 | 4.6 | Non-inducer |
| **RIS model** | | | | |
| RIS score *in vitro* | 0.027 | 0.041 | 0.051 | |
| % Decrease in AUC of midazolam predicted | 47 | 55 | 56 | Weak-to-moderate inducer |

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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388)

b : AUCR calculated based on mechanistic static model for induction of hepatic CYP3A4 using following calculation parameters: $f_m$ midazolam = 0.95; $[I]_{max,u} = C_{max,ss}$ for M-1a (M-1a total $[I]_{max}$ = 1.605 µM [604 µg/L] and unbound fraction = 0.0582); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.093 µM ($[I]_{in,max,u} = fu \times ([I]_{max} + (Fa \times Fg \times Ka \times Dose)/Qh/RB)$, equals $[I]_{max,u}$ as Dose of M-1a = 0 mg)

CTD-CKD 2.6.5.16 Table 16-73 のデータを、フィネレノン 40mg 投与時の主代謝物 M-1b の全身曝露量を考慮して更新した。

Test article: Finerenone

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

Location: 4.2.2.4.1
Report no.: PH-39130

| | | | |
|---|---|---|---|
| Species / race: | 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 [mg] | - | - | - | |
| Total $C_{max,ss}$[a] [µg/L] | 123 | 123 | 123 | |
| Unbound $C_{max,ss}$ [µg/L] | 4.8 | 4.8 | 4.8 | |
| **PXR regulation** | | | | yes |
| **Mechanistic static model** | | | | |
| AUCRliver[b] | 0.99 | 0.99 | 0.99 | |
| % Decrease in AUC of midazolam predicted | 0.55 | 0.94 | 1.2 | Non-inducer |
| **RIS model** | | | | |
| RIS score *in vitro* | 0.0061 | 0.010 | 0.013 | |
| % Decrease in AUC of midazolam predicted | 26 | 31 | 36 | Weak inducer |

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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388)

b : AUCR calculated based on mechanistic static model for induction of hepatic CYP3A4 using following calculation parameters: $f_m$ midazolam = 0.95; $[I]_{max,u}$ = $C_{max,ss}$ for M-1b (M-1b total $[I]_{max}$ = 0.327 µM [123 µg/L] and unbound fraction = 0.0582); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.013 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times K_a \times Dose)/Q_h/R_B)$, equals $[I]_{max,u}$ as Dose of M-1b = 0 mg)

CTD-CKD 2.6.5.16 Table 16-74 のデータを、フィネレノン 40mg 投与時の主代謝物 M-2a の全身曝露量を考慮して更新した。

Test article: Finerenone

**Table 16-17: Pharmacokinetics: Induction potential of metabolites towards human CYP isoforms**

Location: 4.2.2.4.1
Report no.: PH-39130

| | | | |
|---|---|---|---|
| Species / race: | 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 [mg] | - | - | - | |
| Total $C_{max,ss}$[a] [µg/L] | 304 | 304 | 304 | |
| Unbound $C_{max,ss}$ [µg/L] | 52.9 | 52.9 | 52.9 | |
| **PXR regulation** | | | | yes |
| **Mechanistic static model** | | | | |
| AUCRliver[b] | 0.95 | 0.95 | 0.91 | |
| % Decrease in AUC of midazolam predicted | 5.4 | 4.6 | 9.0 | Non-inducer |
| **RIS model** | | | | |
| RIS score *in vitro* | 0.061 | 0.051 | 0.11 | |
| % Decrease in AUC of midazolam predicted | 58 | 58 | 65 | Moderate inducer |

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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388)

b : AUCR calculated based on mechanistic static model for induction of hepatic CYP3A4 using following calculation parameters: $f_m$ midazolam = 0.95; $[I]_{max,u} = C_{max,ss}$ for M-2a (M-2a total $[I]_{max}$ = 0.775 µM [304 µg/L] and unbound fraction = 0.174); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.135 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times K_a \times Dose)/Q_h/R_B)$, equals $[I]_{max,u}$ as Dose of M-2a = 0 mg)

CTD-CKD 2.6.5.16 Table 16-90 のデータを、新たに実施した試験（太字で示す）に基づき更新した。

Test article: Finerenone

**Table 16-18: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by finerenone following 40 mg OD 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 | CTD-CKD 4.2.2.7.3, PH-40886 |
| P-gp | LLC-PK1-MDR1 | Digoxin (20 µM) | 121 | 96% at 600 µM | No | CTD-CKD 4.2.2.7.3, PH-40886 |
| **P-gp** | **Caco-2** | **Digoxin (10 µM)** | **7.74** | **4.7% at 100 µM** | **Yes** | **4.2.2.7.3, B003719** |
| BCRP | MDCKII-BCRP | Topotecan (2 µM) | 18.1 | 90% at 200 µM | Yes | CTD-CKD 4.2.2.7.5, PH-40885 |
| BCRP | MDCKII-BCRP | PhIP (2 µM) | 17.4 | 90% at 300 µM | Yes | CTD-CKD 4.2.2.7.5, PH-40885 |
| BSEP | SCHH (BEI) | d8-TCA (5 µM) | >100 | 0% at 100 µM | No | CTD-CKD 4.2.2.7.6, R-11129 |
| NTCP/BSEP | SCHH ($CL_{Biliary}$) | d8-TCA (5 µM) | >100 | 0% at 100 µM | No | CTD-CKD 4.2.2.7.6, R-11129 |
| MATE1 | HEK293-MATE1 | Metformin (50 µM) | >5 | 10% at 5 µM | No | CTD-CKD 4.2.2.7.7, R-11196 |
| MATE2K | HEK293-MATE2K | Metformin (50 µM) | >5 | 35% at 5 µM | No | CTD-CKD 4.2.2.7.7, R-11196 |
| OATP1B1 | HEK293-OATP1B1 | Pravastatin (5 µM) | 3.2 | 79% at 10 µM | Yes | CTD-CKD 4.2.2.7.9, PH-40952 |
| OATP1B3 | HEK293-OATP1B3 | Pravastatin (5 µM) | >10 | 47% at 10 µM | Yes (EMA guideline only) | CTD-CKD 4.2.2.7.9, PH-40952 |
| OAT1 | HEK293-OAT1 | PAH (10 µM) | >3 | -5% at 3 µM | No | CTD-CKD 4.2.2.7.10, R-9494 |
| OAT3 | HEK293-OAT3 | Furosemide (5 µM) | >3 | -13% at 3 µM | No | CTD-CKD 4.2.2.7.10, R-9494 |
| **OCT1** | **HEK293-OCT1** | **$MPP^+$ (5 µM)** | **>15** | **2.4% at 15 µM** | **No** | **4.2.2.7.2, R-14427** |
| OCT2 | HEK293-OCT2 | $MPP^+$ (5 µM) | >3 | 1.1% at 3 µM | No | CTD-CKD 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 guidance, is provided in Table 16-19 and Table 16-20, 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 co-transporting 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 = Lily Laboratories cells - porcine kidney epithelial cells; 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 = taurocholic acid; PAH = p-aminohippuric acid; $MPP^+$ = 1-methyl-4-phenylpyridinium; PhIP = 2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine; OD = once daily

Additional information: $IC_{50}$ values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

CTD-CKD 2.6.5.16 Table 16-91 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-19: Pharmacokinetics: Drug-drug interaction, transporter inhibition by 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI's between finerenone (40 mg OD) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

| Transporter | Location, report number | $[I]_{max}$ [µM] | $[I]_{max,u}$ [µM] | $[I]_{in,max,u}$ [µM] | $[I]_{gut}$ [µM] | $IC_{50}$ [µM] | $[I]/IC_{50}$ | Threshold cutoff for potential DDI |
|---|---|---|---|---|---|---|---|---|
| | | | | Intestinal | | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | - | - | - | 423 | 47 | 9.0 | $[I]/IC_{50} \geq 10$ |
| **P-gp** | **4.2.2.7.3, B003719** | **-** | **-** | **-** | **423** | **7.74** | **54.6** | **$[I]/IC_{50} \geq 10$** |
| **P-gp** | **4.2.2.7.3, B003719** | **-** | **-** | **-** | **211[b]** | **7.74** | **27.3** | **$[I]/IC_{50} \geq 10$** |
| BCRP | CTD-CKD 4.2.2.7, PH-40885 | - | - | - | 423 | 17.4 | 24.3 | $[I]/IC_{50} \geq 10$ |
| | | | | Systemic | | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 1.00 | - | - | - | 47 | 0.018 | $[I]/IC_{50} \geq 0.1$ |
| **P-gp** | **4.2.2.7.3, B003719** | **1.00** | **-** | **-** | **-** | **7.74** | **0.129** | **$[I]/IC_{50} \geq 0.1$** |
| **P-gp** | **4.2.2.7.3, B003719** | **0.518[b]** | **-** | **-** | **-** | **7.74** | **0.067** | **$[I]/IC_{50} \geq 0.1$** |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 1.00 | - | - | - | 17.4 | 0.058 | $[I]/IC_{50} \geq 0.1$ |
| BSEP | CTD-CKD 4.2.2.7.6, R-11129 | - | 0.0834 | - | - | >100 | <0.0008 | $[I]/IC_{50} \geq 0.1$ |
| MATE1 | CTD-CKD 4.2.2.7.7, R-11196 | - | 0.0834 | - | - | >5 | <0.017 | $[I]/IC_{50} \geq 0.1$ |
| MATE2K | CTD-CKD 4.2.2.7.7, R-11196 | - | 0.0834 | - | - | >5 | <0.017 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | - | - | 0.596 | - | 3.2 | 0.186 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | - | - | 0.596 | - | >10 | <0.060 | $[I]/IC_{50} \geq 0.1$ |
| OAT1 | CTD-CKD 4.2.2.7.10, R-9494 | - | 0.0834 | - | - | >3 | <0.028 | $[I]/IC_{50} \geq 0.1$ |
| OAT3 | CTD-CKD 4.2.2.7.10, R-9494 | - | 0.0834 | - | - | >3 | <0.028 | $[I]/IC_{50} \geq 0.1$ |
| **OCT1** | **4.2.2.7.2, R-14427** | **-** | **-** | **0.596** | **-** | **>15** | **<0.040** | **$[I]/IC_{50} \geq 0.1$** |
| OCT2 | CTD-CKD 4.2.2.7.12, R-9440 | - | 0.0834 | - | - | >3 | <0.028 | $[I]/IC_{50} \geq 0.1$ |

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

b = calculated for a dose of 20 mg once daily finerenone; based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1, B002563) (finerenone total $[I]_{max}$ = 0.518 µM [196 µg/L])

Abbreviations: FDA = Food and Drug Administration; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 40 mg finerenone, based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1 B002563) (finerenone total $[I]_{max}$ = 1.00 µM [379 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.596 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times K_a \times Dose)/Qh/R_B)$, 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 (CTD-CKD 4.3.48)], observed absorption rate constant ($K_a$) = 0.153 $min^{-1}$ (CTD-CKD 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; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

CTD-CKD 2.6.5.16 Table 16-92 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-20: Pharmacokinetics: Drug-drug interaction, transporter inhibition by 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between finerenone (40 mg OD) 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 | CTD-CKD 4.2.2.7.3, PH-40886 | 47 | - | - | 42.28 | $K_i \le (0.1 \times Dose/250)$ |
| **P-gp** | **4.2.2.7.3, B003719** | **7.74** | **-** | **-** | **42.28** | **$K_i \le (0.1 \times Dose/250)$** |
| **P-gp** | **4.2.2.7.3, B003719** | **7.74** | **-** | **-** | **21.14[c]** | **$K_i \le (0.1 \times Dose/250)$** |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 17.4 | - | - | 42.28 | $K_i \le (0.1 \times Dose/250)$ |
| | | | Systemic | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 47 | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| **P-gp** | **4.2.2.7.3, B003719** | **7.74** | **4.17** | **-** | **-** | **$K_i \le (50 \times [I]_{max,u})$** |
| **P-gp** | **4.2.2.7.3, B003719** | **7.74** | **2.16[c]** | **-** | **-** | **$K_i \le (50 \times [I]_{max,u})$** |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 17.4 | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| BSEP | CTD-CKD 4.2.2.7.6, R-11129 | >100 | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| MATE1 | CTD-CKD 4.2.2.7.7, R-11196 | >5 | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| MATE2K | CTD-CKD 4.2.2.7.7, R-11196 | >5 | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | 3.2 | - | 14.9 | - | $K_i \le (25 \times [I]_{in,max,u})$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | >10 | - | 14.9 | - | $K_i \le (25 \times [I]_{in,max,u})$ |
| OAT1 | CTD-CKD 4.2.2.7.10, R-9494 | >3[d] | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| OAT3 | CTD-CKD 4.2.2.7.10, R-9494 | >3[d] | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |
| **OCT1** | **4.2.2.7.2, R-14427** | **>15** | **-** | **14.9** | **-** | **$K_i \le (25 \times [I]_{in,max,u})$** |
| OCT2 | CTD-CKD 4.2.2.7.12, R-9440 | >3[d] | 4.17 | - | - | $K_i \le (50 \times [I]_{max,u})$ |

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 = calculated for a dose of 20 mg once daily finerenone; based on median $C_{max,ss}$ derived from popPK analysis of study 20103 (5.3.3.5.1, B002563) (finerenone total $[I]_{max}$ = 0.518 µM [196 µg/L])

d = inhibition at a concentration of 3.0 µM: OAT1 = -5%; OAT3 = -13%; OCT2 = 1.1%

Abbreviations: EMA = European Medicines Agency; DDI = drug-drug interaction; $[I]_{max,u}$ = unbound maximum plasma concentration in humans treated with 40 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 (CTD-CKD 5.3.3.5.3, R-9543) (finerenone total $[I]_{max}$ = 1.00 µM [379 µg/L] and unbound fraction = 0.0833); $[I]_{in,max,u}$ = estimated unbound maximum plasma concentration at the inlet to the liver, 0.596 µM ($[I]_{in,max,u} = f_u \times ([I]_{max} + (F_a \times F_g \times K_a \times Dose)/Qh/R_B)$, 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 (CTD-CKD 4.3.48)], observed absorption rate constant ($K_a$) = 0.153 $min^{-1}$ (CTD-CKDTD 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; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 378.42 g/mol for finerenone

CTD-CKD 2.6.5.16 Table 16-93 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-1a 全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-21: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117267 (M-1a) following 40 mg OD finerenone**

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 | CTD-CKD 4.2.2.7.3, PH-40886 |
| P-gp | LLC-PK1-MDR1 | Digoxin (20 µM) | >100 | 25.7% at 100 µM | No | CTD-CKD 4.2.2.7.3, PH-40886 |
| BCRP | MDCKII-BCRP | Topotecan (2 µM) | >20 | 41.0% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BCRP | MDCKII-BCRP | PhIP (2 µM) | >20 | 30.1% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BSEP | SCHH (BEI) | d8-TCA (5 µM) | >30 | 7.0% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| NTCP/BSEP | SCHH ($CL_{Biliary}$) | d8-TCA (5 µM) | >30 | 0% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| MATE1 | HEK293-MATE1 | Metformin (50 µM) | >5 | -3.0% at 5 µM | No | CTD-CKD 4.2.2.7.23, R-11820 |
| MATE2K | HEK293-MATE2K | Metformin (50 µM) | >5 | 22.5% at 5 µM | No | CTD-CKD 4.2.2.7.23, R-11820 |
| OATP1B1 | HEK293-OATP1B1 | Pravastatin (5 µM) | 3.8 | 73.0% at 10 µM | Yes (EMA guideline only) | CTD-CKD 4.2.2.7.9, PH-40952 |
| OATP1B3 | HEK293-OATP1B3 | Pravastatin (5 µM) | 7.6 | 55.8% at 10 µM | No | CTD-CKD 4.2.2.7.9, PH-40952 |
| **OAT1** | **HEK293-OAT1** | **PAH (10 µM)** | **>5** | **-4.4% at 5 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OAT3** | **HEK293-OAT3** | **Furosemide (5 µM)** | **>50** | **46.6% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| OCT1 | HEK293-OCT1 | $MPP^+$ (5 µM) | >8.5 | -20.7% at 8.5 µM | No | CTD-CKD 4.2.2.7.25, R-9701 |
| **OCT2** | **HEK293-OCT2** | **$MPP^+$ (5 µM)** | **>50** | **-10% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |

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 Table 16-22 and Table 16-23, 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; OD = once daily
Additional information: $IC_{50}$ values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

CTD-CKD 2.6.5.16 Table 16-94 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-1a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-22: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117267 (M-1a) following 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117267 (M-1a) (following 40 mg OD finerenone) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

| Transporter | Location, report number | $[I]_{max}$ [µM] | $[I]_{max,u}$ [µM] | $IC_{50}$ [µM] | $[I]_{max,u}/IC_{50}$ | Threshold cutoff for potential DDI |
|---|---|---|---|---|---|---|
| | | | Systemic | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 1.61 | | 70 | 0.023 | $[I]/IC_{50} \geq 0.1$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 1.61 | | >20 | <0.0805 | $[I]/IC_{50} \geq 0.1$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | - | 0.093 | >30 | <0.0031 | $[I]/IC_{50} \geq 0.1$ |
| MATE1 | CTD-CKD 4.2.2.7.23, R-11820 | - | 0.093 | >5 | <0.0186 | $[I]/IC_{50} \geq 0.1$ |
| MATE2K | CTD-CKD 4.2.2.7.23, R-11820 | - | 0.093 | >5 | <0.0186 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.093 | 3.8 | 0.0245 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.093 | 7.6 | 0.0112 | $[I]/IC_{50} \geq 0.1$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **-** | **0.093** | **>5** | **<0.0186** | **$[I]/IC_{50} \geq 0.1$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **-** | **0.093** | **>50** | **<0.00186** | **$[I]/IC_{50} \geq 0.1$** |
| OCT1 | CTD-CKD 4.2.2.7.25, R-9701 | - | 0.093 | >8.5 | <0.0109 | $[I]/IC_{50} \geq 0.1$ |
| **OCT2** | **4.2.2.7.2, R-14427** | **-** | **0.093** | **>50** | **<0.00186** | **$[I]/IC_{50} \geq 0.1$** |

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 of M-1a in humans treated with 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-1a total $[I]_{max}$ = 1.61 µM [604 µg/L] and unbound fraction = 0.0582); $IC_{50}$ = concentration required for 50% inhibition; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

CTD-CKD 2.6.5.16 Table 16-95 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-1a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-23: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117267 (M-1a) following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117267 (M-1a) (following 40 mg OD 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] | Threshold cutoff for potential DDI |
|---|---|---|---|---|
| | | Systemic | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 70 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | >20 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | >30 | 4.67 | $Ki \leq (50 \times [I]_{max,u})$ |
| MATE1 | CTD-CKD 4.2.2.7.23, R-11820 | >5 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| MATE2K | CTD-CKD 4.2.2.7.23, R-11820 | >5 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | 3.8 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | 7.6 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **>5** | **4.67** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **>50** | **4.67** | **$K_i \leq (50 \times [I]_{max,u})$** |
| OCT1 | CTD-CKD 4.2.2.7.25, R-9701 | >8.5 | 4.67 | $K_i \leq (50 \times [I]_{max,u})$ |
| **OCT2** | **4.2.2.7.2, R-14427** | **>50** | **4.67** | **$K_i \leq (50 \times [I]_{max,u})$** |

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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-1a total $[I]_{max}$ = 1.61 µM [604 µg/L] and unbound fraction = 0.0582); $K_i$ = inhibition constant (reversible); OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1a

CTD-CKD 2.6.5.16 Table 16-96 のデータを、フィネレノン 40mg 投与時の M-1b の全身曝露量に基づく評価後に再掲した。

Test article: Finerenone

**Table 16-24: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117266 (M-1b) following 40 mg OD finerenone**

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 | CTD-CKD 4.2.2.7.3, PH-40886 |
| P-gp | LLC-PK1-MDR1 | Digoxin (20 µM) | >30 | 24.2% at 30 µM | No | CTD-CKD 4.2.2.7.3, PH-40886 |
| BCRP | MDCKII-BCRP | Topotecan (2 µM) | >30 | 30.2% at 30 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BSEP | SCHH (BEI) | d8-TCA (5 µM) | >30 | 5.8% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| NTCP/BSEP | SCHH ($CL_{Biliary}$) | d8-TCA (5 µM) | >30 | 2.2% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| MATE1 | HEK293-MATE1 | Metformin (50 µM) | >5 | -66.8% at 5 µM | No | CTD-CKD 4.2.2.7.23, R-11820 |
| MATE2K | HEK293-MATE2K | Metformin (50 µM) | >5 | 25.1% at 5 µM | No | CTD-CKD 4.2.2.7.23, R-11820 |
| OATP1B1 | HEK293-OATP1B1 | Pravastatin (5 µM) | 3.9 | 75.0% at 10 µM | No | CTD-CKD 4.2.2.7.9, PH-40952 |
| OATP1B3 | HEK293-OATP1B3 | Pravastatin (5 µM) | 7.3 | 56.3% at 10 µM | No | CTD-CKD 4.2.2.7.9, PH-40952 |
| OAT1 | HEK293-OAT1 | PAH (10 µM) | >5.2 | 0.4% at 5.2 µM | No | CTD-CKD 4.2.2.7.24, R-9702 |
| OAT3 | HEK293-OAT3 | Furosemide (5 µM) | >5.2 | 24.3% at 5.2 µM | No | CTD-CKD 4.2.2.7.24, R-9702 |
| OCT1 | HEK293-OCT1 | $MPP^+$ (5 µM) | >7.2 | -21.2% at 7.2 µM | No | CTD-CKD 4.2.2.7.25, R-9701 |
| OCT2 | HEK293-OCT2 | $MPP^+$ (5 µM) | >5.2 | 2.5% at 5.2 µM | No | CTD-CKD 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 Table 16-25 and Table 16-26, 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; OD = once daily

Additional information: $IC_{50}$ values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

CTD-CKD 2.6.5.16 Table 16-97 のデータを、フィネレノン 40mg 投与時の M-1b の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-25: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117266 (M-1b) following 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI between BAY 111726 (M-1b) (following 40 mg OD finerenone) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

| Transporter | Location, report number | $[I]_{max}$ [µM] | $[I]_{max,u}$ [µM] | $IC_{50}$ [µM] | $[I]/IC_{50}$ | Threshold cutoff for potential DDI |
|---|---|---|---|---|---|---|
| | | | Systemic | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 0.327 | - | 31 | 0.0105 | $[I]/IC_{50} \geq 0.1$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 0.327 | - | >30 | <0.0109 | $[I]/IC_{50} \geq 0.1$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | - | 0.013 | >30 | <0.00043 | $[I]/IC_{50} \geq 0.1$ |
| MATE1 | CTD-CKD 4.2.2.7.23, R-11820 | - | 0.013 | >5 | <0.0026 | $[I]/IC_{50} \geq 0.1$ |
| MATE2K | CTD-CKD 4.2.2.7.23, R-11820 | - | 0.013 | >5 | <0.0026 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.013 | 3.9 | 0.0033 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.013 | 7.3 | 0.0018 | $[I]/IC_{50} \geq 0.1$ |
| OAT1 | CTD-CKD 4.2.2.7.24, R-9702 | - | 0.013 | >5.2 | <0.0025 | $[I]/IC_{50} \geq 0.1$ |
| OAT3 | CTD-CKD 4.2.2.7.24, R-9702 | - | 0.013 | >5.2 | <0.0025 | $[I]/IC_{50} \geq 0.1$ |
| OCT1 | CTD-CKD 4.2.2.7.25, R-9701 | - | 0.013 | >7.2 | <0.0018 | $[I]/IC_{50} \geq 0.1$ |
| OCT2 | CTD-CKD 4.2.2.7.25, R-9701 | - | 0.013 | >5.2 | <0.0025 | $[I]/IC_{50} \geq 0.1$ |

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 of M-1b in humans treated with 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-1b total $[I]_{max}$ = 0.327 µM [123 µg/L] and unbound fraction = 0.0388); $IC_{50}$ = concentration required for 50% inhibition; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

CTD-CKD 2.6.5.16 Table 16-98 のデータを、フィネレノン 40mg 投与時の M-1b の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-26: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117266 (M-1b) following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117266 (M-1b) (following 40 mg OD 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] | Threshold cutoff for potential DDI |
|---|---|---|---|---|
| | | Systemic | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 31 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | >30 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | >30 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| MATE1 | CTD-CKD 4.2.2.7.23, R-11820 | >5 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| MATE2K | CTD-CKD 4.2.2.7.23, R-11820 | >5 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | 3.9 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | 7.3 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OAT1 | CTD-CKD 4.2.2.7.24, R-9702 | >5.2 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OAT3 | CTD-CKD 4.2.2.7.24, R-9702 | >5.2 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OCT1 | CTD-CKD 4.2.2.7.25, R-9701 | >7.2 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |
| OCT2 | CTD-CKD 4.2.2.7.25, R-9701 | >5.2 | 0.63 | $K_i \leq (50 \times [I]_{max,u})$ |

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 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-1b total $[I]_{max}$ = 0.327 µM [123 µg/L] and unbound fraction = 0.0388); $K_i$ = inhibition constant (reversible) ; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 376.41 g/mol for M-1b

CTD-CKD 2.6.5.16 Table 16-99 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-2a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-27: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117268 (M-2a) following 40 mg OD finerenone**

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 | CTD-CKD 4.2.2.7.3, PH-40886 |
| P-gp | LLC-PK1-MDR1 | Digoxin (20 µM) | >30 | -5.4% at 30 µM | No | CTD-CKD 4.2.2.7.3, PH-40886 |
| BCRP | MDCKII-BCRP | Topotecan (2 µM) | >20 | 14.8% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BCRP | MDCKII-BCRP | PhIP (2 µM) | >20 | 24.8% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BSEP | SCHH (BEI) | d8-TCA (5 µM) | >30 | 2.9% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| NTCP/BSEP | SCHH ($CL_{Biliary}$) | d8-TCA (5 µM) | >30 | 0% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| **MATE1** | **HEK293-MATE1** | **Metformin (50 µM)** | **>50** | **19.0% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| **MATE2K** | **HEK293-MATE2K** | **Metformin (50 µM)** | **>7** | **-7.36% at 7 µM** | **No** | **4.2.2.7.2, R-14427** |
| OATP1B1 | HEK293-OATP1B1 | Pravastatin (5 µM) | >10 | 42.6% at 10 µM | No | CTD-CKD 4.2.2.7.9, PH-40952 |
| OATP1B3 | HEK293-OATP1B3 | Pravastatin (5 µM) | >10 | 22.7% at 10 µM | No | CTD-CKD 4.2.2.7.9, PH-40952 |
| **OAT1** | **HEK293-OAT1** | **PAH (10 µM)** | **>7** | **-7.65% at 7 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OAT3** | **HEK293-OAT3** | **Furosemide (5 µM)** | **>50** | **17.6% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OCT1** | **HEK293-OCT1** | **$MPP^+$ (5 µM)** | **>50** | **-11% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OCT2** | **HEK293-OCT2** | **$MPP^+$ (5 µM)** | **>7** | **-1.6% at 7 µM** | **No** | **4.2.2.7.2, R-14427** |

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 Table 16-28 and Table 16-29, 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

CTD-CKD 2.6.5.16 Table 16-100 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-2a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-28: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117268 (M-2a) following 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117268 (M-2a) (following 40 mg OD finerenone) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

| Transporter | Location, report number | $[I]_{max}$ [µM] | $[I]_{max,u}$ [µM] | $IC_{50}$ [µM] | $[I]/IC_{50}$ | Threshold cutoff for potential DDI |
|---|---|---|---|---|---|---|
| | | | Systemic | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 0.775 | - | >30 | 0.0258 | $[I]/IC_{50} \geq 0.1$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | 0.775 | - | >20 | 0.0388 | $[I]/IC_{50} \geq 0.1$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | - | 0.135 | >30 | <0.045 | $[I]/IC_{50} \geq 0.1$ |
| **MATE1** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>50** | **<0.027** | **$[I]/IC_{50} \geq 0.1$** |
| **MATE2K** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>7** | **<0.0193** | **$[I]/IC_{50} \geq 0.1$** |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.135 | >10 | <0.0135 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.135 | >10 | <0.0135 | $[I]/IC_{50} \geq 0.1$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>7** | **<0.0193** | **$[I]/IC_{50} \geq 0.1$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>50** | **<0.0027** | **$[I]/IC_{50} \geq 0.1$** |
| **OCT1** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>50** | **<0.0027** | **$[I]/IC_{50} \geq 0.1$** |
| **OCT2** | **4.2.2.7.2, R-14427** | **-** | **0.135** | **>7** | **<0.0193** | **$[I]/IC_{50} \geq 0.1$** |

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 of M-2a in humans treated with 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-2a total $[I]_{max}$ = 0.775 µM [304 µg/L] and unbound fraction = 0.174); $IC_{50}$ = concentration required for 50% inhibition; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

CTD-CKD 2.6.5.16 Table 16-101 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-2a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-29: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117268 (M-2a) following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117268 (M-2a) (following 40 mg OD 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] | Threshold cutoff for potential DDI |
|---|---|---|---|---|
| | | Systemic | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | >30 | 6.74 | $K_i \leq (50 \times [I]_{max,u})$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | >20 | 6.74 | $K_i \leq (50 \times [I]_{max,u})$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | >30 | 6.74 | $K_i \leq (50 \times [I]_{max,u})$ |
| **MATE1** | **4.2.2.7.2, R-14427** | **>50** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **MATE2K** | **4.2.2.7.2, R-14427** | **>7** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | >10 | 6.74 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | >10 | 6.74 | $K_i \leq (50 \times [I]_{max,u})$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **>7** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **>50** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OCT1** | **4.2.2.7.2, R-14427** | **>50** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OCT2** | **4.2.2.7.2, R-14427** | **>7** | **6.74** | **$K_i \leq (50 \times [I]_{max,u})$** |

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-2a in humans treated with 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-2a total $[I]_{max}$ = 0.775 µM [304 µg/L] and unbound fraction = 0.174); $K_i$ = inhibition constant (reversible) OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 392.41 g/mol for M-2a

CTD-CKD 2.6.5.16 Table 16-102 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-3a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-30: Pharmacokinetics: Inhibition of human P-gp-, BCRP-, BSEP-, MATE1-, MATE2K-, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT1- and OCT2-mediated transport by BAY 1117271 (M-3a) following 40 mg OD finerenone**

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 | CTD-CKD 4.2.2.7.3, PH-40886 |
| P-gp | LLC-PK1-MDR1 | Digoxin (20 µM) | >30 | 8.2% at 30 µM | No | CTD-CKD 4.2.2.7.3, PH-40886 |
| BCRP | MDCKII-BCRP | Topotecan (2 µM) | >20 | -28.5% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BCRP | MDCKII-BCRP | PhIP (2 µM) | >20 | 16.7% at 20 µM | No | CTD-CKD 4.2.2.7.5, PH-40885 |
| BSEP | SCHH (BEI) | d8-TCA (5 µM) | >30 | 0.0% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| NTCP/BSEP | SCHH ($CL_{Biliary}$) | d8-TCA (5 µM) | >30 | 0% at 30 µM | No | CTD-CKD 4.2.2.7.22, R-11130 |
| **MATE1** | **HEK293-MATE1** | **Metformin (50 µM)** | **>50** | **-5.0% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| **MATE2K** | **HEK293-MATE2K** | **Metformin (50 µM)** | **>29** | **-7.96% at 29 µM** | **No** | **4.2.2.7.2, R-14427** |
| OATP1B1 | HEK293-OATP1B1 | Pravastatin (5 µM) | >10 | 49.3% at 10 µM | Yes | CTD-CKD 4.2.2.7.9, PH-40952 |
| OATP1B3 | HEK293-OATP1B3 | Pravastatin (5 µM) | 3.4 | 74.7% at 10 µM | Yes (EMA guideline only) | CTD-CKD 4.2.2.7.9, PH-40952 |
| **OAT1** | **HEK293-OAT1** | **PAH (10 µM)** | **>29** | **-6.25% at 29 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OAT3** | **HEK293-OAT3** | **Furosemide (5 µM)** | **>50** | **7.4% at 50 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OCT1** | **HEK293-OCT1** | **$MPP^+$ (5 µM)** | **>29** | **6.42% at 29 µM** | **No** | **4.2.2.7.2, R-14427** |
| **OCT2** | **HEK293-OCT2** | **$MPP^+$ (5 µM)** | **>29** | **4.54% at 29 µM** | **No** | **4.2.2.7.2, R-14427** |

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 Table 16-31 and Table 16-32, 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; OD = once daily

Additional information: $IC_{50}$ values for OATP1B1 and 1B3 were determined following 1 h pre-incubation

CTD-CKD 2.6.5.16 Table 16-103 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-3a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-31: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117271 (M-3a) following 40 mg OD finerenone (FDA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117271 (M-3a) (following 40 mg OD finerenone) and co-administered substrates of various transporters, based on the FDA guidance (2020)[a]

| Transporter | Location, report number | $[I]_{max}$ [µM] | $[I]_{max,u}$ [µM] | $IC_{50}$ [µM] | $[I]/IC_{50}$ | Threshold cutoff for potential DDI |
|---|---|---|---|---|---|---|
| | | | Systemic | | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | 0.343 | - | >30 | <0.0114 | $[I]/IC_{50} \geq 0.1$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40855 | 0.343 | - | >20 | <0.0172 | $[I]/IC_{50} \geq 0.1$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | - | 0.232 | >30 | <0.0077 | $[I]/IC_{50} \geq 0.1$ |
| **MATE1** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>50** | **<0.0046** | **$[I]/IC_{50} \geq 0.1$** |
| **MATE2K** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>29** | **<0.008** | **$[I]/IC_{50} \geq 0.1$** |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.232 | >10 | <0.0232 | $[I]/IC_{50} \geq 0.1$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | - | 0.232 | 3.4 | 0.0682 | $[I]/IC_{50} \geq 0.1$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>29** | **<0.008** | **$[I]/IC_{50} \geq 0.1$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>50** | **<0.0046** | **$[I]/IC_{50} \geq 0.1$** |
| **OCT1** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>29** | **<0.008** | **$[I]/IC_{50} \geq 0.1$** |
| **OCT2** | **4.2.2.7.2, R-14427** | **-** | **0.232** | **>29** | **<0.008** | **$[I]/IC_{50} \geq 0.1$** |

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 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-3a total $[I]_{max}$ = 0.343 µM [139.2 µg/L] and unbound fraction = 0.678); $IC_{50}$ = concentration required for 50% inhibition; OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a

CTD-CKD 2.6.5.16 Table 16-104 のデータを、新たに実施した試験（太字で示す）及びフィネレノン 40mg 投与時の M-3a の全身曝露量に基づき更新した。

Test article: Finerenone

**Table 16-32: Pharmacokinetics: Drug-drug interaction, transporter inhibition by BAY 1117271 (M-3a) following 40 mg OD finerenone (EMA)**

Table: Assessment of risk for *in vivo* DDI between BAY 1117271 (M-3a) (following 40 mg OD 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] | Threshold cutoff for potential DDI |
|---|---|---|---|---|
| | | Systemic | | |
| P-gp | CTD-CKD 4.2.2.7.3, PH-40886 | >30 | 11.6 | $K_i \leq (50 \times [I]_{max,u})$ |
| BCRP | CTD-CKD 4.2.2.7.5, PH-40885 | >20 | 11.6 | $K_i \leq (50 \times [I]_{max,u})$ |
| BSEP | CTD-CKD 4.2.2.7.22, R-11130 | >30 | 11.6 | $K_i \leq (50 \times [I]_{max,u})$ |
| **MATE1** | **4.2.2.7.2, R-14427** | **>50** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **MATE2K** | **4.2.2.7.2, R-14427** | **>29** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |
| OATP1B1 | CTD-CKD 4.2.2.7.9, PH-40952 | >10 | 11.6 | $K_i \leq (50 \times [I]_{max,u})$ |
| OATP1B3 | CTD-CKD 4.2.2.7.9, PH-40952 | 3.4 | 11.6 | $K_i \leq (50 \times [I]_{max,u})$ |
| **OAT1** | **4.2.2.7.2, R-14427** | **>29** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OAT3** | **4.2.2.7.2, R-14427** | **>50** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OCT1** | **4.2.2.7.2, R-14427** | **>29** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |
| **OCT2** | **4.2.2.7.2, R-14427** | **>29** | **11.6** | **$K_i \leq (50 \times [I]_{max,u})$** |

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-3a in humans treated with 40 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 (CTD-CKD 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 (CTD-CKD 4.2.2.7.19, PH-40388) (M-3a total $[I]_{max}$ = 0.343 µM [139.2 µg/L] and unbound fraction = 0.678); $K_i$ = inhibition constant (reversible); OD = once daily

Additional information: conversion of molar to mass units and *vice versa* performed considering a molecular mass of 406.39 g/mol for M-3a