2.6.4.8 その他の薬物動態試験

ヒトトランスポーター主要分子種（P-gp，BCRP，BSEP，OATP1B1，OATP1B3，OAT1，OAT3，OCT1，OCT2，MATE1 及び MATE2-K）に対するタゼメトスタット及びその代謝物の基質認識性及び阻害活性を評価するための一連の in vitro 試験を実施した。

2.6.4.8.1 タゼメトスタットの P-gp，BCRP に対する基質認識性及び阻害能の評価（添付資料 5.3.2.3.2 [試験番号 DMPKA20[redacted]-003]）

P-gp を発現する LLC-PK1 細胞及び BCRP を発現する MDCK 細胞を用いて，タゼメトスタットの P-gp 及び BCRP に対する基質認識性，並びに阻害作用について評価した（5.3.2.3.2）。基質認識性の結果を表 2.6.4-36 に示し，阻害活性を表 2.6.4-38 に示す。

対照細胞における輸送比（刷子縁膜から基底膜への輸送に対する基底膜から刷子縁膜への輸送比率）で補正した P-gp 発現細胞でのタゼメトスタットの輸送比（CR_E 値）は，実測濃度約 6，約 22～32 及び約 80～86 μmol/L で，それぞれ 133.6，59.0 及び 5.1 であり，P-gp の阻害剤であるエラクリダーによって CR_E 値は 2.4～3.5 に低下した。したがって，タゼメトスタットは P-gp の基質であることが示された。一方，BCRP 発現細胞でのタゼメトスタットの CR_E 値は，実測濃度約 4～5，約 18～19 及び約 41～58 μmol/L で，それぞれ 0.7，0.9 及び 1.5 であり，BCRP の阻害剤である Ko143 によってこれらの値に際立った変化が無かったことから，タゼメトスタットは BCRP の基質ではないことが示された（以上，表 2.6.4-36 より）。

タゼメトスタットは，P-gp を介した[^{3}H]ジゴキシンの輸送に対して，濃度依存的な阻害作用を示し，IC_{50} は 5.9 μmol/L であった。また，タゼメトスタットは，BCRP を介した[^{3}H]プラゾシンの輸送に対して，濃度依存的な阻害作用を示し，IC_{50} は 34.1 μmol/L であった（以上，表 2.6.4-38 より）。

表 2.6.4-36 P-gp 又は BCRP 発現細胞単層膜系におけるタゼメトスタットの経細胞輸送

Transporter	R_E or CR_E	Tazemetostat					
		4~6 μmol/L[a]		18~32 μmol/L[a]		41~86 μmol/L[a]	
		Without Inhibitor	With Inhibitor	Without Inhibitor	With Inhibitor	Without Inhibitor	With Inhibitor
P-gp	$R_{E\ (LLC\text{-}PK1)}$	1.3	0.9	0.7	0.8	0.9	0.8
	$R_{E\ (LLC\text{-}MDR1)}$	173.7	2.2	41.3	2.8	4.6	1.9
	CR_E	133.6	2.4	59.0	3.5	5.1	2.4
BCRP	$R_{E\ (MDCK\text{-}mock)}$	36.0	3.1	3.9	1.9	1.1	0.8
	$R_{E\ (MDCK\text{-}BCRP)}$	25.3	2.8	3.6	2.0	1.6	1.1
	CR_E	0.7	0.9	0.9	1.1	1.5	1.4

Inhibitor of P-gp: elacridar (5 μmol/L), and inhibitor of BCRP: Ko143 (10 μmol/L).
BCRP = breast cancer resistance protein, CR_E = corrected efflux ratio, LLC-MDR1 = P-gp-transfected LLC-PK1, MDCK-BCRP = BCRP-transfected MDCK, P-gp = P-glycoprotein, R_E = efflux ratio.
a: Measured concentrations.
出典：添付資料 5.3.2.3.2 (DMPKA20[redacted]-003)

2.6.4.8.2 タゼメトスタットの OATP1B1，OATP1B3，OCT2，OAT1 及び OAT3 に対する基質認識性並びに阻害能の評価（添付資料 5.3.2.3.3［試験番号 DMPKA20[redacted]-076]）

OATP1B1，OATP1B3，OCT2 又は OAT1 発現 CHO 細胞，並びに OAT3 発現 HEK293 細胞を

用いて，タゼメトスタットのトランスポーターに対する基質認識性，並びに阻害作用について評価した（5.3.2.3.3）。検討した各トランスポーターに対する基質認識性の結果を表 2.6.4-37 に示し，阻害活性を表 2.6.4-38 に示す。

OAT3 におけるタゼメトスタットの fold uptake 値は 0.7～0.9 と小さく OAT3 の基質でないと考えられた。また，OATP1B1，OATP1B3，OCT2 及び OAT1 のタゼメトスタットの fold uptake 値は各トランスポーターの選択的阻害剤存在下で著しく低下しなかったことから，これらのトランスポーターの基質でないことが示唆された（以上，表 2.6.4-37 より）。

タゼメトスタットは，OAT1 を阻害しなかった（IC_{50}：>100 μmol/L）が，OATP1B1，OATP1B3，OCT2 及び OAT3 に対する阻害効果が認められ，これらのトランスポーターのプローブ基質の輸送に対する IC_{50} はそれぞれ 19.7，14.4，14.7 及び 10.0 μmol/L であった（以上，表 2.6.4-38 より）。なお，この後に実施された試験番号 OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102（2.6.4.8.4 項，表 2.6.4-39 参照）において，タゼメトスタットは 20 μmol/L で OCT2 の活性を阻害しなかった。

表 2.6.4-37 OATP1B1，OATP1B3，OCT2，OAT1 又は OAT3 発現細胞における タゼメトスタットの取り込み

Transporter	Fold Uptake[a]							
	1 μmol/L		3 μmol/L		10 μmol/L		Probe Substrate	
	Tazemeto.	Tazemeto. +Inhibitor	Tazemeto.	Tazemeto. +Inhibitor	Tazemeto.	Tazemeto. +Inhibitor	Substrate	Substrate +Inhibitor
OATP1B1[b]	ND	4.2	3.6	3.9	5.1	5.2	4.4	2.8
OATP1B3[c]	3.0	3.4	3.6	2.3	4.0	4.0	4.3	2.2
OCT2[d]	2.7	1.7	1.8	1.9	1.9	1.6	10.3	1.2
OAT1[e]	2.1	1.9	1.6	1.7	1.8	1.7	3.6	1.9
OAT3[f]	0.7	0.9	0.7	0.8	0.9	1.0	13.7	2.2

この後に行われた試験（試験番号 OPT-20[redacted]-073 and OPT-20[redacted]-103［2.6.4.8.5 項及び表 2.6.4-41 参照］においても，タゼメトスタットは OATP1B1 及び OATP1B3 の基質ではないことが推察された。

ND = not determined due to below the limit of quantitation, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, Tazemeto. = tazemetostat.

a: Fold Uptake = Transfected uptake velocity / Parental uptake velocity.

b: [^{3}H]estrone 3-sulfate is the probe substrate and rifampicin is the selective inhibitor.

c: [^{3}H]estradiol 17β-glucuronide is the probe substrate and rifampicin is the selective inhibitor.

d: [^{14}C]metformin is the probe substrate and quinidine is the selective inhibitor.

e: [^{3}H]*p*-aminohippuric acid is the probe substrate and probenecid is the selective inhibitor.

f: [^{3}H]estrone 3-sulfate is the probe substrate and probenecid is the selective inhibitor.

出典：添付資料 5.3.2.3.3 (DMPKA20[redacted]-076)

2.6.4.8.3 タゼメトスタットの BSEP に対する阻害能の評価（添付資料 5.3.2.3.4［試験番号 DMPKA20[redacted]-118］）

BSEP に対するタゼメトスタットの阻害作用について，BSEP 発現膜ベシクルを用いて評価した（5.3.2.3.4）。BSEP に対する阻害活性を表 2.6.4-38 に示す。

タゼメトスタットは，BSEP を介した[^{3}H]タウロコール酸の輸送に対して，濃度依存的な阻害作用を示し，IC_{50} は 20.0 μmol/L であった。

表 2.6.4-38 タゼメトスタットの各種薬物トランスポーター対する阻害活性

Transporter	IC_{50} (μmol/L)	Probe Substrate	Selective Inhibitor	Data Source
P-gp	5.9	[^{3}H]digoxin	5 μmol/L elacridar	5.3.2.3.2 (DMPKA20[redacted]-003)
BCRP	34.1	[^{3}H]prazosin	10 μmol/L Ko143	5.3.2.3.2 (DMPKA20[redacted]-003)
OATP1B1	19.7	[^{3}H]estrone 3-sulfate	50 μmol/L rifampicin	5.3.2.3.3 (DMPKA20[redacted]-076)
OATP1B3	14.4	[^{3}H]estradiol 17β-glucuronide	50 μmol/L rifampicin	5.3.2.3.3 (DMPKA20[redacted]-076)
OCT2	14.7 [a]	[^{14}C]metformin	100 μmol/L quinidine	5.3.2.3.3 (DMPKA20[redacted]-076)
OAT1	>100	[^{3}H]*p*-aminohippuric acid	100 μmol/L probenecid	5.3.2.3.3 (DMPKA20[redacted]-076)
OAT3	10.0	[^{3}H]estrone 3-sulfate	100 μmol/L probenecid	5.3.2.3.3 (DMPKA20[redacted]-076)
BSEP	20.0	[^{3}H]taurocholic acid	100 μmol/L cyclosporin A	5.3.2.3.4 (DMPKA20[redacted]-118)

BCRP = breast cancer resistance protein, BSEP = bile salt export pump, IC_{50} = half-maximal inhibitory concentration, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, P-gp = P-glycoprotein.
a: この後に行われた試験（試験番号 OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102［2.6.4.8.4 項及び表 2.6.4-39 参照］では，タゼメトスタットは 20 μmol/L で OCT2 の活性を阻害しなかった。

2.6.4.8.4 (1) 主要代謝物 EPZ-6930，EPZ006931 及び EPZ034163 の BCRP，P-gp，MATE1，MATE2-K，OAT1，OAT3，OCT1，OCT2，OATP1B1 及び OATP1B3 に対する阻害能の評価，(2) タゼメトスタットの MATE1，MATE2-K 及び OCT2 に対する阻害能の評価（添付資料 5.3.2.3.5［試験番号 OPT-20[redacted]-072，OPT-20[redacted]-074，OPT-10[redacted]-101，OPT-20[redacted]-102］）

タゼメトスタットの MATE1，MATE2-K 及び OCT2 に対する阻害能を検討した（5.3.2.3.5）。実験条件及び得られた結果を表 2.6.4-39 及び 2.6.5.16 項（試験番号 OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102）に示す。

タゼメトスタットは 20 μmol/L で OCT2 の活性を阻害しなかった。媒体対照と比較して，タゼメトスタットは MATE1 及び MATE2-K の活性をそれぞれ 87.7%及び 84.6%阻害した。フォローアップ試験を行い，MATE1 及び MATE2-K を介した輸送に対するタゼメトスタットの阻害効果を 0.3～30 μmol/L の濃度範囲でさらに検討した。タゼメトスタットの MATE1 及び MATE2-K に対する最大阻害はそれぞれ 92.6%及び 96.9%であった。タゼメトスタットの MATE1 及び MATE2-K に対する IC_{50} 値はそれぞれ 2.65 及び 1.89 μmol/L であった。

タゼメトスタットの主要代謝物 EPZ-6930，EPZ006931 及び EPZ034163 の各トランスポーター（BCRP，P-gp，MATE1，MATE2-K，OAT1，OAT3，OCT1，OCT2，OATP1B1 及び OATP1B3）に対する阻害能を検討した（5.3.2.3.5）。実験条件及び得られた結果を表 2.6.4-40 及び 2.6.5.16 項（試験番号 OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102）に示す。

EPZ-6930 は 25 μmol/L で OAT1，OAT3，OCT1，OATP1B1，OATP1B3 及び BCRP の活性を阻害しなかった。媒体対照と比較して，EPZ-6930 は OCT2，MATE1，MATE2-K 及び P-gp の活性をそれぞれ 25.7%，79.9%，64.4%及び 54.6%阻害した。

EPZ006931 は 10 μmol/L で OAT1，OAT3，OCT1，OCT2，OATP1B1，OATP1B3 及び BCRP の活性を阻害しなかった。媒体対照と比較して，EPZ006931 は MATE1，MATE2-K 及び P-gp の活性をそれぞれ 65.4%，35.8%及び 39.7%阻害した。

EPZ034163 は 10 μmol/L で OAT1，OAT3，OCT1，OCT2，OATP1B1，OATP1B3，BCRP 及び P-gp を阻害しなかった。媒体対照と比較して，EPZ034163 は MATE1 及び MATE2-K の活性をそれぞれ 48.7%及び 23.0%阻害した。

フォローアップ試験を行い，MATE1 及び MATE2-K を介した輸送に対する EPZ-6930 の阻害効果を 0.3～50 μmol/L の濃度範囲でさらに検討した。EPZ-6930 の MATE1 及び MATE2-K に対する最大阻害はそれぞれ 88.8%及び 77.4%であった。EPZ-6930 の MATE1 及び MATE2-K に対する IC_{50} 値はそれぞれ 4.79 及び 12.1 μmol/L であった。

表 2.6.4-39 タゼメトスタットの MATE1，MATE2-K 及び OCT2 に対する阻害

Test System	1. MDCK-II cells expressing human solute carrier transporter MATE1, MATE2-K, or OCT2 2. MDCK-II control cells transfected with a control vector
Probe Substrate	1. MATE1: 10 μmol/L [^{14}C]metformin 2. MATE2-K: 10 μmol/L [^{14}C]metformin 3. OCT2: 10 μmol/L [^{14}C]metformin
Selective Inhibitor	1. MATE1: 10 μmol/L cimetidine 2. MATE2-K: 10 μmol/L cimetidine 3. OCT2: 1000 μmol/L quinidine
Test Article Concentration	Tazemetostat: 20 μmol/L
Incubation Time	Five minutes for MATE1, MATE2-K, and OCT2.
Results and Summaries	タゼメトスタットは 20 μmol/L で OCT2 の活性を阻害しなかった [a,b]。媒体対照と比較して，タゼメトスタットは MATE1 及び MATE2-K の活性をそれぞれ 87.7%及び 84.6%阻害した。
	フォローアップ試験を行い，MATE1 及び MATE2-K を介した輸送に対するタゼメトスタットの阻害効果を 0.3～30 μmol/L の濃度範囲でさらに検討した。タゼメトスタットの MATE1 及び MATE2-K に対する最大阻害はそれぞれ 92.6%及び 96.9%であった。タゼメトスタットの MATE1 及び MATE2-K に対する IC_{50} 値はそれぞれ 2.65 及び 1.89 μmol/L であった。

IC_{50} = half-maximal inhibitory concentration, MATE = multidrug and toxin extrusion, OCT = organic cation transporter.
a: この回の評価で，タゼメトスタットは 20 μmol/L で OCT1 の活性を阻害しなかった。
b: 前報 試験番号 DMPKA20[redacted]-076（2.6.4.8.2 項及び表 2.6.4-37 参照）では，タゼメトスタットの OCT2 を介した輸送に対する阻害効果が認められ，IC_{50} 値は 14.7 μmol/L であった。
出典：添付資料 5.3.2.3.5 (OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102)

表 2.6.4-40 主要代謝物 EPZ-6930，EPZ006931 及び EPZ034163 の BCRP，P-gp，MATE1，MATE2-K，OAT1，OAT3，OCT1，OCT2，OATP1B1 及び OATP1B3 に対する阻害

Test System	1. MDCK-II cells expressing human solute carrier transporter MATEI, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or BCRP 2. MDCK-II control cells transfected with a control vector 3. MDCK-II cells expressing P-gp
Probe Substrate	1. MATE1: 10 µmol/L [^{14}C]metformin 2. MATE2-K: 10 µmol/L [^{14}C]metformin 3. OCT1: 2 µmol/L [^{3}H]MPP+ 4. OCT2: 10 µmol/L [^{14}C]metformin 5. OAT1: 2 µmol/L [^{3}H]*p*-aminohippuric acid 6. OAT3: 10 µmol/L [^{3}H]*p*-aminohippuric acid 7. OATP1B1: 2 µmol/L [^{3}H]estradiol 17β-glucuronide 8. OATP1B3 2 µmol/L [^{3}H]CCK-8 9. BCRP: 2 µmol/L [^{3}H]prazosin 10. P-gp: 100 nmol/L [^{3}H]quinidine
Selective Inhibitor	1. MATE1: 10 µmol/L cimetidine 2. MATE2-K: 10 µmol/L cimetidine 3. OCT1: 1000 µmol/L quinidine 4. OCT2: 1000 µmol/L quinidine 5. OAT1: 100 µmol/L probenecid 6. OAT3: 100 µmol/L probenecid 7. OATP1B1: 100 µmol/L rifampicin 8. OATP1B3: 100 µmol/L rifampicin 9. BCRP: 1 µmol/L Ko143 10. P-gp: 3 µmol/L elacridar
Paracellular Marker for Efflux Assays	100 µmol/L mannitol
Test Article Concentration	EPZ-6930: 25 µmol/L EPZ006931: 10 µmol/L EPZ034163: 10 µmol/L
Incubation Time	Five minutes for MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3. Ninety minutes for BCRP and P-gp.
Results and Summaries	EPZ-6930 は 25 µmol/L で OAT1，OAT3，OCT1，OATP1B1，OATP1B3 及び BCRP の活性を阻害しなかった。媒体対照と比較して，EPZ-6930 は OCT2，MATE1，MATE2-K 及び P-gp の活性をそれぞれ 25.7%，79.9%，64.4%及び 54.6%阻害した。
	EPZ006931 は 10 µmol/L で OAT1，OAT3，OCT1，OCT2，OATP1B1，OATP1B3 及び BCRP の活性を阻害しなかった。媒体対照と比較して，EPZ006931 は MATE1，MATE2-K 及び P-gp の活性をそれぞれ 65.4%，35.8%及び 39.7%阻害した。
	EPZ034163 は 10 µmol/L で OAT1，OAT3，OCT1，OCT2，OATP1B1，OATP1B3，BCRP 及び P-gp を阻害しなかった。媒体対照と比較して，EPZ034163 は MATE1 及び MATE2-K の活性をそれぞれ 48.7%及び 23.0%阻害した。
	フォローアップ試験を行い，MATE1 及び MATE2-K を介した輸送に対する EPZ-6930 の阻害効果を 0.3～50 µmol/L の濃度範囲でさらに検討した。EPZ-6930 の MATE1 及び MATE2-K に対する最大阻害はそれぞれ 88.8%及び 77.4%であった。EPZ-6930 の MATE1 及び MATE2-K に対する IC_{50} 値はそれぞれ 4.79 及び 12.1 µmol/L であった。

BCRP = breast cancer resistance protein, CCK-8 = cholecystokinin octapeptide, IC_{50} = half-maximal inhibitory concentration, MATE = multidrug and toxin extrusion, MPP+ = 1-methyl-4-phenylpyridinium, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, P-gp = P-glycoprotein.
出典：添付資料 5.3.2.3.5 (OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102)

2.6.4.8.5 タゼメトスタットの OATP1B1，OATP1B3 及び MATE1 に対する基質認識性の評価（添付資料 5.3.2.3.6［試験番号 OPT-20[redacted]-073 and OPT-20[redacted]-103］）

タゼメトスタットの OATP1B1，OATP1B3 及び MATE1 に対する基質認識性について評価した（5.3.2.3.6）。実験条件及び得られた結果を表 2.6.4-41 及び 2.6.5.16 項（試験番号 OPT-20[redacted]-073

and OPT-20[redacted]-103）に示す。

タゼメトスタット（1, 3 及び 10 μmol/L）の対照細胞及びそれぞれのトランスポーター発現細胞への取り込みは類似していた（差異：2 倍未満であった）。これと同じ知見は，タゼメトスタット（10 μmol/L）をリファンピシン 100 μmol/L（OATP1B1 及び OATP1B3 に対する阻害剤）及びシメチジン 10 μmol/L（MATE1 に対する阻害剤）とともにインキュベートした場合にも観察された。これらの結果よりタゼメトスタットは，今回のアッセイ条件下で OATP1B1，OATP1B3 又は MATE1 の基質ではないことが推察された。

表 2.6.4-41 タゼメトスタットの OATP1B1，OATP1B3 及び MATE1 に対する基質認識性

Test System	1. MDCK-II cells expressing human solute carrier transporter OATP1B1, OATP1B3, or MATE1 2. MDCK-II control cells transfected with a control vector
Probe Substrate	1. OATP1B1: 2 μmol/L [^{3}H]estradiol 17β-glucuronide 2. OATP1B3: 2 μmol/L [^{3}H]CCK-8 3. MATE1: 10 μmol/L [^{14}C]metformin
Selective Inhibitor	1. OATP1B1: 100 μmol/L rifampicin 2. OATP1B3: 100 μmol/L rifampicin 3. MATE1: 10 μmol/L cimetidine
Test Article Concentration	Tazemetostat: 1, 3, 10 μmol/L, and 10 μmol/L +/– selective inhibitor of each transporter
Incubation Time	Five minutes for OATP1B1, OATP1B3, and MATE1.
Results and Summaries	タゼメトスタット（1, 3 及び 10 μmol/L）の対照細胞及びそれぞれのトランスポーター発現細胞への取り込みは類似していた（差異：2 倍未満であった）。これと同じ知見は，タゼメトスタット（10 μmol/L）をリファンピシン 100 μmol/L（OATP1B1 及び OATP1B3 に対する阻害剤）及びシメチジン 10 μmol/L（MATE1 に対する阻害剤）とともにインキュベートした場合にも観察された。これらの結果よりタゼメトスタットは，今回のアッセイ条件下で OATP1B1，OATP1B3 又は MATE1 の基質ではないことが示された[a]。

CCK-8 = cholecystokinin octapeptide, MATE = multidrug and toxin extrusion, OATP = organic anion transporting polypeptide.
a: 前報 試験番号 DMPKA20[redacted]-076（2.6.4.8.2 項及び表 2.6.4-37 参照）においても，タゼメトスタットは OATP1B1 及び OATP1B3 の基質ではなかった。
出典：添付資料 5.3.2.3.6 (OPT-20[redacted]-073 and OPT-20[redacted]-103)

2.6.4.9 考察及び結論

タゼメトスタットは，毒性評価動物種である SD ラット及びカニクイザルにおいて類似の PK プロファイルを示した。雄 SD ラット及び雄カニクイザルに単回静脈内投与後，タゼメトスタットは，中程度から高いクリアランス（ラット：3.49 L/h/kg，サル：1.39 L/h/kg）及び中程度の分布容積（ラット：1.80 L/kg，サル：2.04 L/kg）を示し，血漿からの $t_{1/2}$（ラット：0.4 時間，サル：1.6 時間）は短かった。雄 SD ラット及び雄カニクイザルに単回経口投与した後のタゼメトスタットの C_{max} 及び暴露量は，検討した投与量範囲内（ラット及びサル：5～100 mg/kg）において，投与量比を上回る増加を示し，投与量 5 mg/kg におけるラット及びサルの F（ラット：3.2%，サル：1.9%）は低かった。単回静脈内投与及び単回経口投与における尿中排泄の検討から，タゼメトスタットのラットでの腎クリアランスは低いことが示唆され，単回静脈内投与における胆汁排泄の検討から，タゼメトスタットのラットでの胆汁排泄クリアランスも低いことが示唆された。

反復経口投与試験におけるタゼメトスタットの暴露量は，雄ラットより雌ラットの方が大きかったが，サルでは暴露量に顕著な性差は認められなかった。反復経口投与後のタゼメトスタットの暴露量は，サルでは投与初日に比べ低下し，ラットでは投与初日と同等若しくは蓄積傾向が認められた。

雄 SD ラット及び雌雄カニクイザルに[^{14}C]タゼメトスタット臭化水素酸塩（50 mg/kg［フリー体換算量］）を単回経口投与後の血漿中放射能濃度の t_{max} は，それぞれ 1 時間及び 2 時間（雌雄ともに）であり，吸収は速やかであった。その後，両動物種の血漿中放射能濃度は速やかに消失し，雄 SD ラットの $t_{1/2}$ は 0.948 時間であった。雄 SD ラット及び雌雄カニクイザルにおける放射能の主たる排泄経路は糞中であり，単回経口投与後 168 時間までに投与量の 82%以上が糞中に回収された。雄 SD ラット及び雌雄カニクイザルにおける単回経口投与後 168 時間までの総放射能回収率は，それぞれ投与量の 94.4%及び 88.0%～91.2%であった。胆管カニューレ挿入雄 SD ラットの放射能の主排泄経路は胆汁排泄であり，単回経口投与後 96 時間までに投与量の 53.5%が胆汁中に回収され，また，17.9%及び 24.0%がそれぞれ尿及び糞中に回収された。ゆえに，SD ラットにおける[^{14}C]タゼメトスタット経口投与後の放射能の主たる排泄経路は，胆汁を介した糞中排泄であることが示された。単回経口投与後の胆汁中及び尿中への放射能回収率より，胆管カニューレ挿入雄 SD ラットにおける[^{14}C]タゼメトスタットの消化管吸収率は，70%以上であると考えられた。

雄 SD ラット及び雄 LE ラットに[^{14}C]タゼメトスタット臭化水素酸塩（50 mg/kg［フリー体換算量］）を単回経口投与後，放射能は速やかに吸収され，中枢神経系組織（小脳，大脳，髄質及び脊髄）及び水晶体を除く組織に広く分布した。雄 SD ラットの大半の組織で，放射能濃度は投与後 1 時間で C_{max} に到達し，それ以外の組織でも投与後 4 時間までに C_{max} に到達した後に低下し始めた。放射能は投与後 168 時間以内に大半の組織からほぼ消失した。大動脈，肝臓，腎皮質及び甲状腺では投与後 168 時間の時点で放射能濃度が検出されたが，いずれの組織でも定量限界値の約 1～4 倍の値であった。雄 LE ラットにおける放射能の組織分布パターンは，メラニン含有組織を除き，雄 SD ラットと類似していた。雄 LE ラットの眼球血管膜や有色皮膚等のメラニン含有組織では，雄 SD ラットよりも放射能濃度が顕著に高く，[^{14}C]タゼメトスタット由来放射能のメラニンに対する親和性が示唆された。有色組織で放射能濃度の低下が認められたことから，メラニンとの結合は可逆的であると考えられた。

タゼメトスタットの in vitro 血漿中タンパク結合率は比較的高く，ウサギ（NZW）：91.1%～91.9%，サル（カニクイ）：83.3%～84.7%，ヒト：87.7%～91.1%であり，これらの動物種では，検討濃度範囲内（1～30 µmol/L）において濃度依存性は認められなかった。一方，マウス（CD-1）及びラット（SD）におけるタゼメトスタットの in vitro 血漿タンパク結合率は 1～30 µmol/L において，それぞれ 91.8%～98.1%及び 88.8%～94.7%であり，10 µmol/L 以上で結合率が低下傾向を示し，濃度依存性が認められた。ヒト血漿中に存在する HSA，α1-AGP 及び HG のうち，タゼメトスタットは HSA に対して最も強い結合を示した。マウス（CD-1），ラット（SD），サル（カニクイ）及びヒトにおけるタゼメトスタット（添加濃度：50～50,000 ng/mL）の in vitro での R_B 値は 0.53～1.06 であり，添加最高濃度（50,000 ng/mL）でやや高値を示したものの，5000 ng/mL 以下では濃度依存性を認めず，また，全般に動物種差も認められなかった。

ラット，サル及びヒトの in vitro 試料及び生体試料の代謝物分析から，これらの動物種におい

てタゼメトスタットの主たる消失経路は代謝によるものと考えられた。いずれの動物種においても，アニリン窒素の脱アルキル化反応が主代謝経路であり，*N*-脱エチルによる EPZ-6930 の生成，*N*-脱テトラヒドロピランによる EPZ006931 の生成及びそれらの逐次代謝物が，血漿中及び排泄物中に存在する代謝物の主要な構成成分であった。In vitro 試料中の代謝物は生体試料中の代謝物と概ね一致し，in vitro 試料及び生体試料中にヒト特異的な代謝物は見出されなかった。

ヒトマスバランス試験（外国 103 試験［EZH-103，5.3.1.1.1，5.3.1.1.2，5.3.1.1.3 及び 5.3.2.2.13］）において，タゼメトスタット（22.40%），EPZ-6930（31.81%）及び EPZ006931（10.99%）が血漿中薬物関連総暴露量の 10%以上を示し，EPZ-6930 及び EPZ006931 がヒト血漿中主代謝物として同定された（2.7.2.2.2.3 項参照）。ラット及びサル 13 週間反復投与毒性試験では，タゼメトスタットに加え EPZ-6930 を定量し，両動物種における EPZ-6930 の暴露量はヒトよりも十分に高いことが示された（2.6.6.9 項，表 2.6.6-18 参照）。代謝物の血漿中暴露量を半定量的に動物種間で比較した試験において，代謝物 EPZ006931 はラット及びサル血漿中の主代謝物の一つであることが示されている。ゆえに，非臨床毒性試験において，主代謝物（EPZ-6930 及び EPZ006931）を含めたタゼメトスタットの毒性学的評価が，適正に行われていると結論づけた。代謝物 EPZ-6930 のヒト血漿中暴露量はタゼメトスタットより大きかったが，in vitro セルフリー系における代謝物 EPZ-6930 の EZH2 に対する阻害活性は，タゼメトスタットに比べて 1/11～1/31 の活性であったことから，EPZ-6930 の薬効への寄与は小さいと考えられた（2.6.2.2.1.3 項参照）。

ヒトにおけるタゼメトスタットの主たる消失経路は代謝であり，ヒト肝ミクロソーム及び各 rCYP 分子種を用いた in vitro 試験から，タゼメトスタットの代謝には主に CYP3A4 が関与していることが示された。タゼメトスタットの臨床 PK プロファイルは，CYP3A 阻害薬及び誘導薬による影響を受ける可能性が考えられたため，臨床薬物相互作用試験（外国 105 試験［EZH-A001-105，5.3.3.4.1 及び 5.3.3.4.2］）において，タゼメトスタットの臨床 PK に対する中程度の CYP3A 阻害薬（フルコナゾール）の影響を評価した（2.7.2.2.2.4 項参照）。1 日 1 回フルコナゾールを 400 mg 反復投与した後，タゼメトスタットの定常状態での C_{max} 及び $AUC_{(0\text{-}t)}$は中程度（それぞれ 2.3 倍及び 3.1 倍）の増加を示した。ゆえに，CYP3A に対する中程度～強い阻害薬との併用により，タゼメトスタットの C_{max} 及び AUC は中程度以上増加する可能性がある。タゼメトスタットは P-gp の基質であるが，P-gp 発現細胞におけるタゼメトスタットの濃度依存的な輸送低下とタゼメトスタットの臨床用量（800 mg BID）を考え合わせると，消化管では P-gp の輸送飽和が生じていると考えられ，P-gp 阻害薬の影響を受ける可能性は低いと考えられた。

In vitro 試験において，タゼメトスタットは複数の CYP 分子種に対して阻害又は誘導作用を示した。タゼメトスタットの各 CYP 分子種に対する in vitro 阻害パラメータ（K_i，IC_{50}，K_I 及び k_{inact}），臨床用量（800 mg BID）及び血漿中暴露量を考え合わせると，タゼメトスタットが CYP3A（消化管及び肝臓），CYP2C8，CYP2C19 及び CYP2D6 を可逆的に阻害し，CYP3A（消化管及び肝臓）を時間依存的に阻害する可能性が示された。In vitro 試験でのタゼメトスタット及び陽性対照による主要 CYP 分子種の mRNA 発現量の変動及びタゼメトスタットの臨床用量での血漿中暴露量を勘案すると，タゼメトスタットが CYP3A4 を誘導する可能性が示された。タゼメトスタットは CYP2B6 に対する誘導能も有しているが，その程度は限定的であると考えられた。タゼメトスタットが CYP3A4 に対する誘導能を示したことから，共通の核内受容体での発現制御が示唆されている CYP2C8，CYP2C9 及び CYP2C19 に対するタゼメトスタットの誘導

能を in vitro で評価した。その結果，CYP2C8 及び CYP2C9 に対するタゼメトスタットの誘導能が示唆された。さらに，タゼメトスタットは複数のトランスポーター分子種に対して阻害作用を示した。タゼメトスタットの各トランスポーター分子種に対する IC_{50} 値，臨床用量（800 mg BID）及び血漿中暴露量を考え合わせると，タゼメトスタットが P-gp，BCRP，OATP1B1，OATP1B3，MATE1 及び MATE2-K を阻害する可能性が示された。未変化体より極性が高く，AUC が未変化体を超える代謝物 EPZ-6930 は，IC_{50} 値及び臨床用量での血漿中暴露量を勘案すると，主要 CYP 分子種を阻害する可能性は低いと考えられた。同様に，代謝物 EPZ-6930 は，MATE1 及び MATE2-K 以外のトランスポーター分子種を阻害する可能性は低いと考えられた。以上の in vitro 試験から得られた知見に基づき，CYP3A 指標薬（ミダゾラム）との併用試験（外国 101 試験［EZH-A001-101，5.3.5.2.1 及び 5.3.5.2.2］）並びに CYP2C8 及び CYP2C19 指標薬（それぞれレパグリニド及びオメプラゾール）との臨床薬物相互作用試験（外国 105 試験［EZH-A001-105，5.3.3.4.1 及び 5.3.3.4.2］）を実施した。In vitro 試験において，タゼメトスタットは，CYP3A に対して阻害及び誘導の相反する作用を示したが，最終的に in vivo では CYP3A 指標薬であるミダゾラムに対して弱い誘導作用を示し，ミダゾラムの $AUC_{(0\text{-}t)}$は 38%低下した。タゼメトスタットとの併用により，CYP2C8 指標薬であるレパグリニドの C_{max} 及び $AUC_{(0\text{-}t)}$はそれぞれ 93%及び 117%上昇した。なお，レパグリニドは CYP2C8 の基質であると同時に，OATP1B1 及び OATP1B3 の基質であることが知られている。タゼメトスタットの CYP2C8 に対する in vitro 阻害活性は，OATP1B1 及び OATP1B3 に対する in vitro 阻害活性よりも 10 倍以上強いことを考えると，レパグリニドの血漿中濃度上昇は主にタゼメトスタットによる CYP2C8 阻害に起因しているものと考えられ，タゼメトスタットが OATP1B1 及び OATP1B3 を阻害する可能性は低いと考えられた。タゼメトスタットは CYP2C19 指標薬であるオメプラゾールに対して影響を与えなかった。タゼメトスタットの CYP2D6 に対する R 値は，カットオフ基準（1.02）よりもわずかに大きかったが，臨床薬物相互作用の認められなかった CYP2C19 に対する R 値よりも小さく，かつタゼメトスタットは CYP2C19 指標薬（オメプラゾール）の PK に影響を与えなかったことを考え合わせると，タゼメトスタットが臨床用量で CYP2D6 を阻害する可能性は低いと考えられた。

以上，これらの試験結果は，動物におけるタゼメトスタットの薬物動態特性，代謝の動物種差並びにヒトにおける薬物代謝酵素及び薬物トランスポーターを介した薬物間相互作用の可能性を評価する上で適切であり，十分なものであると考えた。

2.6.4.10 図表

本文中の図表は，本文中の適切な場所に記載した。

2.6.4.11 参考文献

Obach RS, Walsky RL, Venkatakrishnan K. Mechanism-based inactivation of human cytochrome P450 enzymes and the prediction of drug-drug interactions. Drug Metabolism and Disposition. 2007;35:246–55.

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2.6.5 薬物動態試験概要表
2.6.5.1 薬物動態試験：一覧表

Test Article: tazemetostat

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Analytical Methods and Validation Reports						
LC-MS/MS method for tazemetostat in plasma	No	Rats, Monkeys	in vitro	Eisai Inc.	DMPKA20[redacted]-004	4.2.2.1.1
LC-MS/MS method for tazemetostat and its metabolite in plasma	No	Rats	in vitro	[redacted]	150536VSMB_ ECM	4.2.2.1.2
LC-MS/MS method for tazemetostat and its metabolite in plasma	No	Rats	in vitro	[redacted]	0130-1309	4.2.2.1.3
LC-MS/MS method for tazemetostat and its metabolite in plasma	No	Rabbits	in vitro	[redacted]	150539VSMB_ ECM	4.2.2.1.4
LC-MS/MS method for tazemetostat and its metabolite in plasma	No	Monkeys	in vitro	[redacted]	0130-1310	4.2.2.1.5
Absorption After a Single Dose						
Single-dose pharmacokinetics of tazemetostat	No	Mice	IV, PO	Eisai Inc.	DMPKA20[redacted]-064	4.2.2.2.1
Single-dose pharmacokinetics of tazemetostat	No	Rats	IV, PO	Eisai Inc.	DMPKA20[redacted]-060, DMPKA20[redacted]-063	4.2.2.2.2
Single-dose pharmacokinetics of tazemetostat	No	Rabbits	PO	[redacted]	20097368	4.2.2.2.3
Single-dose pharmacokinetics of tazemetostat	No	Monkeys	IV, PO	Eisai Inc.	1045-022	4.2.2.2.4
Single-dose pharmacokinetics of radioactivity	No	Rats	PO	[redacted]	45N-1402	4.2.2.5.1

Test Article: tazemetostat

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Single-dose pharmacokinetics of radioactivity	No	Monkeys	IV, PO	[redacted]	11661	4.2.2.5.2
Absorption After Repeated Dose						
Repeated-dose pharmacokinetics (toxicokinetics, 7 days)	No	Rats	PO	Eisai Co., Ltd.	T[redacted]032	4.2.3.2.1
Repeated-dose pharmacokinetics (toxicokinetics, 4 weeks)	Yes	Rats	PO	Eisai Co., Ltd.	K[redacted]004	4.2.3.2.2
Repeated-dose pharmacokinetics (toxicokinetics, 13 weeks)	Yes	Rats	PO	Eisai Co., Ltd.	K[redacted]009	4.2.3.2.3
Repeated-dose pharmacokinetics (toxicokinetics, 5 days)	No	Monkeys	PO	[redacted]	20024292	4.2.3.2.4
Repeated-dose pharmacokinetics (toxicokinetics, 4 weeks)	Yes	Monkeys	PO	[redacted]	20024293	4.2.3.2.5
Repeated-dose pharmacokinetics (toxicokinetics, 13 weeks)	Yes	Monkeys	PO	[redacted]	20047690	4.2.3.2.6
Organ Distribution						
Single-dose tissue distribution of radioactivity	No	Rats	PO	[redacted]	45N-1402	4.2.2.5.1
Single-dose tissue distribution of radioactivity	No	Rats (pigmented)	PO	[redacted]	45N-1402	4.2.2.5.1

Test Article: tazemetostat

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Plasma Protein Binding						
Plasma protein binding of tazemetostat	No	Mice, Rats, Dogs, Monkeys, Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-142	5.3.2.1.1
Plasma protein binding of tazemetostat	No	Mice, Rats, Rabbits, Monkeys, Humans	in vitro	[redacted]	161025	5.3.2.1.2
Binding to serum protein	No	Humans	in vitro	[redacted]	AL-7384-G	5.3.2.1.3
Study in Pregnant or Nursing Animals (Placental Transfer and Excretion Into the Milk)						
NA						
Other Distribution Study						
Blood to plasma concentration ratio of tazemetostat	No	Mice, Rats, Monkeys, Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-062	5.3.2.3.1
Metabolism In Vitro						
Metabolic stability in liver microsomes and hepatocytes	No	Mice, Rats, Dogs, Monkeys, Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-041	5.3.2.2.1
Metabolic stability in hepatocytes	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-117	5.3.2.2.2
Metabolism in liver microsomes and hepatocytes	No	Mice, Rats, Dogs, Monkeys, Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-042	5.3.2.2.3
Metabolism in hepatocytes	No	Rats, Rabbits, Monkeys, Humans	in vitro	[redacted]	45N-1404	5.3.2.2.4
CYP isoforms for tazemetostat metabolism	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-044	5.3.2.2.5
CYP isoforms for metabolism of tazemetostat and its metabolites	No	Humans	in vitro	[redacted]	151341	5.3.2.2.11

Test Article: tazemetostat

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Metabolism In Vivo						
Metabolites in plasma, urine, bile, and feces	No	Rats	PO	[redacted]	45N-1403	4.2.2.4.1
Metabolites in plasma, urine, and feces	No	Monkeys	IV, PO	[redacted]	514N-1502	4.2.2.4.2
Metabolites in plasma and urine	No	Rats, Rabbits, Monkeys, Humans	PO	[redacted]	14099&14430	5.3.2.2.8
Induction/Inhibition of Drug Metabolizing Enzymes						
Inhibition of CYPs by tazemetostat	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-002, DMPKA20[redacted]-171	5.3.2.2.6
Inhibition of CYPs by tazemetostat	No	Humans	in vitro	[redacted]	151245/151340/160432	5.3.2.2.12
Inhibition of CYPs by tazemetostat metabolites	No	Humans	in vitro	[redacted]	151295	5.3.2.2.10
Induction of CYPs by tazemetostat	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-040	5.3.2.2.7
Induction of CYPs by tazemetostat	No	Humans	in vitro	[redacted]	151294	5.3.2.2.9
Excretion						
Single-dose excretion of tazemetostat	No	Rats	IV, PO	Eisai Inc.	DMPKA20[redacted]-060, DMPKA20[redacted]-063	4.2.2.2.2
Single-dose excretion of radioactivity	No	Rats	PO	[redacted]	45N-1402	4.2.2.5.1
Single-dose excretion of radioactivity	No	Monkeys	IV, PO	[redacted]	11661	4.2.2.5.2
Excretion Into Bile						
Single-dose excretion of radioactivity	No	Rats	PO	[redacted]	45N-1402	4.2.2.5.1

Test Article: tazemetostat

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Drug-Drug Interactions (Pharmacokinetic)						
NA						
Other Pharmacokinetic Studies						
Substrate susceptibility and inhibitory effects of tazemetostat to P-gp and BCRP	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-003	5.3.2.3.2
Substrate susceptibility and inhibitory effects of tazemetostat to OATP1B1, OATP1B3, OCT2, OAT1, and OAT3	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-076	5.3.2.3.3
Inhibitory effects of tazemetostat to BSEP	No	Humans	in vitro	Eisai Inc.	DMPKA20[redacted]-118	5.3.2.3.4
(1) Inhibitory effects of tazemetostat main metabolites to BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 (2) Inhibitory effects of tazemetostat to MATE1, MATE2-K, and OCT2	No	Humans	in vitro	[redacted]	OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102	5.3.2.3.5
Substrate susceptibility of tazemetostat to OATP1B1, OATP1B3, and MATE1	No	Humans	in vitro	[redacted]	OPT-20[redacted]-073 and OPT-20[redacted]-103	5.3.2.3.6

BCRP = breast cancer resistance protein, BSEP = bile salt export pump, CTD = Common Technical Document, CYP = cytochrome P450, GLP = Good Laboratory Practice, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, MATE = multidrug and toxin extrusion, NA = not applicable, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, P-gp = P-glycoprotein, PO = oral.

a: An entry of "Yes" indicates that the study includes a GLP compliance statement.

2.6.5.2 分析方法及びバリデーション試験

Test Article: tazemetostat hydrobromide

Study Number/Location in CTD		**DMPKA20[redacted]-004/4.2.2.1.1**	
Species/Strain		Rat/Sprague Dawley	Monkey/Cynomolgus
Sample Matrix/Sample Volume		Plasma/55 µL	Plasma/55 µL
Extraction Method / Assay		Protein precipitation extraction / LC-MS/MS	Protein precipitation extraction / LC-MS/MS
Analyte		Tazemetostat	Tazemetostat
IS		Propranolol	Albendazole
Quantification Range (ng/mL)[a]		1 (LLOQ) to 1000	1 (LLOQ) to 1000
Calibration Curve	r^2	≥0.996423	≥0.992438
Intra-Assay[b]	Accuracy (%)	–13.1 to 7.8	–5.9 to 11.7
	Precision (%)	3.2 to 18.5	0.9 to 16.3
Inter-Assay[b]	Accuracy (%)	–13.3 to 8.9	–14.3 to 7.6
	Precision (%)	2.9 to 14.0	0.9 to 8.2
Recovery	Analyte (%)	63.2 to 81.0	54.9 to 74.5
	IS (%)	81.2	64.7
Stability	Processed samples at 4 °C	96 hours	69 hours
	Plasma samples at rt	6.5 hours	3 hours
	Plasma samples at approximately –80 °C	36 days	46 days
	Freeze/Thaw cycle	7 cycles	5 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLOQ = lower limit of quantification, r^2 = regression coefficient, rt = room temperature.

a: Concentrations were expressed as the free base of tazemetostat.

b: The results include the samples that were also diluted in the concentration.

Additional Information: There were no interfering peaks observed at the retention time of tazemetostat or IS in blank samples.

2.6.5.2 分析方法及びバリデーション試験（続き）

Test Article: tazemetostat hydrobromide, EPZ-6930

Study Number/Location in CTD		**0130-1309/4.2.2.1.3**	
Species/Strain		Rat/Sprague Dawley	
Sample Matrix/Sample Volume		Plasma/50 µL	
Extraction Method / Assay		Liquid-liquid extraction / LC-MS/MS	
Analyte		Tazemetostat	EPZ-6930
IS		ER-899694-00 (Tazemetostat-d_5)	ER-899694-00 (Tazemetostat-d_5)
Quantification Range (ng/mL)[a]		1.00 (LLOQ) to 1000	1.00 (LLOQ) to 1000
Calibration Curve	r^2	≥0.9946	≥0.9934
Intra-Assay	Accuracy (%)	–18.3 to 5.0	–8.7 to 8.3
	Precision (%)	2.0 to 10.3	1.6 to 7.7
Inter-Assay	Accuracy (%)	–9.8 to 2.3	–2.6 to 5.2
	Precision (%)	2.9 to 10.2	2.9 to 7.2
Recovery	Analyte (%)	85.4 to 86.4	82.0 to 85.2
	IS (%)	78.4 to 78.9	
Stability	Processed samples at 2 to 8 °C	41 hours	41 hours
	Plasma samples at rt	6 hours	15 hours
	Plasma samples at –20 °C	90 days	90 days
	Plasma samples at –80 °C	84 days	84 days
	Freeze/Thaw cycle	6 cycles	6 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLOQ = lower limit of quantification, r^2 = regression coefficient, rt = room temperature.

a: Concentrations were expressed as the free base of analyte.

Additional Information: The results for the selectivity experiments met the acceptance criteria.

2.6.5.2 分析方法及びバリデーション試験（続き）

Test Article: tazemetostat hydrobromide, EPZ-6930

Study Number/Location in CTD		**0130-1310/4.2.2.1.5**	
Species/Strain		Monkey/Cynomolgus	
Sample Matrix/Sample Volume		Plasma/50 µL	
Extraction Method / Assay		Liquid-liquid extraction / LC-MS/MS	
Analyte		Tazemetostat	EPZ-6930
IS		ER-899694-00 (Tazemetostat-d_5)	ER-899694-00 (Tazemetostat-d_5)
Quantification Range (ng/mL)[a]		1.00 (LLOQ) to 1000	1.00 (LLOQ) to 1000
Calibration Curve	r^2	≥0.9939	≥0.9946
Intra-Assay	Accuracy (%)	–6.8 to 8.3	–4.7 to 15.0
	Precision (%)	1.5 to 9.8	1.2 to 6.8
Inter-Assay	Accuracy (%)	–2.4 to 4.7	1.8 to 8.2
	Precision (%)	3.0 to 8.9	4.0 to 6.3
Recovery	Analyte (%)	67.2 to 69.3	71.2 to 75.4
	IS (%)	52.9 to 56.6	
Stability	Processed samples at 2 to 8 °C	43 hours	15 hours
	Plasma samples at rt	15 hours	15 hours
	Plasma samples at –20 °C	90 days	90 days
	Plasma samples at –80 °C	84 days	84 days
	Freeze/Thaw cycle	4 cycles	4 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLOQ = lower limit of quantification, r^2 = regression coefficient, rt = room temperature.

a: Concentrations were expressed as the free base of analyte.

Additional Information: The results for the selectivity experiments met the acceptance criteria.

2.6.5.2 分析方法及びバリデーション試験（続き）

Test Article:　tazemetostat hydrobromide, EPZ-6930

Study Number/Location in CTD		**150536VSMB_ECM/4.2.2.1.2**	
Species/Strain		Rat/Sprague Dawley	
Sample Matrix/Sample Volume		Plasma/20 µL	
Extraction Method / Assay		Protein precipitation / LC-MS/MS	
Analyte		Tazemetostat	EPZ-6930
IS		ER-899694-00 (Tazemetostat-d_5)	ER-899694-00 (Tazemetostat-d_5)
Quantification Range (ng/mL)[a]		1.00 (LLOQ) to 2000	1.00 (LLOQ) to 2000
Calibration Curve	Accuracy (%)	–3.8 to 2.8	–3.8 to 3.5
	r^2	≥0.9948	≥0.9943
Intra-Assay	Accuracy (%)	–5.7 to 8.0	–8.9 to 7.0
	Precision (%)	≤8.4	<9.3
Inter-Assay	Accuracy (%)	–2.3 to 6.0	–4.2 to 0.2
	Precision (%)	≤7.1	≤9.1
Recovery	Analyte (%)	80.5 to 85.9	76.9 to 84.3
	IS (%)	83.6	
Stability	Processed samples at rt	99 hours	99 hours
	Plasma samples at rt	24 hours	24 hours
	Plasma samples at –20 °C	101 days	101 days
	Plasma samples at –70 °C	101 days	101 days
	Freeze/Thaw cycle	5 cycles	5 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLOQ = lower limit of quantification, r^2 = regression coefficient, rt = room temperature.

a:　Concentrations were expressed as the free base of analyte.

Additional Information:　The results for the selectivity experiments met the acceptance criteria.

2.6.5.2 分析方法及びバリデーション試験（続き）

Test Article: tazemetostat hydrobromide, EPZ-6930

Study Number/Location in CTD		**150539VSMB_ECM/4.2.2.1.4**	
Species/Strain		Rabbit/New Zealand White	
Sample Matrix/Sample Volume		Plasma/20 µL	
Extraction Method / Assay		Protein precipitation / LC-MS/MS	
Analyte		Tazemetostat	EPZ-6930
IS		ER-899694-00 (Tazemetostat-d_5)	ER-899694-00 (Tazemetostat-d_5)
Quantification Range (ng/mL)[a]		1.00 (LLOQ) to 2000	1.00 (LLOQ) to 2000
Calibration Curve	Accuracy (%)	–3.8 to 2.0	–4.0 to 3.0
	r^2	≥0.9951	≥0.9941
Intra-Assay	Accuracy (%)	–6.0 to 8.0	–10.1 to 13.3
	Precision (%)	≤9.7	≤10.1
Inter-Assay	Accuracy (%)	–3.3 to 5.3	–5.2 to 6.0
	Precision (%)	≤6.0	≤7.4
Recovery	Analyte (%)	81.7 to 83.3	82.5 to 86.4
	IS (%)	83.3	
Stability	Processed samples at rt	69 hours	69 hours
	Plasma samples at rt	24 hours	24 hours
	Plasma samples at –20 °C	206 days	206 days
	Plasma samples at –70 °C	206 days	206 days
	Freeze/Thaw cycle	5 cycles	5 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLOQ = lower limit of quantification, r^2 = regression coefficient, rt = room temperature.

a: Concentrations were expressed as the free base of analyte.

Additional Information: The results for the selectivity experiments met the acceptance criteria.

2.6.5.3 薬物動態試験：吸収：単回投与

Test Article: tazemetostat hydrobromide

Mice **Study Number: DMPKA20[redacted]-064** **Location in CTD: 4.2.2.2.1**

Strain/Gender/Number of Animals	CD-1/Male/5
Feeding Condition	IV administration was performed under feeding, and PO administration was performed under fasting.
Vehicle/Formulation	Sterile saline with 1.0% (v/v) 0.1 mol/L HCl (IV dose); 0.5% (w/v) methylcellulose and 0.1% (v/v) Tween 80 in deionized water (PO doses)
Method of Administration	IV and PO
Dose[a]	IV: 10 mg/kg, PO: 10, 30, and 100 mg/kg
Sample/Analyte / Assay	Plasma/Tazemetostat / LC-MS/MS

Pharmacokinetic Parameters

Route	Dose[a] (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	C_{max}/D^b (ng/mL/D)	CL (L/h/kg)	V_{ss} (L/kg)	$AUC_{(0\text{-inf})}$ (ng·h/mL)	$AUC_{(0\text{-inf})}/D^b$ (ng·h/mL/D)	$t_{1/2}$ (h)	F[c] (%)
IV	10	NA	NA	NA	1.36	1.10	6428.14	733.81	1.4	NA
PO	10	2210.65	0.167	252.36	NA	NA	2462.92	281.16	1.1	38.3
	30	4958.83	0.167	188.69	NA	NA	8788.13	334.40	1.0	45.6
	100	6719.48	0.167	76.71	NA	NA	14121.97	161.21	2.5	22.0

Each parameter was calculated using the concentration obtained from pooled plasma sample of 5 animals at each time point. Concentrations were expressed as the free base of tazemetostat.

$AUC_{(0\text{-inf})}$ = AUC from zero time extrapolated to infine time, CL = total plasma clearance, CTD = Common Technical Document, D = dose, F = absolute bioavailability, HBr = hydrobromide, HCl = hydrochloric acid, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, PO = oral, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, V_{ss} = volume of distribution at steady state, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.

b: Calculated using free base equivalents of the tazemetostat HBr salt.

c: $F(\%) = (AUC_{(0\text{-inf}),PO} \times Dose_{IV}) / (AUC_{(0\text{-inf}),IV} \times Dose_{PO}) \times 100$.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method.

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: tazemetostat hydrobromide

Rats **Study Number: DMPKA20[redacted]-060, DMPKA20[redacted]-063** **Location in CTD: 4.2.2.2.2**

Strain/Gender/Number of Animals	Sprague Dawley/Male/4
Feeding Condition	IV administration was performed under feeding, and PO administration was performed under fasting.
Vehicle/Formulation	Sterile saline with 1.0% (v/v) 0.1 mol/L HCl (IV doses); 0.5% (w/v) methylcellulose and 0.1% (v/v) Tween 80 in deionized water (PO doses)
Method of Administration	IV and PO
Dose[a]	IV: 5 and 10 mg/kg, PO: 5, 30, and 100 mg/kg
Sample/Analyte / Assay	Plasma/Tazemetostat / LC-MS/MS

Pharmacokinetic Parameters

Dose[a] (mg/kg) Route	**C_{max} (ng/mL)**	**t_{max}[b] (h)**	**C_{max}/D[c] (ng/mL/D)**	**$AUC_{(0\text{-}inf)}$ (ng·h/mL)**	**$AUC_{(0\text{-}inf)}/D$[c] (ng·h/mL/D)**	**CL (L/h/kg)**	**V_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**F (%)**
5 IV	NA	NA	NA	1262.93	288.34	3.49	1.80	0.4	NA
10 IV[d]	NA	NA	NA	2791.88	318.71	3.53	2.56	0.7	NA
5 PO	41.86	0.5	9.56	NC	NC	NA	NA	NC	3.2[e]
30 PO	836.13	0.5	31.79	1624.04	61.75	NA	NA	0.9	21.4[f]
100 PO	4964.99	4.0	56.68	21652.97	247.18	NA	NA	1.1	85.7[f]

Each parameter is presented as the mean of 4 animals. Concentrations were expressed as the free base of tazemetostat.

$AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0\text{-}2h)}$ = AUC from zero time to 2 hours, CL = total plasma clearance, CTD = Common Technical Document, D = dose, F = absolute bioavailability, HBr = hydrobromide, HCl = hydrochloric acid, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NC = not calculated due to insufficient data, PO = oral, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, V_{ss} = volume of distribution at steady state, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.

b: Median value.

c: Calculated using free base equivalents of the tazemetostat HBr salt.

d: Bile duct cannulated rats were used.

e: F (%) = Mean $AUC_{(0\text{-}2h)\ 5mg/kg\ PO}$ / Mean $AUC_{(0\text{-}2h)\ 5mg/kg\ IV}$ ×100, where $AUC_{(0\text{-}2h)\ 5mg/kg\ PO}$ = 39 ng·h/mL and $AUC_{(0\text{-}2h)\ 5mg/kg\ IV}$ = 1230 ng·h/mL.

f: F (%) = (Mean $AUC_{(0\text{-}inf)\ PO}$ × $Dose_{5\ mg/kg\ IV}$) / (Mean $AUC_{(0\text{-}inf)\ 5mg/kg\ IV}$ × $Dose_{PO}$) ×100.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. DMPKA20[redacted]-004). This study also investigated the role of renal and biliary excretion of tazemetostat clearance in rats (Section 2.6.5.13 and 2.6.5.14 , respectively).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Strain/Gender/Number of Animals	Sprague Dawley/Male/6
Feeding Condition	Fasted[a]
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water
Method of Administration / Dose	Oral, by gavage / 50 mg/kg[b]
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)
Sample/Analyte/Assay	Plasma/Radioactivity/LSC
Pharmacokinetic Parameters	
C_{max} (µg eq./mL)	11.656±2.8
t_{max} (h)	1±0
$t_{1/2}$ (h)	0.948±0.1
$AUC_{(0\text{-}inf)}$ (µg eq.·h/mL)	27.167±6.6

Values represent the mean ±SD of 6 animals.

$AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, CTD = Common Technical Document, eq. = equivalent, LSC = liquid scintillation counter, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

Additional Information: This study also investigated the distribution of radioactivity in organs and tissues (Section 2.6.5.5), the excretion of radioactivity in urine and feces (Section 2.6.5.13), and the biliary excretion of radioactivity (Section 2.6.5.14).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: tazemetostat hydrobromide

Rabbits **Study Number: 20097368** **Location in CTD: 4.2.2.2.3**

Strain/Gender/Number of Animals	New Zealand White/Female/3
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% (w/v) Tween 80 in reverse osmosis membrane-processed deionized water
Method of Administration	PO administration under feeding
Dose[a]	100, 300, and 600 mg/kg
Sample/Analyte / Assay	Plasma/Tazemetostat and EPZ-6930 / LC-MS/MS
Pharmacokinetic Parameters	

Analyte	**Dose[a] (mg/kg)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$AUC_{(0-t)}$ (ng·h/mL)**	**$t_{1/2}$ (h)**	**$AUC_{(0-t)}$ Exposure Ratio of EPZ-6930 to Tazemetostat**
Tazemetostat	100	2270±418	1.50±0.866	5170±217	0.589±0.0778	NA
	300	13,400±5440	3.33±2.31	96,900±35,300	1.74±0.194	NA
	600	18,500±1510	6.67±1.15	228,000±46,500	NR	NA
EPZ-6930	100	3480±295	1.67±0.577	9970±752	1.92±1.61	1.89±0.0665
	300	9200±608	4.00±0.00	89,900±10,500	1.88±0.236	1.02±0.374
	600	13,900±862	6.67±1.15	189,000±28,200	NR	0.835±0.0822

Each parameter is presented as the mean ±SD of 3 animals. Concentrations were expressed as the free base of analytes.

$AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NR = not reportable, PO = oral, $t_{1/2}$ = terminal elimination phase half life, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.

a: Dose of HBr salt.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. 150539VSMB_ECM).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: tazemetostat hydrobromide

Monkeys **Study Number: 1045-022** **Location in CTD: 4.2.2.2.4**

Strain/Gender/Number of Animals	Cynomolgus/Male/4
Vehicle/Formulation	Saline (IV dose); 0.5% (w/v) carboxymethylcellulose and 0.1% (v/v) Tween 80 in deionized water (PO doses)
Method of Administration	IV and PO
Dose[a]	IV: 3.09 mg/kg, PO: 5, 30, and 100 mg/kg
Sample/Analyte / Assay	Plasma/tazemetostat / LC-MS/MS

Pharmacokinetic Parameters

Dose[a] (mg/kg) (Route, Feeding Condition)		**C_{max} (ng/mL)**	**t_{max} (h)**	**C_{max}/D^b (ng/mL/D)**	**$AUC_{(0\text{-}inf)}$ (ng·h/mL)**	**$AUC_{(0\text{-}inf)}/D^b$ (ng·h/mL/D)**	**CL (L/h/kg)**	**V_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**F[c] (%)**
3.09[d]	Mean	NA	NA	NA	2081.01	767.90	1.39	2.04	1.6	NA
(IV, fasted)	±SD				540.84	199.57	0.43	0.40	0.2	
5	Mean	29.07	2.0[e]	6.64	145.36[f]	33.19[f]	NA	NA	2.8[f]	1.9[g]
(PO, fasted)	±SD	17.27		3.94	NA	NA			NA	1.4
30	Mean	1081.41	2.0[e]	41.15	2954.59	112.43	NA	NA	1.9	15.3
(PO, fasted)	±SD	124.84		4.75	351.68	13.38			0.2	3.7
30	Mean	112.90	2.0[e]	4.30	622.65	23.69	NA	NA	2.3	3.2
(PO, fed)	±SD	27.91		1.06	44.33	1.69			0.6	0.8
100	Mean	2110.24	4.0[e]	24.09	8420.28	96.12	NA	NA	2.7	14.0
(PO, fasted)	±SD	891.25		10.17	2344.23	26.76			0.5	7.7

The mean and SD of 4 individual values are presented for the pharmacokinetic parameters except t_{max}. Concentrations were expressed as the free base of tazemetostat.
$AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0\text{-}t)}$ = AUC from zero time to time of last quantifiable concentration, CL = total plasma clearance, CTD = Common Technical Document, D = dose, F = absolute bioavailability, HBr = hydrobromide, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, PO = oral, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, V_{ss} = volume of distribution at steady state, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.
b: Calculated using free base equivalents of the tazemetostat HBr salt.
c: $(AUC_{(0\text{-}inf),PO} \times Dose_{IV})/(AUC_{(0\text{-}inf),IV} \times Dose_{PO}) \times 100$.
d: Dose was corrected by comparing concentrations of pre and post-filtering dosing formulation.
e: Median value.
f: n=1.
g: For 3 out of 4 cases, F was calculated from $AUC_{(0\text{-}t)}$.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method. With respect to a potential food effect, the administration of tazemetostat with food significantly decreased the absorption of tazemetostat at 30 mg/kg compared to the fasted state. As a result, the mean bioavailability in the fed state was roughly 5-fold lower than that in fasted state.

2.6.5.4 薬物動態試験：吸収：反復投与

Test Article: tazemetostat hydrochloride

Rats (Toxicokinetics, 7 Days) **Study Number: T[redacted]032** **Location in CTD: 4.2.3.2.1**

Strain/Gender/Number of Animals		Sprague Dawley/Male and female/3					
Feeding Condition		Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.					
Vehicle/Formulation		0.5% (w/v) methylcellulose 400 solution including 0.1% Tween 80 suspension					
Method of Administration		Oral by gavage					
Dosing Regimen / Dose		Once daily for 7 days / 100, 300, or 1000 mg/kg/day[a]					
Sample/Assay Date		Plasma/Days 1 and 7					
Analyte / Assay		Tazemetostat / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
C_{max} (μg/mL)	Day 1	1.151±0.612	3.642±1.336	7.125±1.414	7.241±3.857	16.386±8.107	22.912±12.527
	Day 7	1.763±0.998	7.412±1.325	18.616±1.682	7.969±2.276	13.384±0.480	31.278±5.182
$AUC_{(0-24h)}$ (μg·h/mL)	Day 1	3.116±1.154	24.537±8.344	133.786±49.871	19.673±7.914	110.630±39.831	362.935±166.554
	Day 7	4.370±2.539	23.027±1.875	213.729±14.197	21.854±5.273	75.222±23.720	554.980±185.476
t_{max} (h)	Day 1	1 (1 – 1)	2 (2 – 4)	8 (4 – 24)	1 (1 – 2)	2 (1 – 4)	4 (4 – 24)
	Day 7	2 (2 – 2)	2 (2 – 2)	2 (2 – 2)	2 (1 – 2)	2 (2 – 2)	2 (2 – 4)

C_{max} and $AUC_{(0-24h)}$ represent the mean ±SD of 3 animals and t_{max} represents the median and range of 3 animals. Concentrations were expressed as the free base of tazemetostat.

$AUC_{(0-24h)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.

a: Dose of hydrochloride salt.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: tazemetostat hydrobromide

Rats (Toxicokinetics, 4 Weeks) **Study Number: K[redacted]004** **Location in CTD: 4.2.3.2.2**

Strain/Gender/Number of Animals		Sprague Dawley/Male and female/4					
Feeding Condition		Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.					
Vehicle/Formulation		0.5% (w/v) methylcellulose 400 solution including 0.1% (w/v) Tween 80 suspension					
Method of Administration		Oral by gavage					
Dosing Regimen / Dose		Once daily for 4 weeks / 100, 300, or 1000 mg/kg/day[a]					
Sample/Assay Date		Plasma/Days 1, 21[b], and 28					
Analyte / Assay		Tazemetostat / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	Day 1	1937±352	3987±1118	12,750±5125	7920±2163	17,403±4030	41,030±11,697
	Day 21[b]	NA	NA	NA	NA	NA	34,324 ±11,963[c]
	Day 28	3376±751	9984±3205	35,422±13,741	13,019±2460	17,031±7862	NA
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	Day 1	4748±658	21,004±5816	170,795±50,826	27,298±4543	13,3415±34,281	585,675±311,855
	Day 21[b]	NA	NA	NA	NA	NA	425,124±12,586[c]
	Day 28	8484±2420	34,764±6004	600,977±495,584[c]	35,707±4930	95,188±44258	NA
t_{max} (h)	Day 1	2.0 (1.0 – 2.0)	2.0 (2.0 – 4.0)	4.0 (2.0 – 24.0)	2.0 (1.0 – 4.0)	2.0 (2.0 – 4.0)	6.0 (4.0 – 8.0)
	Day 21[b]	NA	NA	NA	NA	NA	2.0 (2.0 – 2.0)[c]
	Day 28	1.5 (1.0 – 2.0)	2.0 (2.0 – 2.0)	3.0 (0.5 – 8.0)	1.5 (1.0 – 2.0)	2.0 (2.0 – 2.0)	NA

C_{max} and $AUC_{(0\text{-}24h)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals. Concentrations were expressed as the free base of tazemetostat.
$AUC_{(0\text{-}24h)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.

a: Dose of HBr salt.

b: Measured on Day 21 because administration of 1000 mg/kg in females of main group was discontinued on Day 21.

c: n=3.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. DMPKA20[redacted]-004).

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: tazemetostat hydrobromide

Rats (Toxicokinetics, 13 Weeks) **Study Number: K[redacted]009** **Location in CTD: 4.2.3.2.3**

Strain/Gender/Number of Animals	Sprague Dawley/Male and female/4
Feeding Condition	Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.
Vehicle/Formulation	0.5% (w/v) methylcellulose 400 solution including 0.1% (w/v) Tween 80 suspension
Method of Administration	Oral by gavage
Dosing Regimen / Dose	Once daily for 13 weeks / 100, 300, or 600 mg/kg/day[a]
Sample/Assay Date	Plasma/Days 1 and 91
Analyte / Assay	Tazemetostat and EPZ-6930 / LC-MS/MS

Pharmacokinetic Parameters of Tazemetostat		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**600 mg/kg**	**100 mg/kg**	**300 mg/kg**	**600 mg/kg**
C_{max} (ng/mL)	Day 1	1931.73±473.22	5135.51±2845.85	7127.35±2152.87	9380.37±3027.80	17,454.81±3427.29	34,243.05±8463.30
	Day 91	4311.09±1119.37	10,017.93±3628.91	19,081.57±1312.76	13,487.76±1229.62	20,720.42±4205.22[b]	24,422.89±6206.59
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	Day 1	6984.92±2238.74	35,381.55±16,630.87	74,736.59±12,781.85	40,362.97±7201.89	160,969.47±19,113.42	408,016.02±136,442.74
	Day 91	18,033.33±3683.13	99,545.61±36,330.28	285,998.15±17,407.02	55,037.33±4248.84	166,304.94±25,837.74[b]	286,031.16±37,495.25
t_{max} (h)	Day 1	2.0 (2.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)	2.0 (2.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)
	Day 91	2.0 (2.0 – 2.0)	4.0 (2.0 – 8.0)	8.0 (4.0 – 8.0)	2.0 (2.0 – 2.0)	2.0 (2.0 – 4.0)[b]	5.0 (2.0 – 8.0)
Pharmacokinetic Parameters of EPZ-6930		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**600 mg/kg**	**100 mg/kg**	**300 mg/kg**	**600 mg/kg**
C_{max} (ng/mL)	Day 1	4842.61±1430.61	11,778.20±3921.99	15,633.33±2038.70	1007.82±400.86	2145.97±678.81	3824.66±710.25
	Day 91	5232.97±1605.71	10,017.47±3716.40	9190.07±3170.72	2398.53±387.74	4378.84±1226.37[b]	7721.94±1288.36
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	Day 1	15,741.12±5929.72	94,102.77±43,930.83	235,642.12±47,180.64	3752.39±967.72	21,705.37±4521.06	61,002.85±15,661.14
	Day 91	22,236.71±6100.65	116,254.92±30,552.68	134,816.24±33,829.86	8766.62±1889.44	39,836.30±12,601.97[b]	103,642.21±13,413.09
t_{max} (h)	Day 1	2.0 (2.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (4.0 – 8.0)	2.0 (2.0 – 2.0)	3.0 (2.0 – 4.0)	8.0 (2.0 – 8.0)
	Day 91	2.0 (2.0 – 2.0)	6.0 (4.0 – 8.0)	8.0 (4.0 – 8.0)	2.0 (2.0 – 2.0)	2.0 (2.0 – 4.0)[b]	6.0 (2.0 – 8.0)

C_{max} and $AUC_{(0\text{-}24h)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals. Concentrations were expressed as the free base of analyte.
$AUC_{(0\text{-}24h)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.
a: Dose of HBr salt.
b: n=3. Animal was found dead on Day 67.
Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. 0130-1309).

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: tazemetostat hydrobromide

Monkeys (Toxicokinetics, 5 Days) **Study Number: 20024292** **Location in CTD: 4.2.3.2.4**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/1			
Feeding Condition		Diet: Provided daily in amounts appropriate for the size and age of the animals. This diet was supplemented with fruit or vegetables at least 2 to 3 times weekly. Water: Available ad libitum. Animals were fasted for at least 2 hours prior to each dose and food was returned at approximately 2 hours after each dose.			
Vehicle/Formulation		0.5% (w/v) methylcellulose 400 solution including 0.1% (v/v) Tween 80 suspension			
Method of Administration		Oral by gavage			
Dosing Regimen / Dose[a]		BID (12 hours apart) 150 or 500 mg/kg for 5 days / 300 or 1000 mg/kg/day			
Sample/Assay Date		Plasma/Days 1 and 5			
Analyte / Assay		Tazemetostat / LC-MS/MS			
Pharmacokinetic Parameters		**Male**		**Female**	
		300 mg/kg	**1000 mg/kg**	**300 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)[b]	Day 1	1997.77	582.42	3077.64	520.57
	Day 5	220.96	7204.91	1019.20	1860.46
$AUC_{(0\text{-}12h)}$ (ng·h/mL)	Day 1	5734.03	2980.86	15,761.09	4079.09
	Day 5	600.39[c]	22,179.07	2892.93	17,864.27
t_{max} (h)[b]	Day 1	2.0	2.0	4.0	4.0
	Day 5	1.0	0.0	2.0	4.0

Pharmacokinetic parameters represent the value of 1 animal. Concentrations were expressed as the free base of tazemetostat.

$AUC_{(0\text{-}12h)}$ = AUC from zero time to 12 hours, BID = twice daily, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.

b: 0-12 hours.

c: $AUC_{(0\text{-}4h)}$.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: tazemetostat hydrobromide

Monkeys (Toxicokinetics, 4 Weeks) **Study Number: 20024293** **Location in CTD: 4.2.3.2.5**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/4					
Feeding Condition		Diet: Provided daily in amounts appropriate for the size and age of the animals. This diet was supplemented with fruit or vegetables at least 2 to 3 times weekly. Water: Available ad libitum. Animals were fasted for at least 2 hours prior to each dose and food was returned at approximately 2 hours after each dose.					
Vehicle/Formulation		0.5% (w/v) methylcellulose 400 solution including 0.1% (v/v) Tween 80 suspension					
Method of Administration		Oral by gavage					
Dosing Regimen / Dose[a]		BID (12 hours apart) 50, 150 or 500/300 mg/kg for 4 weeks / 100, 300, or 1000/600[b] mg/kg/day					
Sample/Assay Date		Plasma/Days 1 and 28					
Analyte / Assay		Tazemetostat / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**1000/600 mg/kg[b]**	**100 mg/kg**	**300 mg/kg**	**1000/600 mg/kg[b]**
C_{max} (ng/mL)[c]	Day 1	820.76±350.73	1800.75±1296.27	9149.56±4324.42	568.51±226.01	2331.34±1152.04	8704.56±3178.62[d]
	Day 28	177.48±87.87	283.26±85.88	2276.74[e]	158.11±54.88	736.12±365.44	2541.41[e]
$AUC_{(0\text{-}12h)}$ (ng·h/mL)	Day 1	1842.36±677.74	6770.24±3128.37	38,373.71±15,194.75	1532.38±333.36	7928.34±3283.40	42,860.66±17,041.31[d]
	Day 28	471.38±175.49	1218.62±420.75	9371.15[e]	537.48±144.08	2596.57±1286.80	14,892.24[e]
t_{max} (h)[c]	Day 1	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)	1.5 (0.5 – 2.0)	2.0 (1.0 – 2.0)	4.0 (4.0 – 4.0)[d]
	Day 28	1.5 (1.0 – 2.0)	2.0 (2.0 – 2.0)	2.0 (2.0 – 2.0)[e]	1.5 (1.0 – 2.0)	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)[e]

C_{max} and $AUC_{(0\text{-}12h)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals. Concentrations were expressed as the free base of tazemetostat.
$AUC_{(0\text{-}12h)}$ = AUC from zero time to 12 hours, BID = twice daily, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.

b: Dose reduced from 1000 mg/kg/day to 600 mg/kg/day on Day 12 (male)/11 (female) due to toxicity.

c: 0-12 hours.

d: n=3.

e: n=2.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. DMPKA20[redacted]-004).

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: tazemetostat hydrobromide

Monkeys (Toxicokinetics, 13 Weeks) **Study Number: 20047690** **Location in CTD: 4.2.3.2.6**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/4						
Feeding Condition		Diet: Provided daily in amounts appropriate for the size and age of the animals. This diet was supplemented with fruit or vegetables at least 2 to 3 times weekly. Water: Available ad libitum. Animals were fasted for at least 2 hours prior to each dose and food was returned at approximately 2 hours after each dose.						
Vehicle/Formulation		0.5% (w/v) methylcellulose 400 solution including 0.1% (v/v) Tween 80 suspension						
Method of Administration		Oral by gavage						
Dosing Regimen / Dose[a]		BID (12 hours apart) 50, 150, or 300 mg/kg for 13 weeks / 100, 300, or 600 mg/kg/day						
Sample/Assay Date		Plasma/Days 1, 43 and 91						
Analyte / Assay		Tazemetostat and EPZ-6930 / LC-MS/MS						
Pharmacokinetic Parameters of Tazemetostat		**Male**			**Female**			
		100 mg/kg	**300 mg/kg**	**600 mg/kg**	**100 mg/kg**	**300 mg/kg**	**600 mg/kg**
C_{max} (ng/mL)[b]	Day 1	483.24±429.11	2481.18±1687.84	4651.02±2691.83	500.77±181.74	1998.49±1333.41	1611.91±1714.10
	Day 43	138.52±85.80	461.53±174.44	1311.80±782.25	142.08±52.40	933.78±722.65	862.51±762.43
	Day 91	147.73±111.23	596.98±301.19	1297.75±878.70	165.85±31.87	725.05±654.09	1241.04±1007.57
$AUC_{(0\text{-}12h)}$ (ng·h/mL)	Day 1	1560.43±1277.57	9707.19±4495.78	23,875.18±15,824.83	1377.75±360.76	7118.46±4685.54	8070.65±9321.69
	Day 43	536.73±259.36	2487.17±990.16	8047.91±5517.46	454.05±181.26	3061.87±2224.65	4291.79±3069.98
	Day 91	641.17±426.70	3136.98±1330.62	8116.86±4921.23	599.05±67.75	3574.93±3327.51	6215.10±4583.22
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	Day 1	4947.25±3360.78	18,786.13±5912.85	39,448.13±25,421.47	3602.58±1604.40	20,126.62±14,078.90	31,864.20±18,111.46
	Day 43	1778.36±668.38	6811.43±3901.28	18,327.30±13,125.40	1320.30±207.95	7960.05±4502.25	13,785.25±5289.90
	Day 91	1451.95±769.99	6304.18±2776.96	15,649.78±10,636.76	1447.49±407.27	8307.28±3595.93	14,689.31±7170.70
t_{max} (h)[b]	Day 1	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (2.0 – 4.0)	1.0 (1.0 – 2.0)	2.0 (2.0 – 8.0)	2.0 (1.0 – 2.0)
	Day 43	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (2.0 – 4.0)	0.5 (0.5 – 2.0)	2.0 (1.0 – 2.0)	2.0 (1.0 – 4.0)
	Day 91	1.5 (0.5 – 4.0)	3.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)	1.5 (0.5 – 2.0)	2.0 (2.0 – 2.0)	4.0 (2.0 – 4.0)

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Test Article: tazemetostat hydrobromide

Monkeys (Toxicokinetics, 13 Weeks) **Study Number: 20047690** **Location in CTD: 4.2.3.2.6**

Pharmacokinetic Parameters of EPZ-6930		Male			Female		
		100 mg/kg	300 mg/kg	600 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
C_{max} (ng/mL)[b]	Day 1	1620.32±1200.01	5835.80±3184.74	7397.79±2096.96	1988.11±432.96	4839.48±2503.08	3767.74±2867.72
	Day 43	1025.11±739.40	2978.53±1267.24	5472.72±3203.27	673.08±201.34	4835.03±2441.87	3434.38±1798.40
	Day 91	859.69±617.23	3427.37±1572.68	4084.09±1747.07	1125.59±772.76	3668.92±1693.42	4507.46±2752.09
$AUC_{(0-12h)}$ (ng·h/mL)	Day 1	4815.45±3380.04	25,036.97±8312.87	47,766.98±17,687.27	4593.11±1821.89	18,033.07±11,220.56	18,889.72±19,323.42
	Day 43	3093.39±1799.03	15,553.68±9042.13	40,679.74±31,970.07	1696.51±836.67	15,422.40±8561.22	17,842.27±9684.77
	Day 91	3154.20±2143.31	20,238.19±9915.13	31,036.15±15,844.07	2877.52±1660.01	18,072.50±11,202.17	26,806.48±18,848.07
$AUC_{(0-24h)}$ (ng·h/mL)	Day 1	19,288.06±7543.24	63,387.11±11,691.04	103,244.36±45,484.28	15,098.01±3464.39	55,245.95±19,879.50	72,190.64±26,784.16
	Day 43	9415.50±4646.89	37,127.20±22,103.15	81,655.69±59,480.21	6311.22±2806.66	38,585.90±15,059.87	51,469.48±15,102.71
	Day 91	8570.13±6007.23	40,548.11±18,595.93	55,226.97±27,327.61	7781.98±2384.99	45,498.74±14,055.41	62,343.78±29,832.31
t_{max} (h)[b]	Day 1	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	3.0 (2.0 – 4.0)	1.0 (1.0 – 2.0)	2.0 (2.0 – 8.0)	2.0 (1.0 – 2.0)
	Day 43	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (2.0 – 4.0)	1.5 (1.0 – 2.0)	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)
	Day 91	2.0 (2.0 – 2.0)	4.0 (2.0 – 4.0)	4.0 (4.0 – 4.0)	2.0 (1.0 – 2.0)	3.0 (2.0 – 4.0)	4.0 (2.0 – 4.0)

C_{max}, $AUC_{(0-12h)}$ and $AUC_{(0-24h)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals. Concentrations were expressed as the free base of analyte.

$AUC_{(0-12h)}$ = AUC from zero time to 12 hours, $AUC_{(0-24h)}$ = AUC from zero time to 24 hours, BID = twice daily, CTD = Common Technical Document, HBr = hydrobromide, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs, v/v = volume per volume, w/v = weight per volume.

a: Dose of HBr salt.

b: 0-12 hours.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. 0130-1310).

2.6.5.5 薬物動態試験：分布

Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number:** 45N-1402 **Location in CTD:** 4.2.2.5.1

Strain/Gender/Number of Animals	Sprague Dawley/Male/6 (1 per timepoint)					
Feeding Condition	Fasted [a]					
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water					
Method of Administration / Dose	Oral, by gavage / 50 mg/kg [b]					
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)					
Analyte/Assay	Radioactivity/Quantitative whole body autoradiography and LSC					
Tissue/Organ	**Concentration of Radioactivity (µg eq./g)**					
	Rat 14; 0.25 h	**Rat 15; 1 h**	**Rat 16; 4 h**	**Rat 17; 24 h**	**Rat 18; 72 h**	**Rat 19; 168 h**
Vascular/Lymphatic						
Plasma (LSC)	1.327	5.782	1.152	0.041	BQL	BQL
Aorta	3.240	11.015	12.515	1.074	1.463	0.955
Blood (cardiac)	1.435	7.549	2.601	0.757	BQL	BQL
Bone marrow	1.518	8.443	3.240	BQL	BQL	BQL
Lymph node	0.666	4.005	2.741	BQL	BQL	BQL
Spleen	2.960	10.065	4.516	0.683	0.327	BQL
Thymus	0.467	2.826	3.412	BQL	BQL	BQL
Excretory/Metabolic						
Bile (in duct)	896.117	2208.596 [c]	331.980	16.632	0.401	BQL
Kidney (cortex)	5.804	20.580	7.395	1.005	0.541	0.405
Kidney (medulla)	8.769	29.099	13.530	0.927	0.292	BQL
Liver	62.215	193.170	38.587	3.578	1.158	0.591
Urinary bladder	0.534	4.108	16.506	BQL	BQL	BQL
Urinary bladder (contents)	4.180	5.625	599.179	2.262	BQL	BQL

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Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number:** 45N-1402 **Location in CTD:** 4.2.2.5.1

Tissue/Organ	Concentration of Radioactivity (µg eq./g)					
	Rat 14; 0.25 h	Rat 15; 1 h	Rat 16; 4 h	Rat 17; 24 h	Rat 18; 72 h	Rat 19; 168 h
Central Nervous System						
Brain (cerebrum)	BQL	BQL	BQL	BQL	BQL	BQL
Brain (cerebellum)	BQL	BQL	BQL	BQL	BQL	BQL
Brain (medulla)	BQL	BQL	BQL	BQL	BQL	BQL
Spinal cord	BQL	BQL	BQL	BQL	BQL	BQL
Endocrine						
Adrenal gland	5.885	16.977	6.238	0.678	BQL	BQL
Pituitary gland	2.202	9.830	3.773	BQL	BQL	BQL
Thyroid	5.060	20.021	6.561	0.605	0.924	0.387
Secretory						
Harderian gland	1.372	6.494	20.599	BQL	BQL	BQL
Mammary gland region	0.613	1.615	1.115	BQL	BQL	BQL
Pancreas	2.616	9.620	2.575	0.278	BQL	BQL
Salivary gland	2.895	11.037	4.046	BQL	BQL	BQL
Fatty						
Adipose (brown)	2.730	7.606	3.365	0.372	BQL	BQL
Adipose (white)	0.421	2.178	1.028	BQL	BQL	BQL
Dermal						
Skin (non-pigmented)	0.555	2.204	3.010	1.777	0.283	BQL
Reproductive						
Epididymis	0.237	1.899	4.831	0.295	BQL	BQL
Prostate gland	0.891	3.548	3.816	BQL	BQL	BQL
Seminal vesicles	0.742	0.864	4.842	BQL	BQL	BQL
Testis	BQL	0.311	1.746	BQL	BQL	BQL

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Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Tissue/Organ	Concentration of Radioactivity (µg eq./g)					
	Rat 14; 0.25 h	Rat 15; 1 h	Rat 16; 4 h	Rat 17; 24 h	Rat 18; 72 h	Rat 19; 168 h
Skeletal/Muscular						
Bone	BQL	1.092	0.753	BQL	BQL	BQL
Heart	2.800	9.365	2.315	BQL	BQL	BQL
Skeletal muscle	0.463	3.779	2.254	BQL	BQL	BQL
Respiratory						
Lung	2.533	10.617	3.427	0.429	BQL	BQL
Alimentary Canal						
Cecum	2.923	5.170	2.439	1.979	BQL	BQL
Cecum (contents)	BQL	8.396	516.510	123.672	0.377	BQL
Colon	0.499	9.172	1.591	0.446	BQL	BQL
Colon (contents)	1.370	28.372	BQL	BQL	0.963	BQL
Esophagus	3.396	8.374	2.129	0.258	BQL	BQL
Oral mucosa	0.832	4.196	2.129	1.695	BQL	BQL
Large intestine	1.268	8.945	5.006	1.356	BQL	BQL
Large intestine (contents)	BQL	43.789	194.013	123.425	0.708	BQL
Small intestine	2.246	24.288	13.904	1.772	BQL	BQL
Small intestine (contents)	131.833	4452.700[e]	3953.535[e]	103.202	0.334	BQL
Stomach (gastric mucosa)	11.181	18.791	7.516	0.775	BQL	BQL
Stomach (contents)	4844.655[e]	3309.447[e]	74.235	124.609	BQL	BQL

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Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Tissue/Organ	Concentration of Radioactivity (µg eq./g)					
	Rat 14; 0.25 h	**Rat 15; 1 h**	**Rat 16; 4 h**	**Rat 17; 24 h**	**Rat 18; 72 h**	**Rat 19; 168 h**
Ocular						
Eye (uvea)	BQL	2.919	0.870	BQL	BQL	BQL
Eye (lens)	BQL	BQL	BQL	BQL	BQL	BQL

BQL = value is below the LLOQ or tissue could not be visualized on autoradioluminograph due to BQL radioactivity, CTD = Common Technical Document, eq. = equivalent, LLOQ = lower limit of quantification ([redacted] µCi/g / [redacted] µCi/µg = 0.237 µg eq./g tissue), LSC = liquid scintillation counter, ULOQ = upper limit of quantification ([redacted] µCi/g / [redacted] µCi/µg = 1929.666 µg eq./g tissue), w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

c: Value is above the ULOQ.

Additional Information: This study also investigated the plasma pharmacokinetics of radioactivity (Section 2.6.5.3), the excretion of radioactivity in urine and feces (Section 2.6.5.13), and the biliary excretion of radioactivity (Section 2.6.5.14).

Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Strain/Gender/Number of Animals	Long-Evans/Male/9 (1 per timepoint)								
Feeding Condition	Fasted[a]								
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water								
Method of Administration / Dose	Oral, by gavage / 50 mg/kg[b]								
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)								
Analyte/Assay	Radioactivity/Quantitative whole body autoradiography and LSC								
Tissue/Organ	**Concentration of Radioactivity (µg eq./g)**								
	Rat 20 0.25 h	**Rat 21 1 h**	**Rat 22 4 h**	**Rat 23 24 h**	**Rat 24 72 h**	**Rat 25 168 h**	**Rat 26 672 h**	**Rat 27 1344 h**	**Rat 28 2016 h**
Vascular/Lymphatic									
Plasma (LSC)	0.103	5.603	0.387	0.023	BQL	BQL	BQL	BQL	BQL
Aorta	BQL	11.867	2.783	1.019	0.652	0.895	0.555	BQL	0.259
Blood (cardiac)	BQL	5.152	1.178	0.593	BQL	BQL	BQL	BQL	BQL
Bone marrow	BQL	9.722	0.950	BQL	BQL	BQL	BQL	BQL	BQL
Lymph node	BQL	6.126	0.884	BQL	BQL	BQL	BQL	BQL	BQL
Spleen	BQL	12.538	1.504	0.380	BQL	BQL	BQL	BQL	BQL
Thymus	BQL	4.929	0.611	BQL	BQL	BQL	BQL	BQL	BQL
Excretory/Metabolic									
Bile (in duct)	55.602	1738.690	167.581	1.145	BQL	BQL	BQL	BQL	BQL
Kidney (cortex)	0.399	28.569	2.965	0.721	0.256	0.325	BQL	BQL	BQL
Kidney (medulla)	BQL	33.503	4.364	BQL	BQL	BQL	BQL	BQL	BQL
Liver	3.137	159.233	28.602	3.911	1.119	0.888	BQL	BQL	BQL
Urinary bladder	BQL	7.488	1.646	0.483	BQL	BQL	BQL	BQL	BQL
Urinary bladder (contents)	BQL	94.036	139.566	0.302	BQL	BQL	BQL	BQL	BQL

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Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number:** 45N-1402 **Location in CTD:** 4.2.2.5.1

Tissue/Organ	Concentration of Radioactivity (µg eq./g)								
	Rat 20 0.25 h	Rat 21 1 h	Rat 22 4 h	Rat 23 24 h	Rat 24 72 h	Rat 25 168 h	Rat 26 672 h	Rat 27 1344 h	Rat 28 2016 h
Central Nervous System									
Brain (cerebrum)	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Brain (cerebellum)	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Brain (medulla)	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Spinal cord	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Endocrine									
Adrenal gland	0.331	19.678	2.375	0.604	0.263	BQL	BQL	BQL	BQL
Pituitary gland	BQL	16.559	3.298	1.069	BQL	BQL	BQL	BQL	BQL
Thyroid	0.238	27.221	2.997	0.583	0.400	0.513	0.249	0.324	BQL
Secretory									
Harderian gland	BQL	9.559	3.843	BQL	BQL	BQL	BQL	BQL	BQL
Mammary gland region	BQL	3.044	0.377	BQL	BQL	BQL	BQL	BQL	BQL
Pancreas	BQL	12.350	0.950	BQL	BQL	BQL	BQL	BQL	BQL
Salivary gland	BQL	13.851	0.912	BQL	BQL	BQL	BQL	BQL	BQL
Fatty									
Adipose (brown)	BQL	7.725	1.276	0.286	BQL	BQL	BQL	BQL	BQL
Adipose (white)	BQL	3.204	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Dermal									
Skin (non-pigmented)	BQL	3.992	0.964	0.699	BQL	BQL	BQL	BQL	BQL
Skin (pigmented)	BQL	3.202	0.613	1.166	0.320	0.921	BQL	BQL	BQL
Reproductive									
Epididymis	BQL	1.991	1.105	BQL	BQL	BQL	BQL	BQL	BQL
Prostate gland	BQL	2.979	0.960	BQL	BQL	BQL	BQL	BQL	BQL
Seminal vesicles	BQL	0.906	1.907	BQL	BQL	BQL	BQL	BQL	BQL
Testis	BQL	0.488	0.334	BQL	BQL	BQL	BQL	BQL	BQL

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Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number:** 45N-1402 **Location in CTD:** 4.2.2.5.1

Tissue/Organ	Concentration of Radioactivity (µg eq./g)								
	Rat 20 0.25 h	Rat 21 1 h	Rat 22 4 h	Rat 23 24 h	Rat 24 72 h	Rat 25 168 h	Rat 26 672 h	Rat 27 1344 h	Rat 28 2016 h
Skeletal/Muscular									
Bone	BQL	0.848	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Heart	BQL	10.505	0.662	BQL	BQL	BQL	BQL	BQL	BQL
Skeletal muscle	BQL	4.905	0.491	BQL	BQL	BQL	BQL	BQL	BQL
Respiratory									
Lung	BQL	9.298	1.613	0.394	BQL	BQL	BQL	BQL	BQL
Alimentary Canal									
Cecum	BQL	4.750	2.366	BQL	BQL	BQL	BQL	BQL	BQL
Cecum (contents)	BQL	8.238	4190.750[e]	7.677	0.365	BQL	BQL	BQL	BQL
Colon	BQL	3.015	0.364	0.407	BQL	BQL	BQL	BQL	BQL
Colon (contents)	NI	34.650	8.837	17.949	0.601	BQL	BQL	BQL	BQL
Esophagus	0.693	5.128	1.338	BQL	BQL	BQL	BQL	BQL	BQL
Oral mucosa	3.567	4.034	1.557	0.303	BQL	BQL	BQL	BQL	BQL
Large intestine	BQL	13.113	1.512	BQL	BQL	BQL	BQL	BQL	BQL
Large intestine (contents)	NI	103.638	36.848	10.702	0.581	BQL	BQL	BQL	BQL
Small intestine	3.505	76.730	1.501	0.250	BQL	BQL	BQL	BQL	BQL
Small intestine (contents)	195.005	7646.411[e]	621.327	0.696	BQL	BQL	BQL	BQL	BQL
Stomach (gastric mucosa)	107.151	18.277	2.364	BQL	BQL	BQL	BQL	BQL	BQL
Stomach (contents)	4615.243[e]	5225.256[e]	11.506	BQL	BQL	BQL	BQL	BQL	BQL

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Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Tissue/Organ	Concentration of Radioactivity (µg eq./g)								
	Rat 20 0.25 h	Rat 21 1 h	Rat 22 4 h	Rat 23 24 h	Rat 24 72 h	Rat 25 168 h	Rat 26 672 h	Rat 27 1344 h	Rat 28 2016 h
Ocular									
Eye (uvea)	BQL	10.628	19.096	17.349	10.190	13.645	15.721	5.573	4.222
Eye (lens)	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

BQL = value is below the LLOQ or tissue could not be visualized on autoradioluminograph due to BQL radioactivity, CTD = Common Technical Document, eq. = equivalent, LLOQ = lower limit of quantification ([redacted] µCi/g / [redacted] µCi/µg = 0.237 µg eq./g tissue), LSC = liquid scintillation counter, NI = not identified, ULOQ = upper limit of quantification ([redacted] µCi/g / [redacted] µCi/µg = 1929.666 µg eq./g tissue), w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

c: Value is above the ULOQ.

Additional Information: None.

Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Strain/Gender/Number of Animals	Long-Evans/Male/9 (1 per timepoint)			
Feeding Condition	Fasted [a]			
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water			
Method of Administration / Dose	Oral, by gavage / 50 mg/kg [b]			
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)			
Analyte/Assay	Radioactivity/Quantitative whole body autoradiography and LSC			
Tissue/Organ	**C_{max} (µg equiv/g)**	**AUC (µCi·h/g)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Aorta	11.867	1092.697	1.0	1231.3
Adipose (brown)	7.725	32.984	1.0	9.3
Adipose (white) [c]	3.204	1.602	1.0	ND
Adrenal gland	19.678	88.763	1.0	23.4
Blood (cardiac) [c]	5.152	29.781	1.0	20.2
Bone [c, d]	0.848	0.424	1.0	ND
Bone marrow [c]	9.722	20.869	1.0	0.9
Brain (cerebellum) [c, d]	ND	ND	ND	ND
Brain (cerebrum) [c, d]	ND	ND	ND	ND
Brain (medulla) [c, d]	ND	ND	ND	ND
Cecum [c]	4.750	13.049	1.0	3.0
Colon [c, d]	3.015	14.286	1.0	ND
Epididymis [c]	1.991	5.640	1.0	3.5
Esophagus [c]	5.128	11.328	1.0	1.5
Eye (lens) [c, d]	ND	ND	ND	ND
Eye (uvea tract) [c]	19.096	20,065.502	4.0	708.6
Harderian gland [c]	9.559	24.883	1.0	2.3
Heart [c]	10.505	22.003	1.0	0.8

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Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Tissue/Organ	C_{max} (µg equiv/g)	AUC (µCi·h/g)	t_{max} (h)	$t_{1/2}$ (h)
Kidney cortex [c]	28.569	142.839	1.0	158.0
Kidney medulla [c]	33.503	73.552	1.0	1.0
Large intestine [c]	13.113	28.494	1.0	1.0
Liver [c]	159.233	865.315	1.0	287.8
Lung [c]	9.298	41.086	1.0	6.1
Lymph node [c]	6.126	13.578	1.0	1.1
Mammary gland region [c]	3.044	6.654	1.0	1.0
Oral mucosa	4.034	29.779	1.0	6.8
Pancreas [c]	12.350	26.125	1.0	0.8
Pituitary gland [c]	16.559	81.735	1.0	7.2
Prostate gland [c]	2.979	7.398	1.0	1.8
Salivary gland [c]	13.851	29.070	1.0	0.8
Seminal vesicles [c, d]	1.907	4.673	4.0	NC
Skeletal muscle [c]	4.905	10.547	1.0	0.9
Skin (non-pigmented) [c]	3.992	26.060	1.0	12.8
Skin (pigmented) [c, d]	3.202	120.346	1.0	NC
Small intestine [c]	76.730	155.792	1.0	7.7
Spinal cord [c, d]	ND	ND	ND	ND
Spleen [c]	12.538	46.172	1.0	5.7
Stomach (gastric mucosa)	107.151	89.106	0.5	0.7

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Test Article: [^{14}C]tazemetostat hydrobromide

Rats **Study Number:** 45N-1402 **Location in CTD:** 4.2.2.5.1

Tissue/Organ	C_{max} (µg equiv/g)	AUC (µCi·h/g)	t_{max} (h)	$t_{1/2}$ (h)
Testis [c]	0.488	1.477	1.0	5.5
Thymus [c]	4.929	10.775	1.0	1.0
Thyroid [c]	27.221	540.019	1.0	1989.2
Urinary bladder [c]	7.488	38.735	1.0	7.1

$AUC_{0\text{-}inf}$ = AUC from 0 time extrapolated to infinite time, AUC_{last} = AUC from 0 time to time of last measurable concentration, CTD = Common Technical Document, LSC = liquid scintillation counter, NC = not calculated, ND = not determined, $t_{1/2}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs, w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

c: Terminal elimination phase half-life values for these tissue/organs were obtained from insufficient data points.

d: Unable to determine $AUC_{0\text{-}inf}$ or AUC_{last} was higher, thus AUC_{last} was used.

e: Tissue with highest exposure before weighing.

Additional Information: None.

2.6.5.6 薬物動態試験：タンパク結合

Test Article: tazemetostat free form

Plasma Protein Binding of Tazemetostat (1) **Study Number: DMPKA20[redacted]-142** **Location in CTD: 5.3.2.1.1**

Study System	in vitro			
Test System	Plasma			
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) overnight (>16 hours) at 37 °C			
Assay / Analyte	LC-MS/MS / tazemetostat			
Concentration	100, 1000, and 10,000 ng/mL as free form			
Species/Strain	**Compound**	**Protein Binding (%)**		
		Concentration (ng/mL)		
		100	**1000**	**10,000**
Mouse/CD-1	Tazemetostat	94.8±0.5	96.4±0.3	90.0±1.0
Rat/Sprague Dawley		86.1±1.0	88.3±1.1	79.8±2.1
Dog/Beagle		75.8±1.9	85.6±3.4	87.5±0.3
Monkey/Cynomolgus		79.1±1.5	81.8±1.4	82.7±1.4
Human/NA		73.7±2.3	83.4±1.5	83.3±0.6

Each value represents the mean ±SD of 3 plasma samples in mouse, rat, dog, monkey, and human.

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable.

Additional Information: None.

2.6.5.6 薬物動態試験：タンパク結合（続き）

Test Article: tazemetostat hydrobromide

Plasma Protein Binding of Tazemetostat (2) **Study Number: 161025** **Location in CTD: 5.3.2.1.2**

Study System	in vitro				
Test System	Plasma				
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) for 6 hours at 37 °C				
Assay / Analyte	LC-MS/MS / tazemetostat				
Concentration	1, 3, 10, and 30 µmol/L				
Concentration (µmol/L)	**Protein Binding (%)**				
	Species/Strain				
	Mouse/CD-1	**Rat/Sprague Dawley**	**Rabbit/New Zealand White**	**Monkey/Cynomolgus**	**Human/NA**
1	98.1±0.0	94.7±0.2	91.9±0.3	83.3±0.4	88.4±0.3
3	97.3±0.1	93.0±0.2	91.8±0.4	84.7±0.4	87.7±0.6
10	94.6±0.1[a]	91.0±2.1	91.4±0.2	83.3±1.5	91.1±3.2
30	91.8±0.1	88.8±0.4	91.1±0.5	84.1±0.7	88.0±0.4
Concentration (µmol/L)	**Unbound (%)**				
	Species/Strain				
	Mouse/CD-1	**Rat/Sprague Dawley**	**Rabbit/New Zealand White**	**Monkey/Cynomolgus**	**Human/NA**
1	1.9±0.0	5.3±0.2	8.1±0.3	16.7±0.4	11.6±0.3
3	2.73±0.1	7.0±0.2	8.2±0.4	15.3±0.4	12.3±0.6
10	5.4±0.1[a]	9.0±2.1	8.6±0.2	16.7±1.5	8.9±3.2
30	8.2±0.1	11.2±0.4	8.9±0.5	15.9±0.7	12.0±0.4

Data represents the mean ±SD of 6 replicates (other than [a]).

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable.

a: The data represents the mean ±SD of 5 replicates.

Additional Information: In this study, blood samples were collected into vacutainer tubes to avoid plasticizer contamination.

2.6.5.6 薬物動態試験：タンパク結合（続き）

Test Article: tazemetostat hydrobromide

Binding to Human Plasma Protein **Study Number: AL-7384-G** **Location in CTD: 5.3.2.1.3**

Study System	in vitro		
Test System	Human protein in blood		
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) for 20 hours at 37 °C		
Assay / Analyte	LC-MS/MS / Tazemetostat		
Concentration	1, 3, and 10 µmol/L		
Plasma Protein (Concentration)	**Protein Binding (%)**		
	1 µmol/L	**3 µmol/L**	**10 µmol/L**
Human serum albumin (40 mg/mL)	63.7±3.2	64.1±1.3	64.2±1.0
Human α1-Acid glycoprotein (1 mg/mL)	12.6±2.3	10.7±3.4	15.1±2.3
Human γ-globulin (12 mg/mL)	15.6±2.4	11.8±5.2	10.6±5.6

Values represent the mean ±SD of 3 determinations.

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry.

Additional Information: None.

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

妊娠又は授乳動物における試験は検討されていない。

2.6.5.8 薬物動態試験：その他の分布試験

Test Article: tazemetostat hydrobromide

Blood to Plasma Concentration Ratio of Tazemetostat **Study Number: DMPKA20[redacted]-062** **Location in CTD: 5.3.2.3.1**

Study System	in vitro			
Test System	Blood			
Method	Incubation for 30 minutes at 37 °C			
Assay / Analyte	LC-MS/MS / Tazemetostat			
Species/Strain	**R_B**			
	Concentration (ng/mL)[a]			
	50	**500**	**5000**	**50,000**
Mouse/CD-1	0.53±0.01	0.53±0.03	0.63±0.03	0.87±0.07
Rat/Sprague Dawley	0.62±0.02	0.61±0.08	0.67±0.06	0.78±0.14
Monkey/Cynomolgus	1.06±0.13	0.82±0.04	0.76±0.09	0.89±0.07
Human/NA	0.77±0.05	0.71±0.05	0.71±0.06	0.96±0.05

Each value represents the mean ±SD (n=3).

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, R_B = blood to plasma concentration ratio.

a: The concentration was expressed in terms of the free base.

Additional Information: None.

2.6.5.9 薬物動態試験：代謝：in vivo

Test Article: tazemetostat

Metabolite Identification: Metabolites Observed in the Rat, Rabbit, Monkey and Human Plasma　Study Number: 14099&14430　Location in CTD: 5.3.2.2.8

Study System		in vivo										
Test System		Plasma samples from rat (SD), rabbit (New Zealand White), monkey (cynomolgus), and human[a]										
Method		Characterization of tazemetostat and metabolites in plasma samples at different time points										
Assay/Analyte		UPLC-HRMS/tazemetostat and metabolites										
Dose		Tazemetostat: rats, 100 mg/kg; rabbits, 400 mg/kg; monkeys, 600 mg/kg; humans, 800 mg										
Identifier	**RT (min)**	***m/z***	**Female Rat Day 1**	**Female Rat Day 91**	**Male Rat Day 1**	**Male Rat Day 91**	**Rabbit DG 7**	**Rabbit DG 19**	**Monkey Day 1**	**Monkey Day 91**	**Human Day 1**	**Human Day 15**
Tazemetostat	8.60	573.34	55%	62%	35%	27%	24%	27%	25%	19%	43%	27%
EPZ006935	2.45	438.27	<5%	<5%	<5%	<5%	<5%	<5%	<5%	<5%	<5%	<5%
EPZ034395	5.18	435.23	ND	ND	ND	ND	ND	ND	<5%	5%	<5%	<5%
EPZ034163 (M1)	5.97	461.25	<5%	<5%	<5%	<5%	<5%	<5%	6%	9%	<5%	13%
EPZ006633 (M2)	7.78	547.33	<5%	<5%	<5%	<5%	ND	ND	<5%	5%	<5%	<5%
EPZ006931 (M3)	9.29	489.29	13%	12%	12%	11%	5%	<5%	11%	9%	11%	15%
EPZ006938 (M4)	9.85	587.32	<5%	<5%	<5%	5%	ND	ND	5%	5%	<5%	<5%
EPZ-6930 (M5)	10.64	545.31	20%	15%	39%	48%	43%	36%	38%	40%	38%	38%
EPZ007028 (M6)	12.81	587.32	8%	7%	<5%	<5%	<5%	<5%	<5%	<5%	<5%	<5%
$M_{rabbit}1$	13.44	575.29	ND	ND	ND	ND	<5%	<5%	ND	ND	ND	ND
EPZ034396 (M7)	14.02	503.26	<5%	<5%	<5%	<5%	ND	ND	<5%	<5%	<5%	<5%

（次頁に続く）

Test Article: tazemetostat

Metabolite Identification: Metabolites Observed in the Rat, Rabbit, Monkey and Human Plasma　Study Number: 14099&14430　Location in CTD: 5.3.2.2.8

Identifier	RT (min)	*m/z*	Female Rat Day 1	Female Rat Day 91	Male Rat Day 1	Male Rat Day 91	Rabbit DG 7	Rabbit DG 19	Monkey Day 1	Monkey Day 91	Human Day 1	Human Day 15
$M_{rabbit}2$	14.10	575.29	ND	ND	ND	ND	6%	9%	ND	ND	ND	ND
$M_{rabbit}3$	14.45	575.29	ND	ND	ND	ND	<5%	<5%	ND	ND	ND	ND
EPZ033883 (M8)	15.63	559.29	<5%	<5%	<5%	<5%	9%	11%	7%	6%	<5%	<5%

The data presented represent the percentage of total drug-related material in pooled plasma from rat, rabbit, and monkeys (0 to 24 hours) and human (0 to 12 hours).
Response factors were applied to the metabolite abundances based on the authentic standard MS response relative to an IS (EPZ007214). A single concentration point was used for comparison of ionization, therefore, these data are considered semi-quantitative.
BID = twice daily, CTD = Common Technical Document, DG = day of gestation, HRMS = high resolution mass spectrometry, IS = internal standard, *m/z* = mass-to-charge ratio of protonated ion, M = metabolite, MS = mass spectrometry, ND = not detected, RT = retention time, SD = Sprague Dawley, UPLC = ultra performance liquid chromatography.
a: Samples came from the following studies:
Rat plasma: 4.2.3.2.3 (Study No. K[redacted]009) (13-week repeated dosing), Day 1 and Day 91, group 100 mg/kg/day;
Rabbit plasma: 4.2.3.5.2.5 (Study No. 20097366) (13-day repeated dosing), DG 7 (Day 1) and DG 19 (Day 13), group 400 mg/kg/day;
Monkey plasma: 4.2.3.2.6 (Study No. 20047690) (13-week repeated BID dosing), Day 1 and Day 91, group 600 mg/kg/day (total dose per day, ie, 300 mg/kg in each dose);
Human plasma: 5.3.5.2.2 (Study E7438-G000-101), Day 1 and Day 15, 800 mg BID, 4 patient subjects (samples were pooled);
Plasma samples were pooled by Hamilton method (AUC pool rule).
Additional Information: **Identifier** カラム中の EPZ 番号の後ろに記載した括弧内 M 番号は，当該 in vivo 代謝試験報告書で規定の代謝物通し番号を示し（2.6.4.5.1.3 項，表 2.6.4-18 参照），2.6.5.10 Study Number: DMPKA20[redacted]-042（44～48 ページ）の M 番号とは M5 以外異なる。$M_{rabbit}1$～3 は当該 in vivo 代謝試験で，ウサギにおいてのみ検出された構造推定代謝物を示す。

2.6.5.10 薬物動態試験：代謝：in vitro

Test Article: tazemetostat hydrobromide

Metabolic Stability: Liver Microsomes and Hepatocytes **Study Number: DMPKA20[redacted]-041** **Location in CTD: 5.3.2.2.1**

Study System	in vitro
Test System	Liver microsomes or cryopreserved hepatocytes of mouse (CD-1), rat (SD), dog (beagle), monkey (cynomolgus), and human
Method	Incubation of tazemetostat with liver microsomes (designated time for each animal) or hepatocytes (for 0, 60, 120, and 240 min) at 37 °C
Assay / Analyte	LC-MS/MS / tazemetostat
Concentration	Tazemetostat: up to 20 μmol/L and liver microsomes protein concentration: 0.2 mg/mL or hepatocyte concentration: 1×10^6 cells/mL

Species	**K_m (μmol/L)**	**V_{max} (pmol/min/mg microsomes)**	**$t_{1/2}$ (min) [a]**	**CL_{int} (μL/min/g liver)**	**CL_{int} (L/h/kg body weight)**	**F_u**	**Q_{hep} (L/h/kg)**	**CL_{hep} (L/h/kg)**	**%Q_{hep}**
Liver Microsomes									
Mouse	2.17	747.2	ND	15,493.5	81.3	0.063	5.4	2.63	48.7
Rat	1.16	1213	ND	47,056.5	112.9	0.153	4.26	3.42	80.3
Dog	3.20	356.4	ND	5013.0	9.6	0.170	3.3	1.09	33.0
Monkey	3.62	5130	ND	63,769.5	114.8	0.188	2.64	2.35	89.0
Human	4.75	1545	ND	14,638.5	22.6	0.199	1.242	0.97	78.1
Hepatocytes									
Mouse	ND	ND	576.7 [a]	144.0 [a]	0.8 [a]	ND	ND	ND	ND
Rat	ND	ND	263.2 [a]	312.0 [a]	0.7 [a]	ND	ND	ND	ND
Dog	ND	ND	155.7 [a]	760.5 [a]	1.5 [a]	ND	ND	ND	ND
Monkey	ND	ND	38.8 [a]	2148.0 [a]	3.9 [a]	ND	ND	ND	ND
Human	ND	ND	284.9 [a]	288.0 [a]	0.4 [a]	ND	ND	ND	ND

The rate of tazemetostat metabolism in hepatocytes was substantially slower than that in liver microsomes and showed no concentration-dependence.

$CL_{hep} = (Q_{hep} \times F_u \times CL_{int})/(Q_{hep} + F_u \times CL_{int})$, $\%Q_{hep} = (CL_{hep}/Q_{hep}) \times 100$.

CL_{hep} = estimated hepatic clearance, CL_{int} = intrinsic clearance, CTD = Common Technical Document, F_u= fraction unbound in plasma, K_m = Michaelis-Menten constant, LC-MS/MS = liquid chromatography with tandem mass spectrometry, ND = not determined, Q_{hep} = hepatic blood flow, SD = Sprague Dawley, $t_{1/2}$ = elimination half-life, V_{max} = maximum velocity.

a: 0.5 μmol/L tazemetostat.

Additional Information: None.

2.6.5.10 薬物動態試験：代謝：in vitro（続き）

Test Article: tazemetostat hydrobromide

Metabolic Stability: Hepatocytes **Study Number: DMPKA20[redacted]-117** **Location in CTD: 5.3.2.2.2**

Study System	in vitro		
Test System	Cryopreserved hepatocytes form human		
Method	Cryopreserved hepatocytes (0.5×10^6 cells/mL) from human were incubated with tazemetostat (0.5 to 10 µmol/L) in a humidified 5% CO_2 incubator for up to 240 minutes in a 48-well plate.		
Assay / Analyte	LC-MS/MS / tazemetostat		
Concentration	Tazemetostat: 0.5, 1, 5, or 10 µmol/L		
Concentration (µmol/L)	**$t_{1/2}$ (min)**	**CL_{int} (µL/min/g liver)**	**CL_{int} (L/h/kg body weight)**
0.5	116.9	1387	2.081
1	123.2	1316	1.974
5	183.5	883.7	1.326
10	281.8	575.5	0.863

CL_{int} (L/h/kg body weight) = CL_{int} (µL/min/g liver) × scaling factor × L/10^6 µL × 60 min/h, where scaling factor is 25 (g liver/kg body weight).
CL_{int} = intrinsic clearance, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, $t_{1/2}$ = elimination half-life.

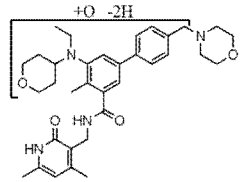
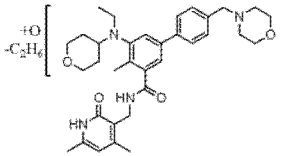
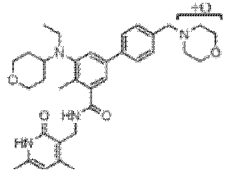
Additional Information: None.

2.6.5.10 薬物動態試験：代謝：in vitro（続き）

Test Article: tazemetostat hydrobromide

Metabolite Identifications **Study Number: DMPKA20[redacted]-042** **Location in CTD: 5.3.2.2.3**

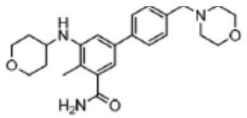
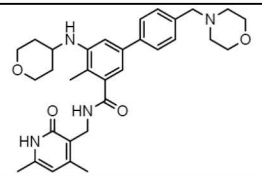
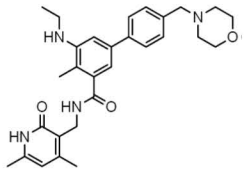
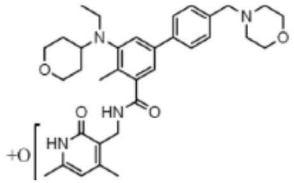
Study System	in vitro
Test System	Liver microsomes or cryopreserved hepatocytes of mouse (CD-1), rat (SD), dog (beagle), monkey (cynomolgus), and human.
Method	Incubation of tazemetostat with liver microsomes or hepatocytes at 37 °C [a]
Assay / Analyte	LC-MS/MS/TOF / Tazemetostat and metabolites
Concentration	Tazemetostat: 20 μmol/L [b]

Metabolite	Species Found	Structure	Description
M1	Mouse, rat, monkey, and human		Oxidation and dehydrogenation
M2	Mouse, rat, monkey, and human		Deethylation and oxidation
M3	Mouse, rat, dog, monkey, and human		Oxidation of the morpholine

（次頁に続く）

Test Article: tazemetostat hydrobromide

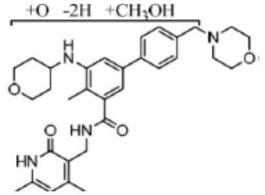
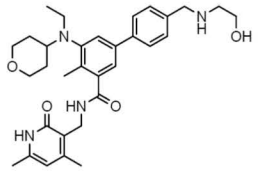
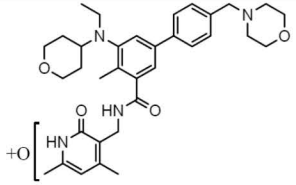
Metabolite Identifications **Study Number: DMPKA20[redacted]-042** **Location in CTD: 5.3.2.2.3**

Metabolite	Species Found	Structure	Description
M4	Mouse, rat, monkey, and human		*N*-deethylation and *N*-dealkylation of the pyridone
M5 [c]	Mouse, rat, monkey, and human		*N*-deethylation
M6	Mouse, rat, monkey, and human		*N*-detetrahydropyran
M7	Mouse, rat, dog, monkey, and human		Oxidation of the pyridone

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Test Article: tazemetostat hydrobromide

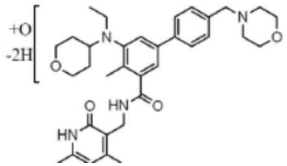
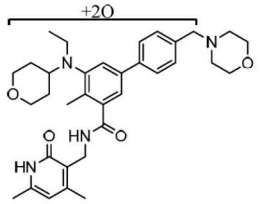
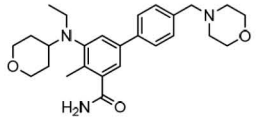
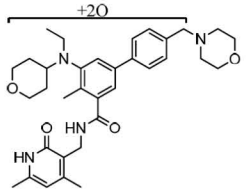
Metabolite Identifications **Study Number: DMPKA20[redacted]-042** **Location in CTD: 5.3.2.2.3**

Metabolite	Species Found	Structure	Description
M8	Mouse, rat, and monkey		*N*-deethylation and addition of co-solvent (methanol) to putative electrophilic quinone intermediate
M9	Mouse, rat, dog, monkey, and human		*N*- and *O*-dealkylation of the morphine
M10	Mouse, dog, monkey, and human		Oxidation of the pyridone

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Test Article: tazemetostat hydrobromide

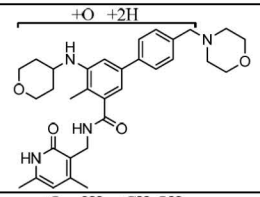
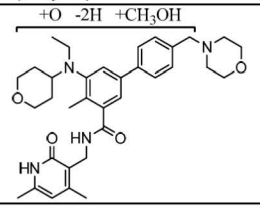
Metabolite Identifications **Study Number: DMPKA20[redacted]-042** **Location in CTD: 5.3.2.2.3**

Metabolite	Species Found	Structure	Description
M11	Mouse, rat, dog, monkey, and human		Oxidation and dehydrogenation
M12	Mouse, rat, dog, monkey, and human		Dual oxidation
M13	Mouse, rat, dog, monkey, and human		*N*-dealkylation of the pyridone
M14	Mouse, rat, dog, monkey, and human		Dual oxidation

（次頁に続く）

Test Article: tazemetostat hydrobromide

Metabolite Identifications **Study Number: DMPKA20[redacted]-042** **Location in CTD: 5.3.2.2.3**

Metabolite	Species Found	Structure	Description
M15	Mouse, rat, dog, monkey, and human		*N*-deethylation, oxidation, and hydrogenation
M16	Mouse, rat, dog, monkey, and human		Addition of co-solvent (methanol) to putative electrophilic quinone intermediate

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, M = metabolite, SD = Sprague Dawley, TOF = time of flight.

a: In the liver microsomes from the mouse, rat, dog, monkey, and human, the 30-, 30-, 30-, 5-, and 20-minute incubations, respectively, were assayed. For the hepatocyte incubations, the 4-hour incubations were assayed for all species tested.

b: Liver microsomes protein concentration for all species was 0.2 mg/mL. Hepatocyte concentration for all species tested was 1×10^6 cells/mL.

c: M5 indicates EPZ-6930. EPZ-number indicates the compound number specified by [redacted]

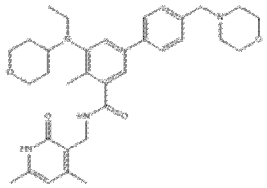
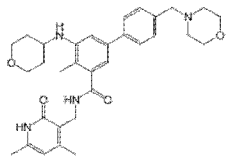
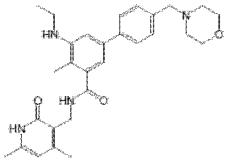
Additional Information: None.

2.6.5.10 薬物動態試験：代謝：in vitro（続き）

Test Article: **[^{14}C]tazemetostat hydrobromide**

Metabolite Identifications **Study Number: 45N-1404** **Location in CTD: 5.3.2.2.4**

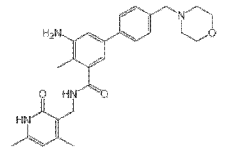
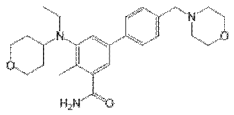
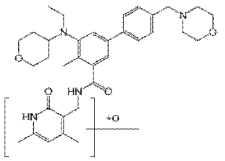
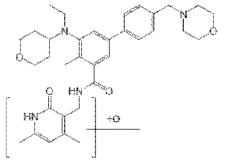
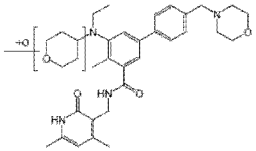
Study System	in vitro
Test System	Cryopreserved hepatocytes of rat (SD), rabbit (New Zealand White), monkey (cynomolgus), and human
Method	The incubation mixture contained [^{14}C]tazemetostat (10 μmol/L) and hepatocytes (1×10^6 cells/mL). Incubation mixture was assayed for 0, 30, 120, and 240 minutes.
Assay / Analyte	LC-MS/Radio flow-through detector / Tazemetostat and metabolites
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB028-3)
Concentration	Tazemetostat: 10 μmol/L

Metabolite	Description	*m/z*	Proposed Structure	Rat	Rabbit	Monkey	Human
Tazemetostat	Parent	573		Yes	Yes	Yes	Yes
H1[a]	*N*-Deethyl product of tazemetostat	545		Yes	Yes	Yes	Yes
H2	*N*-Detetrahydropyran product of tazemetostat	489		Yes	Yes	Yes	Yes

（次頁に続く）

Test Article: **[^{14}C]tazemetostat hydrobromide**

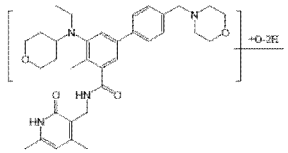
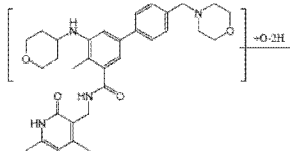
Metabolite Identifications **Study Number: 45N-1404** **Location in CTD: 5.3.2.2.4**

Metabolite	Description	*m/z*	Proposed Structure	Rat	Rabbit	Monkey	Human
H3	Loss of both ethyl and tetrahydropyran moieties from tazemetostat	461		b	Yes	b	b
H4	Loss of (4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl moiety from tazemetostat	438		Yes	Yes	Yes	Yes
H5	Monooxygenation product of tazemetostat	589		Yes	Yes	Yes	Yes
H6	Monooxygenation product of tazemetostat	589		Yes	Yes	Yes	Yes
H7	Monooxygenation product of tazemetostat	589		Yes	Yes	Yes	Yes

（次頁に続く）

Test Article: **[^{14}C]tazemetostat hydrobromide**

Metabolite Identifications **Study Number: 45N-1404** **Location in CTD: 5.3.2.2.4**

Metabolite	Description	*m/z*	Proposed Structure	Rat	Rabbit	Monkey	Human
H8	Oxidation product of tazemetostat	587		Yes	Yes	Yes	Yes
H9	Oxidation product of EPZ-6930	559		Yes	Yes	Yes	Yes
H10	NA	NA	NA	Yes	Yes	Yes	Yes

Yes in the table indicates that metabolite was detected.

CTD = Common Technical Document, H = metabolite, LC-MS = liquid chromatography with mass spectrometry, *m/z* = mass-to-charge ratio of protonated ion, NA = not applicable, SD = Sprague Dawley.

a: H1 indicates EPZ-6930. EPZ-number indicates the compound number specified by [redacted]

b: Detected only by LC-MS in trace amount.

Additional Information: None.

2.6.5.10 薬物動態試験：代謝：in vitro（続き）

Test Article: tazemetostat hydrobromide

CYP Isoforms for Metabolism **Study Number: DMPKA20[redacted]-044** **Location in CTD: 5.3.2.2.5**

Study System	in vitro	
Test System	HLMs with CYP-selective chemical inhibitors; rCYPs	
Method	Incubation of tazemetostat with HLMs in the presence and absence of CYP-selective chemical inhibitors at 37 °C up to 30 minutes; incubation of tazemetostat with rCYP at 37 °C up to 30 minutes	
Assay / Analyte	LC-MS/MS / tazemetostat	
Concentration	Tazemetostat: 1 µmol/L and HLMs protein concentration: 0.5 mg/mL; tazemetostat: 0.1 µmol/L and rCYP: 5 pmol CYP/mL	
CYP Tested in Human Liver Microsomes	**CYP-Selective Inhibitors/Concentrations (µmol/L)**	**Percentage of Inhibition (%)**
CYP1A2	Furafylline/10	no effect observed
CYP2B6	2-Phenyl-2-(1-piperidinyl) propane/10	0.4
CYP2C8	Montelukast/10	35.3
CYP2C9	Sulfaphenazole/5	no effect observed
CYP2C19	(*S*)-Benzylnirvanol/5	8.2
CYP2D6	Quinidine/5	20.3
CYP3A	Ketoconazole/1	94.8
Recombinant CYP Isoforms	**Time-Dependent Depletion of Tazemetostat**	
CYP1A2	ND	
CYP2B6	ND	
CYP2C8	ND	
CYP2C9	ND	
CYP2C19	ND	
CYP2D6	ND	
CYP3A4	Detected	

CTD = Common Technical Document, CYP = cytochrome P450, HLM = human liver microsomes, LC-MS/MS = liquid chromatography with tandem mass spectrometry, ND = not detected, rCYP = recombinant human cytochrome P450.

Additional Information: None.

2.6.5.10 薬物動態試験：代謝：in vitro（続き）

Test Article: tazemetostat hydrobromide, EPZ-6930

CYP Isoforms for Metabolism **Study Number: 151341** **Location in CTD: 5.3.2.2.11**

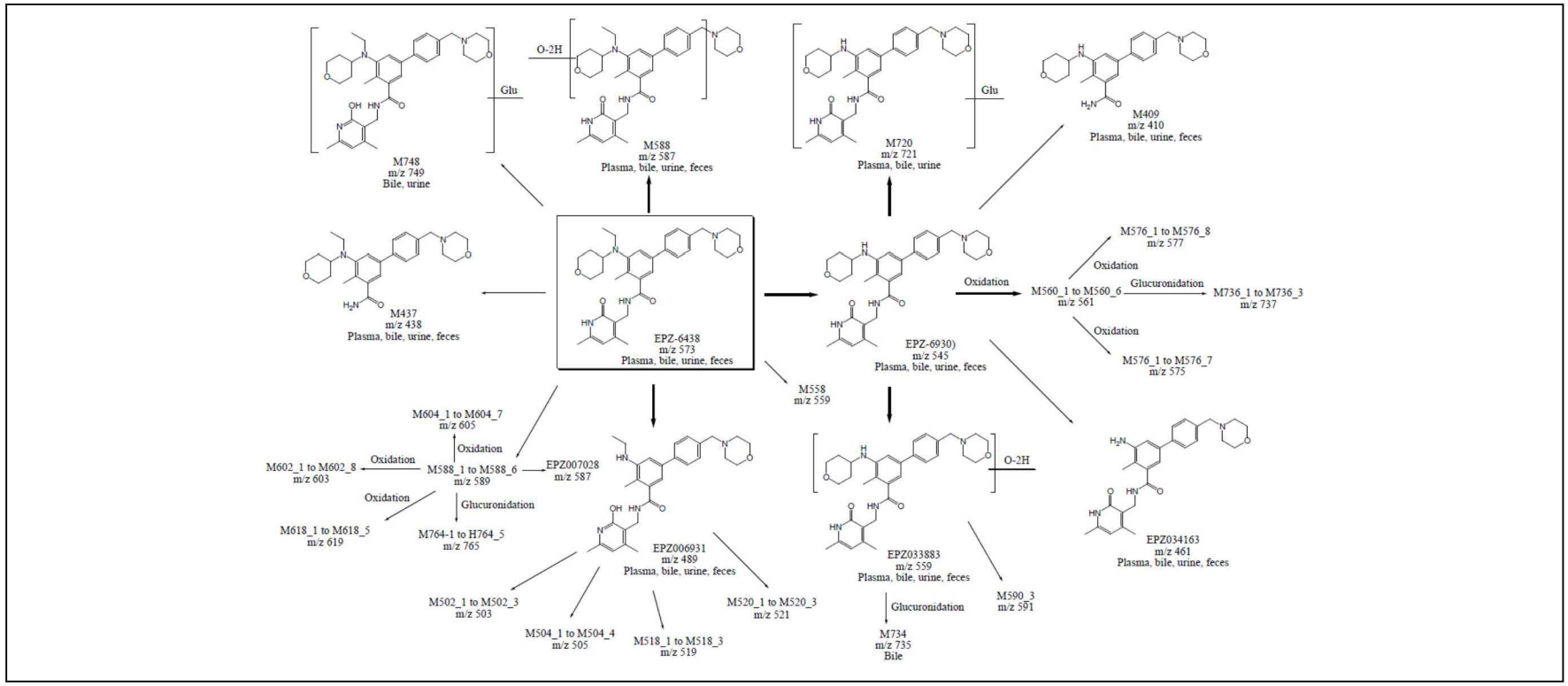
Study System	in vitro					
Test System	Pooled HLM, rCYP Supersomes™					
Method	Pooled HLM or rCYP Supersomes™ incubated with tazemetostat or EPZ-6930 over time (0, 1, 3, 15, 30, 60, and 120 min). Samples quenched with 50:50 acetonitrile:water containing internal standard					
Assay / Analyte	LC-MS/MS / tazemetostat and metabolite EPZ-6930					
Concentration	Tazemetostat and EPZ-6930: 0.2 and 2 µmol/L					
Estimated Fraction of Tazemetostat Metabolized						
rCYP	**CL_{int} (µL/min/mg)**		**Scaled $CL_{int, HLM}$ (µL/min/mg)**		**$f_{m, CYP}$**	
	0.2 µmol/L	**2 µmol/L**	**0.2 µmol/L**	**2 µmol/L**	**0.2 µmol/L**	**2 µmol/L**
rCYP2J2	274	95.6	2.83	0.989	0.005	0.003
rCYP3A4	2944	1712	533	310	0.99	0.99
rCYP3A5	334	165	2.84	1.4	0.005	0.004
Estimated Fraction of EPZ-6930 Metabolized						
rCYP	**CL_{int} (µL/min/mg)**		**Scaled $CL_{int, HLM}$ (µL/min/mg)**		**$f_{m, CYP}$**	
	0.2 µmol/L	**2 µmol/L**	**0.2 µmol/L**	**2 µmol/L**	**0.2 µmol/L**	**2 µmol/L**
rCYP2J2	107	80.8	1.1	0.836	0.11	0.08
rCYP3A4	51.6	56	9.34	10.1	0.89	0.92

CL_{int} = intrinsic clearance, $CL_{int,HLM}$ = intrinsic clearance in human liver microsomes, CTD = Common Technical Document, CYP = cytochrome P450, $f_{m,CYP}$ = fraction metabolized by a particular CYP, HLM = human liver microsomes, LC-MS/MS = liquid chromatography with tandem mass spectrometry, rCYP = recombinant human cytochrome P450, scaled $CL_{int,HLM}$ = scaled intrinsic clearance in human liver microsomes.

Additional Information: None.

2.6.5.11 薬物動態試験：推定代謝経路

Proposed Metabolic Pathways Based on the Metabolites Observed In Vivo (Rat)

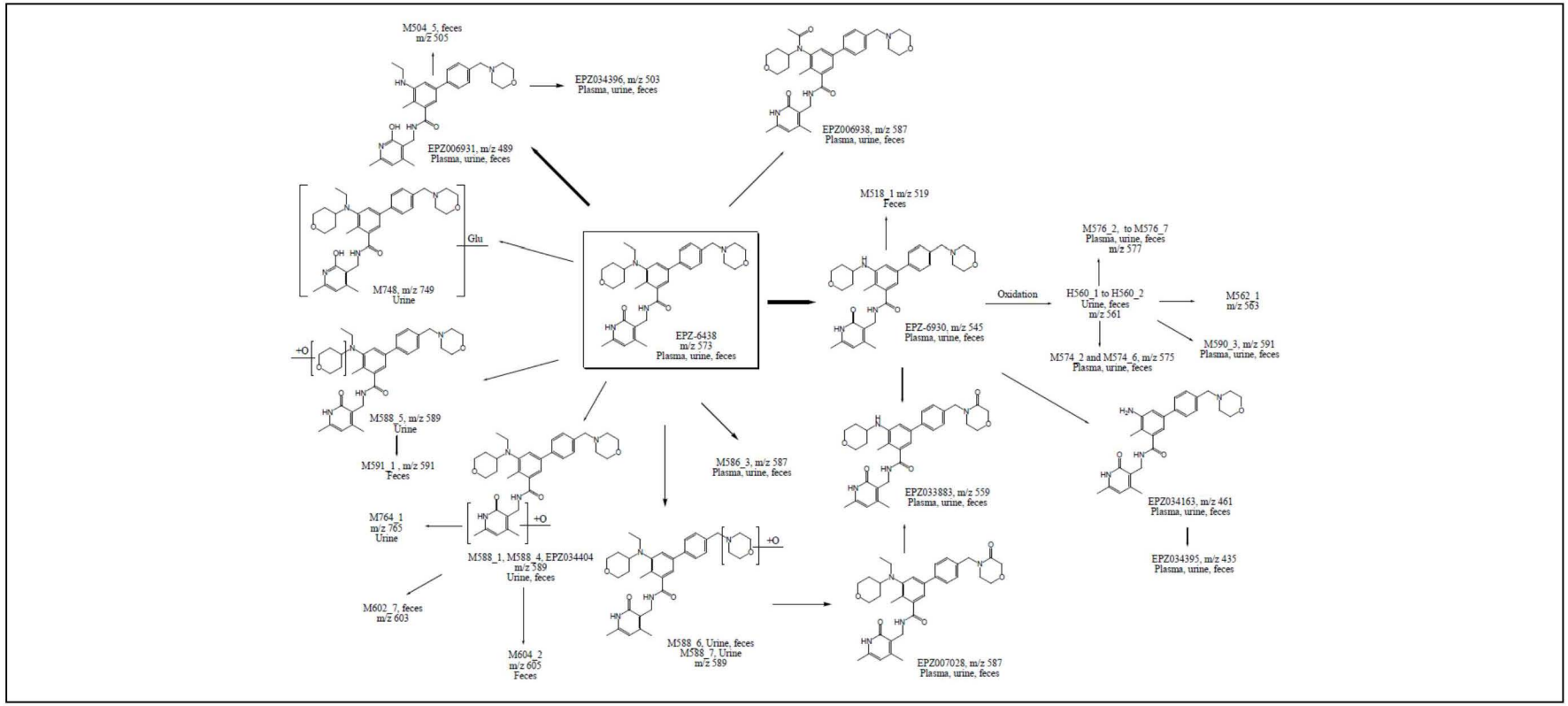


EPZ-6438 = tazemetostat, *m/z* = mass-to-charge ratio of protonated ion.

Additional Information: The M number indicates the metabolite serial number in the original report. The EPZ number indicates the compound number defined by [redacted] The metabolic pathways were prepared based on 4.2.2.4.1 (Study No. 45N-1403).

2.6.5.11 薬物動態試験：推定代謝経路（続き）

Proposed Metabolic Pathways Based on the Metabolites Observed In Vivo (Monkey)



EPZ-6438 = tazemetostat, *m/z* = mass-to-charge ratio of protonated ion.

Additional Information: The M number indicates the metabolite serial number in the original report. The EPZ number indicates the compound number defined by [redacted] The metabolic pathways were prepared based on 4.2.2.4.2 (Study No. 514N-1502).

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害

Test Article: tazemetostat hydrobromide, tazemetostat hydrochloride

Inhibition of CYPs In Vitro **Study Number: DMPKA20[redacted]-002, DMPKA20[redacted]-171** **Location in CTD: 5.3.2.2.6**

Study System	in vitro
Test System	Pooled HLMs
Method	For assessment of reversible inhibition (no pre-incubation), incubation of tazemetostat with HLMs and CYP-selective probe substrates in the presence of NADPH for 5 or 10 minutes at 37 °C; For assessment of mechanism-based inactivation (time-dependent inhibition), pre-incubation of tazemetostat with HLMs in the presence of NADPH for 0 to 30 minutes and measurement of remaining CYP activity by 20-fold dilution and incubation with CYP-selective probe substrates in the presence of additional NADPH
Assay / Analyte	LC-MS/MS / Metabolites formed by CYP-mediated metabolism
Concentration	Tazemetostat: 0 to 20 μmol/L (reversible inhibition); 0 to 100 μmol/L for time-dependent inhibition

CYP Isoform	**Probe Reaction**	**Reversible Inhibition (No Pre-Incubation)**	**Time-Dependent Inhibition**	
		IC_{50} (μmol/L)	**K_I (μmol/L)**	**k_{inact} (min^{-1})**
CYP1A2	Phenacetin *O*-deethylation	>20	NA	NA
CYP2B6	Bupropion hydroxylation	>20	NA	NA
CYP2C8	Amodiaquine *N*-deethylation	6.3	ND	ND
CYP2C9	Tolbutamide 4′-hydroxylation	9.0	ND	ND
CYP2C19	(*S*)-Mephenytoin 4′-hydroxylation	3.8	ND	ND
CYP2D6	(±)-Bufuralol 1′-hydroxylation	15.5	ND	ND
CYP2E1	Chlorzoxazone 6-hydroxylation	>20	NA	NA
CYP3A	Midazolam 1′-hydroxylation	12.7	NA	NA
	Nifedipine dehydrogenation	19.4	NA	NA
	Testosterone 6β-hydroxylation	5.9	6.4	0.077

CTD = Common Technical Document, CYP = cytochrome P450, HLM = human liver microsomes, IC_{50} = half-maximal inhibitory concentration, K_I = half-maximal inhibitory concentration of the maximal inactivation rate constant, k_{inact} = maximal inactivation rate constant, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NADPH = reduced form of β-nicotinamide adenine dinucleotide phosphate, ND = no inactivation observed.

Additional Information: Time-dependent inhibition of CYP3A (testosterone 6β-hydroxylation) by tazemetostat was not reversible by the addition of potassium ferricyanide.

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

Test Article: tazemetostat hydrobromide

Inhibition of CYPs In Vitro **Study Number: 151245/151340/160432** **Location in CTD: 5.3.2.2.12**

Study System	in vitro		
Test System	HLMs		
Method	For reversible inhibition, no pre-incubation with inhibitor. For IC_{50}, pre-incubation with inhibitor in the presence or absence of NADPH for 30 minutes		
Assay / Analyte	LC-MS/MS / Metabolites of CYP probe substrates formed by CYP-mediated metabolism		
Concentration	Tazemetostat: 0.0365 to 50 µmol/L (a total of 7 concentrations)		
CYP Isoform	**Tazemetostat K_i (µmol/L) (No Pre-Incubation)**	**Tazemetostat IC_{50} With 30 min Pre-Incubation (µmol/L)**	
		Without NADPH	**With NADPH**
CYP2C8	1.27±0.07	1.78±0.18	4.13±0.45
CYP2C9	15.0±0.6	13.7±0.8	14.3±1.6
CYP2C19	6.65±0.57	7.08±0.44	13.4±1.1
CYP2D6	9.16±1.04	12.0±0.5	21.6±0.6
CYP3A	3.06±0.17	ND	ND

CTD = Common Technical Document, CYP = cytochrome P450, HLM = human liver microsomes, IC_{50} = half-maximal inhibitory concentration; K_i = inhibitory constant, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NADPH = reduced form of β-nicotinamide adenine dinucleotide phosphate, ND = not determined.

Additional Information: None.

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

Test Article: EPZ-6930, EPZ006931, EPZ034163

Inhibition of CYPs In Vitro (Tazemetostat Metabolites) **Study Number: 151295** **Location in CTD: 5.3.2.2.10**

Study System	in vitro		
Test System	HLMs		
Method	Incubation of tazemetostat metabolites with HLM, a CYP probe substrate (at its K_m concentration), and NADPH (1 mmol/L) in triplicate		
Assay / Analyte	LC-MS/MS / Metabolites of CYP probe substrates formed by CYP-mediated metabolism		
Concentration	EPZ-6930 and EPZ034163: 0.146 to 200 µmol/L; EPZ006931: 0.0838 to 115 µmol/L		
CYP Isoform	**IC_{50} (µmol/L)**		
	EPZ-6930	**EPZ06931**	**EPZ034163**
CYP1A2	>200	>115	122±12.5
CYP2B6	>200	>115	>200
CYP2C8	152±21.1	45.9±6.55	>200
CYP2C9	172±35.0	>115	91.7±12.2
CYP2C19	>200	>115	>200
CYP2D6	>200	>115	>200
CYP3A (midazolam)	>200	>115	>200
CYP3A (testosterone)	113±14.0	52.8±2.70	130±9.08

CYP3A inhibition was evaluated using 2 probe substrates (midazolam and testosterone).

CTD = Common Technical Document, CYP = cytochrome P450, HLM = human liver microsomes, IC_{50} = half-maximal inhibitory concentration, K_m = Michaelis-Menten constant, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NADPH = reduced form of β-nicotinamide adenine dinucleotide phosphate.

Additional Information: None.

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

Test Article: tazemetostat hydrobromide

Induction of CYPs In Vitro **Study Number: DMPKA20[redacted]-040** **Location in CTD: 5.3.2.2.7**

Study System	in vitro
Test System	Cryopreserved human hepatocytes from 3 donors (Lot Nos. 226, 246, and 267)
Method	Cells were plated on 24-well plates at 0.375 $\times 10^6$ cell/well or on 96-well plates at 0.06 $\times 10^6$ cells/well in plating medium. Following the overnight plating period, cells were treated with inducers for a 48-hour incubation at 37 °C
Assay / Analyte	Quantitative RT-PCR / mRNA; LC-MS/MS / CYP-selective probe activities of CYP1A2-mediated phenacetin *O*-deethylation, CYP2B6-mediated bupropion hydroxylation, CYP2C9-mediated tolbutamide methylhydroxylation, or CYP3A-mediated midazolam 1′-hydroxylation
Concentration	Tazemetostat: 0 to 30 μmol/L

CYP Isoform	**Treatment (Concentration) (μmol/L)**	**Fold Induction**					
		Lot 226		**Lot 246**		**Lot 267**	
		Enzyme Activity	**mRNA Level**	**Enzyme Activity**	**mRNA Level**	**Enzyme Activity**	**mRNA Level**
CYP1A2	β-Naphthoflavone (10)	2.51	81.26	11.00	125.15	6.74	82.31
	Tazemetostat (0.03)	1.19	1.00	1.12	1.16	1.15	0.89
	Tazemetostat (0.1)	1.16	0.95	1.21	1.19	1.14	0.81
	Tazemetostat (0.3)	1.22	1.19	1.39	1.40	1.20	1.07
	Tazemetostat (1)	1.19	1.43	1.63	2.34	1.27	1.58
	Tazemetostat (3)	1.60	1.90	1.94	2.64	1.32	1.93
	Tazemetostat (10)	1.71	2.50	2.09	3.76	1.47	3.62
	Tazemetostat (30)	1.33	1.97	1.32	4.82	1.64	3.62
CYP2B6	Phenobarbital (1000)	4.50	6.88	2.81	7.25	1.85	3.07
	Tazemetostat (0.03)	1.05	1.23	0.79	1.09	1.08	1.13
	Tazemetostat (0.1)	1.50	1.08	0.87	1.06	1.12	1.09
	Tazemetostat (0.3)	1.45	1.26	0.92	1.17	1.23	1.18
	Tazemetostat (1)	1.68	1.50	1.05	1.66	1.19	1.52
	Tazemetostat (3)	2.23	1.98	2.09	2.16	1.38	1.58
	Tazemetostat (10)	2.82	2.45	3.81	2.56	1.73	1.52
	Tazemetostat (30)	1.77	1.81	4.78	2.77	1.62	1.43

（次頁に続く）

Induction of CYPs In Vitro **Test Article: tazemetostat hydrobromide**
Study Number: DMPKA20[redacted]-040 **Location in CTD: 5.3.2.2.7**

CYP Isoform	Treatment (Concentration) (µmol/L)	Fold Induction					
		Lot 226		Lot 246		Lot 267	
		Enzyme Activity	mRNA Level	Enzyme Activity	mRNA Level	Enzyme Activity	mRNA Level
CYP2C9	Rifampicin (10)	1.75	1.27	4.48	1.99	2.52	1.69
	Tazemetostat (0.03)	1.00	0.97	0.79	1.05	1.01	0.97
	Tazemetostat (0.1)	1.02	0.97	0.76	1.05	1.03	1.00
	Tazemetostat (0.3)	1.12	1.09	1.00	1.15	1.03	1.05
	Tazemetostat (1)	1.36	1.07	1.27	1.31	1.26	1.18
	Tazemetostat (3)	1.69	1.20	2.14	1.59	1.48	1.47
	Tazemetostat (10)	2.25	1.30	3.49	1.96	2.55	1.71
	Tazemetostat (30)	2.93	1.32	3.60	1.87	3.48	2.11
CYP3A or CYP3A4	Rifampicin (10)	5.84	14.87	20.91	132.05	6.56	22.41
	Tazemetostat (0.03)	1.00	1.10	1.10	1.56	0.95	1.13
	Tazemetostat (0.1)	0.99	1.29	1.30	3.21	1.19	1.36
	Tazemetostat (0.3)	0.90	2.04	1.88	7.09	1.20	2.49
	Tazemetostat (1)	1.14	3.49	2.88	18.47	1.36	6.06
	Tazemetostat (3)	1.26	9.11	4.73	49.08	1.63	11.05
	Tazemetostat (10)	1.56	14.01	3.67	96.73	1.37	17.40
	Tazemetostat (30)	1.01	9.03	1.89	97.43	1.06	17.50

CYP3A4 Induction by Tazemetostat

Lot	E_{max} (Fold)	EC_{50} (µmol/L)	Fold Induction of 10 µmol/L Rifampicin
226	15.62	2.69	14.87
246	103.5	2.96	132.05
267	18.60	2.18	22.41

For the measurement of CYP1A2 induction, β-naphthoflavone was used as a positive control. For CYP2B6 induction, phenobarbital was used as a positive control. For induction of CYP2C9 or CYP3A or 3A4, rifampicin was used as the positive control.

CTD = Common Technical Document, CYP = cytochrome P450, EC_{50} = concentration causing half maximal effect, E_{max} = maximum induction effect, LC-MS/MS = liquid chromatography with tandem mass spectrometry, mRNA = messenger RNA, RT-PCR = reverse transcription-polymerase chain reaction.

Additional Information: None.

2.6.5.12 薬物動態試験：薬物代謝酵素の誘導/阻害（続き）

Test Article: tazemetostat hydrobromide

Induction of CYPs In Vitro **Study Number: 151294** **Location in CTD: 5.3.2.2.9**

Study System	in vitro							
Test System	Cryopreserved human hepatocytes from 3 donors							
Method for CYP Activity Assay	Cells were seeded on 48-well plates at 0.14 $\times 10^6$ cells/well in plating medium. Following the 24-hour plating period, cells were treated with either 0.1% DMSO as vehicle control, 50 µmol/L tazemetostat, 50 µmol/L rifampicin (CYP3A, positive control), 100 µmol/L omeprazole (CYP1A2 positive control), or 1000 µmol/L phenobarbital (CYP2B6 positive control) for 72 hours.							
Assay / Analyte	RT-PCR and qPCR / mRNA, LC-MS/MS / metabolites of phenacetin (CYP1A2 probe substrate), bupropion (CYP2B6 probe substrate), and testosterone (CYP3A probe substrate)							
Concentration	0.2, 0.5, 1.3, 3.2, 8.0, 20, and 50 µmol/L for CYP mRNA; 50 µmol/L for CYP activity							
CYP Enzyme	**mRNA Level**					**Enzyme Activity**		
	Maximal Fold-Induction of CYP mRNA by Tazemetostat			**Tazemetostat EC_{50} (µmol/L)**	**Positive Control[b]**	**Fold-Induction of CYPs Activities by 50 µmol/L of Tazemetostat**		
	EJW[a]	**FLO[a]**	**YJM[a]**		**Fold-Induction**	**EJW[a]/Positive Control[c]**	**FLO[a]/Positive Control[c]**	**YJM[a]/Positive Control[c]**
CYP1A2	1.84	1.61	2.37	NA	40.6 to 102	0.13/30.1	0.28/37.3	0.79/23.5
CYP2B6	2.26	1.9	3.16	4.45	2.76 to 9.94	0.42/21.6	1.36/17.4	1.03/13.9
CYP2C8	3.32	2.9	4.29	3.36	3.95 to 6.55	ND	ND	ND
CYP2C9	3.19	1.55	2.83	NA	1.16 to 4.33	ND	ND	ND
CYP2C19	1.06	1.57	1.15	NA	0.83 to 2.16	ND	ND	ND
CYP3A or 3A4	9.14	9.61	15.3	2.41	15.7 to 29.4	0.44/30.8	2.07/23	1.68/19

CTD = Common Technical Document, CYP = cytochrome P450, DMSO = dimethyl sulfoxide, EC_{50} = concentration causing half maximal effect, LC-MS/MS = liquid chromatography with tandem mass spectrometry, mRNA = messenger RNA, NA = not available due to insufficient data for EC_{50} estimation, ND = not determined, qPCR = quantitative polymerase chain reaction, RT-PCR = reverse transcription-polymerase chain reaction.

a: Lots of cryopreserved human hepatocytes.

b: 100 µmol/L omeprazole for CYP1A2, 1000 µmol/L phenobarbital for CYP2B6, 50 µmol/L rifampicin for CYP3A or 3A4, CYP2C8, CYP2C9, and CYP2C19.

c: Positive controls for CYP1A2; 100 µmol/L omeprazole, for CYP2B6; 1000 µmol/L phenobarbital, and for CYP3A or 3A4; 50 µmol/L rifampicin.

Additional Information: In this table, the method focusing on CYP activity assay is described.

2.6.5.13 薬物動態試験：排泄

Test Article: tazemetostat hydrobromide

Rats (Excretion Into Urine) **Study Number: DMPKA20[redacted]-060, DMPKA20[redacted]-063** **Location in CTD: 4.2.2.2.2**

Strain/Gender/Number of Animals	Sprague Dawley/Male/4			
Feeding Condition	IV administration was performed under feeding, and PO administration was performed under fasting.			
Vehicle/Formulation	Sterile saline with 1.0% (v/v) 0.1 mol/L HCl (IV dose); 0.5% (w/v) methylcellulose and 0.1% (v/v) Tween 80 in deionized water (PO dose)			
Method of Administration	IV and PO			
Dose	IV: 5 mg/kg, PO: 100 mg/kg			
Sample/Analyte / Assay	Urine/Tazemetostat / LC-MS/MS			
Pharmacokinetic Parameters				
Dose[a] (mg/kg) Route	**X_{u0-t}[b] (ng) 0 to 48 hours**	**Total Dose[c] (mg)**	**A_e[d] (%) 0 to 48 hours**	**CL_{ren}[e] (L/h/kg)**
5 IV	6246.2±1437.4	1.6±0.1	0.4±0.1	0.02±0.01
100 PO	95,225.0±95,674.8	27.6±0.9	0.4±0.3	0.01±0.01

Each parameter is presented as the mean ±SD of 4 animals. Concentrations were expressed as the free base of tazemetostat.

A_e = percentage of tazemetostat dose excreted in urine, $AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, CL_{ren} = renal clearance, CTD = Common Technical Document, HBr = hydrobromide, HCl = hydrochloric acid, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, PO = oral, v/v = volume per volume, w/v = weight per volume, X_{u0-inf} = cumulative amount of tazemetostat collected in urine from zero time extrapolated to infinite time, X_{u0-48h} = cumulative amount of tazemetostat collected in urine from zero time to 48 hours, X_{u0-t} = cumulative amount of tazemetostat collected in urine from zero time to last quantifiable time.

a: Dose of HBr salt.

b: Cumulative amount (ng) of tazemetostat collected up to 48 hours including case wash.

c: Total dose = Dose concentration × Dose volume × 0.876 salt factor.

d: Percentage (%) of tazemetostat collected based off total dose administered (X_{u0-t} / Total Dose ×100).

e: $CL_{ren} = X_{u0-48h} / AUC_{(0-inf)}$ / Body weight; assumes that X_{u0-48h} is approximately equal to X_{u0-inf}.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method. This study also investigated the role of biliary excretion of tazemetostat clearance in rats (Section 2.6.5.14).

2.6.5.13 薬物動態試験：排泄（続き）

Test Article: **[^{14}C]tazemetostat hydrobromide**

Rats **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Strain/Gender/Number of Animals	Sprague Dawley/Male/3
Feeding Condition	Fasted[a]
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water
Method of Administration / Dose	Oral, by gavage / 50 mg/kg[b]
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)
Analyte/Assay	Radioactivity/LSC

Cumulative Excretion of Radioactivity (% of Dose)

Sample	Urine (0 – 168 hours)	Feces (0 – 168 hours)	Cage Rinse (0 – 144 hours)	Cage Wash and Wipe (168 hours)	Total Recovery
	8.0±1.2	86.1±3.0	0.3±0.2	0.0±0.0	94.4±3.1

Values represent the mean ±SD of 3 animals.

CTD = Common Technical Document, LSC = liquid scintillation counter, w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

Additional Information: This study also investigated the plasma pharmacokinetics of radioactivity (Section 2.6.5.3), the distribution of radioactivity in organs and tissues (Section 2.6.5.5), and the biliary excretion of radioactivity (Section 2.6.5.14).

2.6.5.13 薬物動態試験：排泄（続き）

Test Article: [^{14}C]tazemetostat hydrobromide

Monkeys **Study Number: 11661** **Location in CTD: 4.2.2.5.2**

Strain/Gender/Number of Animals	Cynomolgus/Male and female/3
Feeding Condition	Fed. Water was given freely.
Vehicle/Formulation	For IV, Saline injection, pH 4.0; for PO, 0.5% (w/w) methylcellulose and 0.1% Tween 80 in water.
Method of Administration / Dose	IV and PO / 5 mg/kg (IV) and 50 mg/kg (PO)[a]
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (8822CJW001-3)
Analyte/Assay	Radioactivity/LSC

Time	**Cumulative Excretion of Radioactivity (% of Dose)**				
	Urine	**Feces**	**Cage Rinse/Wash**	**Cage Wipe**	**Total Recovery**
0 – 48 hours (IV)	4.88±2.03 (M)	72.79±10.61 (M)	ND	ND	77.67 (M)
0 – 168 hours (IV)	5.15±2.12 (M)	79.15±2.61 (M)	1.36±0.52 (M)	0.96±0.51 (M)	86.62±2.56 (M)
0 – 48 hours (PO)	3.84±2.55 (M)	79.46±10.63 (M)	ND	ND	83.29 (M)
	3.24±1.93 (F)	63.11±20.51 (F)	ND	ND	66.35 (F)
0 – 168 hours (PO)	4.03±2.69 (M)	81.64±10.15 (M)	1.84±1.98 (M)	0.45±0.21 (M)	87.97±7.07 (M)
	3.33±1.97 (F)	81.48±6.67 (F)	6.09±5.07 (F)	0.26±0.30 (F)	91.17±3.59 (F)

Values represent the mean ±SD of 3 animals; total recovery for 0 to 48 hours represents the mean value.

CTD = Common Technical Document, F = females, IV = intravenous, LSC = liquid scintillation counter, M = males, ND = not determined, PO = oral, w/w = weight per weight.

a: The dose was expressed in terms of the free base.

Additional Information: This study also investigated the blood and plasma levels of radioactivity (Section 2.6.5.3).

2.6.5.14 薬物動態試験：排泄：胆汁中

Test Article: tazemetostat hydrobromide

Rats (Excretion Into Bile) **Study Number: DMPKA20[redacted]-060, DMPKA20[redacted]-063** **Location in CTD: 4.2.2.2.2**

Strain/Gender/Number of Animals	Sprague Dawley (Bile duct-cannulated rat)/Male/4			
Feeding Condition	Administration was performed under feeding.			
Vehicle/Formulation	Sterile saline with 1.0% (v/v) 0.1 mol/L HCl			
Method of Administration	IV			
Dose	10 mg/kg			
Sample/Analyte / Assay	Bile/Tazemetostat / LC-MS/MS			
Pharmacokinetic Parameters				
Dose[a] (mg/kg) Route	**$X_{b0\text{-}t}$[b] (ng) 0 to 24 hours**	**Total Dose[c] (mg)**	**A_e[d] (%) 0 to 24 hours**	**CL_{bil}[e] (L/h/kg)**
10 IV	96,633.3±31,880.1	2.7±0.3	3.5±1.0	0.13±0.08

Each parameter is presented as the mean ±SD of 4 animals. Concentrations were expressed as the free base of tazemetostat.

A_e = percentage of tazemetostat dose excreted in bile, $AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, CL_{bil} = biliary clearance, CTD = Common Technical Document, HBr = hydrobromide, HCl = hydrochloric acid, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, v/v = volume per volume, $X_{b0\text{-}inf}$ = cumulative amount of tazemetostat collected in bile from zero time extrapolated to infinite time, $X_{b0\text{-}48h}$ = cumulative amount of tazemetostat collected in bile from zero time to 48 hours, $X_{b0\text{-}t}$ = cumulative amount of tazemetostat collected in bile from zero time to last quantifiable time.

a: Dose of HBr salt.

b: Cumulative amount (ng) of tazemetostat collected up to 24 hours.

c: Total dose = Dose concentration × Dose volume × 0.876 salt factor.

d: Percentage (%) of tazemetostat collected based off total dose administered ($X_{b0\text{-}t}$ / Total Dose ×100).

e: $CL_{bil} = X_{b0\text{-}24h} / AUC_{(0\text{-}inf)}$ / Body weight; assumes that $X_{b0\text{-}24h}$ is approximately equal to $X_{b0\text{-}inf}$.

Additional Information: Quantification was conducted by a qualified LC-MS/MS method. This study also investigated the role of urinary excretion of tazemetostat clearance in rats (Section 2.6.5.13).

2.6.5.14 薬物動態試験：排泄：胆汁中（続き）

Test Article: [^{14}C]tazemetostat hydrobromide

Rats (Excretion Into Bile) **Study Number: 45N-1402** **Location in CTD: 4.2.2.5.1**

Strain/Gender/Number of Animals	Sprague Dawley (Bile duct-cannulated rat)/Male/3					
Feeding Condition	Fasted[a]					
Vehicle/Formulation	0.5% (w/v) methylcellulose and 0.1% Tween 80 in sterile water					
Method of Administration / Dose	Oral, by gavage / 50 mg/kg[b]					
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (7783CDB030-4-Sol)					
Analyte/Assay	Radioactivity/LSC					
Cumulative Excretion of Radioactivity (% of Dose)						
Sample	**Urine (0 – 96 hours)**	**Feces (0 – 96 hours)**	**Bile (0 – 96 hours)**	**Cage Rinse (0 – 72 hours)**	**Cage Wash and Wipe (96 hours)**	**Total Recovery**
	17.9±5.9	24.0±9.4	53.5±5.1	0.3±0.1	0.3±0.2	96.1±6.6

Values represent the mean ±SD of 3 animals.

CTD = Common Technical Document, LSC = liquid scintillation counter, w/v = weight per volume.

a: Food (Certified Rodent Diet) was removed for overnight fasting (at least 12 hours) prior to and for 4 hours following dosing. Water was given freely.

b: The dose was expressed in terms of the free base.

Additional Information: This study also investigated the plasma pharmacokinetics of radioactivity (Section 2.6.5.3), the distribution of radioactivity in organs and tissues (Section 2.6.5.5), and the excretion of radioactivity in urine and feces (Section 2.6.5.13).

2.6.5.15 薬物動態試験：薬物相互作用

非臨床 in vivo における薬物間相互作用試験は検討されていない。

In vitro における薬物間相互作用（CYP 誘導及び CYP 阻害を含む）にかかわる試験はヒト生体試料を用いて評価した（2.6.5.12 及び 2.7.2.1.1 項）。ヒトトランスポーターの基質となるか，又はそれらを阻害する可能性については，2.6.5.16 及び 2.7.2.1.1 項に記した。

2.6.5.16 薬物動態試験：その他

Test Article: tazemetostat hydrobromide

Transport by P-gp or BCRP **Study Number: DMPKA20[redacted]-003** **Location in CTD: 5.3.2.3.2**

Study System	in vitro
Test System	LLC-PK1 and LLC-MDR1 cells for P-gp; MDCK-mock and MDCK-BCRP cells for BCRP
Method	For P-gp and BCRP susceptibility, measurement of bi-directional transport of tazemetostat across monolayers
Assay / Analyte	LC-MS/MS / Tazemetostat
Concentration	Measured concentrations shown in the table below[a]

In Vitro Data for the Transport of Tazemetostat by P-gp or BCRP

Transporter	R_E or CR_E	Tazemetostat					
		4 – 6 µmol/L[a]		18 – 32 µmol/L[a]		41 – 86 µmol/L[a]	
		Without Inhibitor	With Inhibitor	Without Inhibitor	With Inhibitor	Without Inhibitor	With Inhibitor
P-gp	$R_{E\ (LLC\text{-}PK1)}$	1.3	0.9	0.7	0.8	0.9	0.8
	$R_{E\ (LLC\text{-}MDR1)}$	173.7	2.2	41.3	2.8	4.6	1.9
	CR_E	133.6	2.4	59.0	3.5	5.1	2.4
BCRP	$R_{E\ (MDCK\text{-}mock)}$	36.0	3.1	3.9	1.9	1.1	0.8
	$R_{E\ (MDCK\text{-}BCRP)}$	25.3	2.8	3.6	2.0	1.6	1.1
	CR_E	0.7	0.9	0.9	1.1	1.5	1.4

Inhibitor of P-gp: elacridar (5 µmol/L), and inhibitor of BCRP: Ko143 (10 µmol/L).
BCRP = breast cancer resistance protein, CR_E = corrected efflux ratio, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLC-MDR1 = P-gp-transfected LLC-PK1, MDCK-BCRP = BCRP-transfected MDCK, P-gp = P-glycoprotein, R_E = efflux ratio.
a: Measured concentrations.
Additional Information: None.

Test Article: tazemetostat hydrobromide

Inhibition of P-gp　　**Study Number: DMPKA20[redacted]-003**　　**Location in CTD: 5.3.2.3.2**

Study System	in vitro
Test System	LLC-MDR1 cells for P-gp
Method	For P-gp inhibition, measurement of bi-directional transport of probe substrates ([^{3}H]digoxin for P-gp) in the absence and presence of tazemetostat.
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]digoxin
Concentration	Measured concentrations shown in the table below [a]

Treatments; Measured Tazemetostat Concentration (nmol/L) [a]	**$R_{E\ (LLC\text{-}PK1)}$**	**$R_{E\ (LLC\text{-}MDR1)}$**	**R_E Diff**	**Remaining Activity (%)**	**IC_{50} (µmol/L)**
0 nmol/L tazemetostat	4.0	68.3	64.3	100.0	5.9
561.36 nmol/L tazemetostat	2.2	66.3	64.1	99.7	
1791.23 nmol/L tazemetostat	1.5	63.3	61.8	96.1	
5275.00 nmol/L tazemetostat	1.2	38.2	37.0	57.1	
17503.94 nmol/L tazemetostat	1.2	6.0	4.8	6.4	
51317.32 nmol/L tazemetostat	1.3	1.3	0.0	–1.1	
32760.74 nmol/L tazemetostat [b]	1.0 [b]	1.1 [b]	0.1 [b]	–0.9 [b]	
5 µmol/L Elacridar (as P-gp inhibitor)	1.1	1.8	0.7	0.0	NA

R_E Diff = $R_{E\ (LLC\text{-}MDR1)} - R_{E\ (LLC\text{-}PK1)}$.

$R_{E\ (LLC\text{-}MDR1)}$: Efflux ratio of [^{3}H]digoxin in LLC-MDR1 cells.

$R_{E\ (LLC\text{-}PK1)}$: Efflux ratio of [^{3}H]digoxin in LLC-PK1 cells.

Remaining activity (%) at measured tazemetostat concentration =
[1– (R_E Diff at 0 µmol/L tazemetostat – R_E Diff at measured tazemetostat concentration) / (R_E Diff at 0 µmol/L tazemetostat – R_E Diff at 5 µmol/L elacridar)] ×100.

CTD = Common Technical Document, IC_{50} = half-maximal inhibitory concentration, LLC-MDR1 = P-gp-transfected LLC-PK1, NA = not applicable, P-gp = P-glycoprotein, R_E = efflux ratio.

a: Measured concentrations.

b: The data were excluded from the calculation of IC_{50} because of leaky monolayer of LLC-MDR1 cells judged by the results of Lucifer Yellow: The permeability of Lucifer Yellow was measured to monitor the integrity of cell monolayers.

Additional Information: Described on the next page.

Test Article: tazemetostat hydrobromide

Inhibition of BCRP **Study Number: DMPKA20[redacted]-003** **Location in CTD: 5.3.2.3.2**

Study System	in vitro
Test System	MDCK-BCRP cells for BCRP
Method	For BCRP inhibition, measurement of bi-directional transport of probe substrates ([^{3}H]prazosin for BCRP) in the absence and presence of tazemetostat.
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]prazosin
Concentration	Measured concentrations shown in the table below [a]

Treatments; Measured Tazemetostat Concentration (nmol/L) [a]	**$R_{E\ (MDCK\text{-}mock)}$**	**$R_{E\ (MDCK\text{-}BCRP)}$**	**R_E Diff**	**Remaining Activity (%)**	**IC_{50} (µmol/L)**
0 nmol/L tazemetostat	1.1	11.9	10.8	100.0	34.1
667.81 nmol/L tazemetostat	1.5	11.7	10.2	94.5	
1809.12 nmol/L tazemetostat	1.3	10.9	9.6	89.0	
5448.57 nmol/L tazemetostat	1.0	11.5	10.5	97.2	
17364.52 nmol/L tazemetostat	1.0	7.5	6.5	60.6	
54889.27 nmol/L tazemetostat	1.2	5.3	4.1	38.5	
35682.32 nmol/L tazemetostat [b]	1.0 [b]	2.8 [b]	1.8 [b]	17.4 [b]	
10 µmol/L Ko 143 (as BCRP inhibitor)	1.3	1.2	–0.1	0.0	NA

R_E Diff = $R_{E\ (MDCK\text{-}BCRP)}$ – $R_{E\ (MDCK\text{-}mock)}$.
$R_{E\ (MDCK\text{-}BCRP)}$: efflux ratio of [^{3}H]prazosin in MDCK-BCRP cells.
$R_{E\ (MDCK\text{-}mock)}$: efflux ratio of [^{3}H]prazosin in MDCK-mock cells.

Remaining activity (%) at measured tazemetostat concentration =
[1– (R_E Diff at 0 µmol/L tazemetostat – R_E Diff at measured tazemetostat concentration) / (R_E Diff at 0 µmol/L tazemetostat – R_E Diff at 10 µmol/L Ko 143)] ×100.

BCRP = breast cancer resistance protein, CTD = Common Technical Document, IC_{50}= half-maximal inhibitory concentration, MDCK-BCRP = BCRP-transfected MDCK, NA = not applicable, R_E = efflux ratio.

a: Measured concentrations.

b: The data were excluded from the calculation of IC_{50} because less amount of organic solvent was included in the treatment of 200 µmol/L tazemetostat (added concentration) that resulted in the precipitation of tazemetostat and lower measured tazemetostat concentration.

Additional Information: In the amendment report information, tazemetostat P-gp and BCRP IC_{50} derived from reanalysis of the data with added concentration was 45 and >200 µmol/L, respectively, in contrast to the values (5.9 and 34.1 µmol/L, respectively) reported in the original report.

2.6.5.16 薬物動態試験：その他（続き）

Test Article: tazemetostat hydrobromide

Transport by OATP1B1, OATP1B3, OCT2, OAT1, or OAT3 **Study Number: DMPKA2[redacted]-076** **Location in CTD: 5.3.2.3.3**

Study System	in vitro
Test System	Control CHO cells and CHO cells expressing OATP1B1, OATP1B3, OCT2, or OAT1. Control HEK293 cells and HEK293 cells expressing OAT3.
Method	Measurement of uptake of tazemetostat into control cells and cells expressing OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.
Assay / Analyte	LC-MS/MS / Tazemetostat
Concentration	1, 3, and 10 µmol/L

In Vitro Data for the Transport of Tazemetostat by OATP1B1, OATP1B3, OCT2, OAT1, or OAT3

Transporter	Fold Uptake[a]							
	1 µmol/L		3 µmol/L		10 µmol/L		Probe Substrate	
	Tazemetostat	Tazemetostat +Inhibitor	Tazemetostat	Tazemetostat +Inhibitor	Tazemetostat	Tazemetostat +Inhibitor	Substrate	Substrate +Inhibitor
OATP1B1[b]	ND	4.2	3.6	3.9	5.1	5.2	4.4	2.8
OATP1B3[c]	3.0	3.4	3.6	2.3	4.0	4.0	4.3	2.2
OCT2[d]	2.7	1.7	1.8	1.9	1.9	1.6	10.3	1.2
OAT1[e]	2.1	1.9	1.6	1.7	1.8	1.7	3.6	1.9
OAT3[f]	0.7	0.9	0.7	0.8	0.9	1.0	13.7	2.2

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, ND = not determined due to below the limit of quantitation, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter.

a: Fold Uptake = Transporter transfected uptake velocity / Parental uptake velocity.

b: [^{3}H]estrone 3-sulfate is the probe substrate and rifampicin is the selective inhibitor.

c: [^{3}H]estradiol 17β-glucuronide is the probe substrate and rifampicin is the selective inhibitor.

d: [^{14}C]metformin is the probe substrate and quinidine is the selective inhibitor.

e: [^{3}H]*p*-aminohippuric acid is the probe substrate and probenecid is the selective inhibitor.

f: [^{3}H]estrone 3-sulfate is the probe substrate and probenecid is the selective inhibitor.

Additional Information: None.

Test Article: tazemetostat hydrobromide

Inhibition of OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 **Study Number: DMPKA20[redacted]-076** **Location in CTD: 5.3.2.3.3**

Study System	in vitro
Test System	CHO and HEK293 cells
Method	Measurement of uptake of probe substrates into parental cells or cells overexpressing OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 in the presence of tazemetostat or control inhibitor
Assay/Analyte	Scintillation counting of radioactivity/probe substrates of transporters
Concentration	0 to 100 or 300 µmol/L

In Vitro Data for the Inhibition of OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 by Tazemetostat

Transporter	Probe Substrate	Probe Substrate Concentration (µmol/L)	Fold Uptake of Probe Substrate in the Absence of Inhibitor	Selective Inhibitor (µmol/L)	Activity Remaining (%) in the Presence of Selective Inhibitor	Tazemetostat IC_{50} (µmol/L)
OATP1B1	[^{3}H]estrone 3-sulfate	0.1	15.4	Rifampicin (50)	27.8	19.7
OATP1B3	[^{3}H]estradiol 17β-glucuronide	0.1	4.7	Rifampicin (50)	8.0	14.4
OCT2	[^{14}C]metformin	8.0	8.6	Quinidine (100)	–1.0	14.7
OAT1	[^{3}H]PAH	0.5	3.3	Probenecid (100)	15.3	>100
OAT3	[^{3}H]estrone 3-sulfate	0.1	34.9	Probenecid (100)	3.9	10.0

Fold uptake = uptake in transporter expressing cells/uptake in parental cells. Activity remaining (%) = (fold uptake with inhibitor/fold uptake without inhibitor) ×100.

CTD = Common Technical Document, IC_{50} = half-maximal inhibitory concentration, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, PAH = *p*-aminohippuric acid.

Additional Information: None.

2.6.5.16 薬物動態試験：その他（続き）

Test Article: tazemetostat hydrobromide

Inhibition of BSEP **Study Number: DMPKA20[redacted]-118** **Location in CTD: 5.3.2.3.4**

Study System	in vitro
Test System	BSEP-enriched membrane vesicles
Method	Measurement of ATP-dependent transport of [^{3}H]taurocholic acid into BSEP-enriched membrane vesicles in the absence and presence of tazemetostat
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]taurocholic acid
Concentration	0 to 100 µmol/L

Treatments	ATP-Dependent Transport (pmol/mg/min)	Activity Remaining (%)	IC_{50} (µmol/L)
[^{3}H]taurocholic acid	14.83	100.0	20.0
[^{3}H]taurocholic acid + 0.3 µmol/L tazemetostat	13.54	91.3	
[^{3}H]taurocholic acid + 1 µmol/L tazemetostat	10.02	67.6	
[^{3}H]taurocholic acid + 3 µmol/L tazemetostat	11.83	79.8	
[^{3}H]taurocholic acid + 10 µmol/L tazemetostat	10.76	72.6	
[^{3}H]taurocholic acid + 30 µmol/L tazemetostat	4.79	32.3	
[^{3}H]taurocholic acid + 100 µmol/L tazemetostat	2.74	18.5	
[^{3}H]taurocholic acid + 100 µmol/L cyclosporine A	9.21	62.1	NA

Percentage of activity remaining = (taurocholic acid ATP-dependent transport with tazemetostat/taurocholic acid ATP-dependent transport without tazemetostat) ×100.

ATP = adenosine triphosphate, BSEP = bile salt export pump, CTD = Common Technical Document, IC_{50} = half-maximal inhibitory concentration, NA = not applicable.

Additional Information: None.

2.6.5.16 薬物動態試験：その他（続き）

Test Article: tazemetostat hydrobromide

Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102

Inhibition of OCT1, OCT2, MATE1, and MATE2-K **Location in CTD: 5.3.2.3.5**

Study System	in vitro	
Test System	Control MDCK-II cells and MDCK-II cells expressing OCT1, OCT2, MATE1, or MATE2-K	
Method	Measurement of net uptake of the probe substrate by OCT1, OCT2, MATE1, and MATE2-K in the absence and presence of tazemetostat	
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]MPP+ (OCT1) and [^{14}C]metformin (OCT2, MATE1, and MATE2-K)	
Concentration	20 µmol/L	
In Vitro Data for the Inhibition of OCT1, OCT2, MATE1, and MATE2-K by Tazemetostat		
Transporter	**Test Conditions**	**Inhibition (%)**
OCT1	20 µmol/L tazemetostat	5.19±12.6
	1000 µmol/L quinidine	99.5±1.51
OCT2	20 µmol/L tazemetostat	12.3±13.3
	1000 µmol/L quinidine	97.8±0.549
MATE1	20 µmol/L tazemetostat	87.7±1.16
	10 µmol/L cimetidine	91.2±0.617
MATE2-K	20 µmol/L tazemetostat	84.6±0.36
	10 µmol/L cimetidine	74.9±2.85

Probe substrate for each transporter was 2 µmol/L MPP+ (OCT1), 10 µmol/L metformin (OCT2, MATE1, and MATE2-K). Selective inhibitor for each transporter was 1000 µmol/L quinidine (OCT1 and OCT2) and 10 µmol/L cimetidine (MATE1 and MATE2-K). Data are expressed as mean ±SD (n=3).

Percentage of inhibition = 100– [(transporter mediated uptake in the presence of inhibitor/transporter mediated uptake in the absence of inhibitor) ×100].

CTD = Common Technical Document, MATE = multidrug and toxin extrusion, MPP+ = 1-methyl-4-phenylpyridinium, OCT = organic cation transporter.

Additional Information: None.

Test Article: tazemetostat hydrobromide

Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102

Location in CTD: 5.3.2.3.5

Inhibition of MATE1 and MATE2-K (IC_{50})

Study System	in vitro
Test System	Control MDCK-II cells and MDCK-II cells expressing MATE1 or MATE2
Method	Measurement of net uptake of the probe substrate by MATE1 and MATE2-K in the absence and presence of tazemetostat
Assay/Analyte	Scintillation counting of radioactivity/[^{14}C]metformin (MATE1 and MATE2-K)
Concentration	0 to 30 µmol/L

In Vitro Data for the Inhibition of MATE1 and MATE2-K by Tazemetostat

Transporter	Concentration	Inhibition (%)	Tazemetostat IC_{50} (µmol/L)
MATE1	0 µmol/L tazemetostat	NA	2.65
	0.3 µmol/L tazemetostat	13.2±10.9	
	1 µmol/L tazemetostat	20.6±9.93	
	3 µmol/L tazemetostat	61.0±6.69	
	10 µmol/L tazemetostat	81.4±0.445	
	15 µmol/L tazemetostat	85.9±2.70	
	30 µmol/L tazemetostat	92.6±1.42	
	10 µmol/L cimetidine	92.9±0.228	NA
MATE2-K	0 µmol/L tazemetostat	NA	1.89
	0.3 µmol/L tazemetostat	–7.90±8.97	
	1 µmol/L tazemetostat	14.5±15.7	
	3 µmol/L tazemetostat	58.1±4.05	
	10 µmol/L tazemetostat	79.4±6.14	
	15 µmol/L tazemetostat	86.6±1.80	
	30 µmol/L tazemetostat	96.9±1.44	
	10 µmol/L cimetidine	68.4±12.1	NA

Probe substrate for the transporter was 10 µmol/L metformin. Data are expressed as mean ±SD (n=3).

Percentage of inhibition = 100– [(transporter mediated uptake in the presence of inhibitor/transporter mediated uptake in the absence of inhibitor) ×100].

CTD = Common Technical Document, IC_{50} = half-maximal inhibitory concentration, MATE = multidrug and toxin extrusion, NA = not applicable.

Additional Information: None.

Test Article: EPZ-6930, EPZ006931, and EPZ034163

Inhibition of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K　　**Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102**　　**Location in CTD: 5.3.2.3.5**

Study System	in vitro	
Test System	Control MDCK-II and MDCK-II cells expressing OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K	
Method	Measurement of net uptake of the probe substrate by OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K in the absence and presence of EPZ-6930, EPZ006931, and EPZ034163	
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]CCK-8 (OATP1B3), [^{3}H]estradiol 17β-glucuronide (OATP1B1), [^{3}H]MPP+ (OCT1), [^{14}C]metformin (OCT2, MATE1, and MATE2-K), and [^{3}H]*p*-aminohippurate (OAT1 and OAT3)	
Concentration	EPZ-6930: 25 µmol/L, EPZ006931: 10 µmol/L, EPZ034163: 10 µmol/L	
In Vitro Data for the Inhibition of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K by Tazemetostat Metabolites		
Transporter	**Test Conditions**	**Inhibition (%)**
OAT1	25 µmol/L EPZ-6930	–3.15±10.3
	10 µmol/L EPZ006931	7.37±5.72
	10 µmol/L EPZ034163	14.3±7.83
	100 µmol/L probenecid	86.8±1.40
OAT3	25 µmol/L EPZ-6930	–8.98±4.09
	10 µmol/L EPZ006931	17.6±16.1
	10 µmol/L EPZ034163	6.38±3.81
	100 µmol/L probenecid	105±4.99
OCT1	25 µmol/L EPZ-6930	9.11±13.0
	10 µmol/L EPZ006931	3.21±6.41
	10 µmol/L EPZ034163	8.39±10.4
	1000 µmol/L quinidine	92.8±1.41
OCT2	25 µmol/L EPZ-6930	25.7±4.81
	10 µmol/L EPZ006931	8.94±5.82
	10 µmol/L EPZ034163	16.6±11.3
	1000 µmol/L quinidine	97.8±0.549
OATP1B1	25 µmol/L EPZ-6930	26.2±8.390
	10 µmol/L EPZ006931	23.4±7.050
	10 µmol/L EPZ034163	16.3±5.380
	100 µmol/L rifampicin	97.7±0.675

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Test Article: EPZ-6930, EPZ006931, and EPZ034163

Inhibition of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K **Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102** **Location in CTD: 5.3.2.3.5**

Transporter	Test Conditions	Inhibition (%)
OATP1B3	25 µmol/L EPZ-6930	27.2±14.8
	10 µmol/L EPZ006931	0.0901±14.0
	10 µmol/L EPZ034163	11.4±7.80
	100 µmol/L rifampicin	98.9±1.39
MATE1	25 µmol/L EPZ-6930	79.9±0.507
	10 µmol/L EPZ006931	65.4±2.24
	10 µmol/L EPZ034163	48.7±6.38
	10 µmol/L cimetidine	90.2±1.62
MATE2-K	25 µmol/L EPZ-6930	64.4±4.75
	10 µmol/L EPZ006931	35.8±8.16
	10 µmol/L EPZ034163	23.0±7.65
	10 µmol/L cimetidine	119±NA

Probe substrate for each transporter was 2 µmol/L *p*-aminohippurate (OAT1), 10 µmol/L *p*-aminohippurate (OAT3), 2 µmol/L MPP+ (OCT1), and 10 µmol/L metformin (OCT2). Probe substrate for each transporter was 2 µmol/L estradiol-17β-glucuronide (OATP1B1), 2 µmol/L CCK-8 (OATP1B3), and 10 µmol/L metformin (MATE1 and MATE2-K). Data are expressed as mean ±SD (n=3).

Percentage of inhibition = 100 – [(transporter mediated uptake in the presence of inhibitor/transporter mediated uptake in the absence of inhibitor) ×100].

CTD = Common Technical Document, MATE = multidrug and toxin extrusion, MPP+ = 1-methyl-4-phenylpyridinium, NA = not applicable, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter.

Additional Information: None.

Test Article: EPZ-6930

Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102

Location in CTD: 5.3.2.3.5

Inhibition of MATE1 and MATE2-K (IC_{50})

Study System	in vitro
Test System	Control MDCK-II cells and MDCK-II cells expressing MATE1 or MATE2
Method	Measurement of net uptake of the probe substrate by MATE1 and MATE2-K in the absence and presence of EPZ-6930
Assay/Analyte	Scintillation counting of radioactivity/[^{14}C]metformin (MATE1 and MATE2-K)
Concentration	0 to 50 µmol/L

In Vitro Data for the Inhibition of MATE1 and MATE2-K by EPZ-6930

Transporter	Concentration	Inhibition (%)	EPZ-6930 IC_{50} (µmol/L)
MATE1	0 µmol/L EPZ-6930	NA	4.79
	0.3 µmol/L EPZ-6930	13.5±6.68	
	1 µmol/L EPZ-6930	22.2±2.72	
	3 µmol/L EPZ-6930	43.1±1.47	
	10 µmol/L EPZ-6930	69.4±1.56	
	25 µmol/L EPZ-6930	81.8±1.19	
	50 µmol/L EPZ-6930	88.8±1.15	
	10 µmol/L cimetidine	89.1±0.228	NA
MATE2-K	0 µmol/L EPZ-6930	NA	12.1
	0.3 µmol/L EPZ-6930	15.9±10.5	
	1 µmol/L EPZ-6930	11.4±15.9	
	3 µmol/L EPZ-6930	34.6±7.51	
	10 µmol/L EPZ-6930	49.7±4.50	
	25 µmol/L EPZ-6930	68.1±9.19	
	50 µmol/L EPZ-6930	77.4±2.56	
	10 µmol/L cimetidine	65.7±1.96	NA

Probe substrate for the transporter was 10 µmol/L metformin. Data are expressed as mean ±SD (n=3).

Percentage of inhibition = 100– [(transporter mediated uptake in the presence of inhibitor/transporter mediated uptake in the absence of inhibitor) ×100].

CTD = Common Technical Document, IC_{50} = half-maximal inhibitory concentration, MATE = multidrug and toxin extrusion, NA = not applicable.

Additional Information: None.

Test Article: EPZ-6930, EPZ006931, and EPZ034163

Inhibition of BCRP and P-gp **Study Number: OPT-20[redacted]-072, OPT-20[redacted]-074, OPT-10[redacted]-101, OPT-20[redacted]-102** **Location in CTD: 5.3.2.3.5**

Study System	in vitro
Test System	MDCK-II cells expressing BCRP or P-gp
Method	Measurement of bi-directional transport of probe substrate by BCRP and P-gp across cells in the absence and presence of EPZ-6930, EPZ006931 and EPZ034163
Assay/Analyte	Scintillation counting of radioactivity/[^{3}H]prazosin or [^{3}H]quinidine
Concentration	EPZ-6930: 25 µmol/L, EPZ006931: 10 µmol/L, EPZ034163: 10 µmol/L

In Vitro Data for the Inhibition of BCRP and P-gp by Tazemetostat Metabolites

Transporter	Test Conditions	$P_{app, B-A}$ ($\times 10^{-6}$ cm/s)	$P_{app, A-B}$ ($\times 10^{-6}$ cm/s)	Efflux Ratio	Inhibition (%)
BCRP	Vehicle	42.3±1.64	6.60±1.50	6.41±0.248	NA
	25 µmol/L EPZ-6930	50.7±3.19	7.66±0.477	6.62±0.417	–3.70±7.70
	10 µmol/L EPZ006931	50.5±5.90	9.46±0.775	5.34±0.624	19.8±11.5
	10 µmol/L EPZ034163	48.3±3.52	7.69±0.355	6.28±0.457	2.41±8.45
	1 µmol/L Ko 143	24.9±0.723	15.9±1.38	1.57±0.0456	89.5±0.841
P-gp	Vehicle	86.6±13.7	4.82±0.573	18.0±2.85	NA
	25 µmol/L EPZ-6930	78.1±1.00	8.98±0.802	8.70±0.112	54.6±0.659
	10 µmol/L EPZ006931	79.9±4.72	7.11±0.231	11.2±0.664	39.7±3.91
	10 µmol/L EPZ034163	89.2±7.33	4.70±0.759	19.0±1.56	–5.84±9.19
	3 µmol/L elacridar	32.7±3.67	15.6±1.07	2.09±0.235	93.6±1.38

Probe substrate for BCRP and P-gp was 2 µmol/L prazosin and 0.1 µmol/L quinidine, respectively. Data are expressed as mean ±SD (n=3).

Efflux ratio = ($P_{app, B-A}$)/($P_{app, A-B}$).

Percentage of inhibition = 100 – [(Efflux ratio in the presence of the inhibitor/efflux ratio in the absence of the inhibitor) ×100].

BCRP = breast cancer resistance protein, CTD = Common Technical Document, NA = not applicable, $P_{app, A-B}$ = apparent permeability in the apical to basolateral direction, $P_{app, B-A}$ = apparent permeability in the basolateral to apical direction, P-gp = P-glycoprotein.

Additional Information: None.

2.6.5.16 薬物動態試験：その他（続き）

Test Article: tazemetostat hydrobromide

Transport by OATP1B1, OATP1B3 or MATE1 **Study Number: OPT-20[redacted]-073 and OPT-20[redacted]-103** **Location in CTD: 5.3.2.3.6**

Study System	in vitro		
Test System	Control MDCK-II cells and MDCK-II cells expressing OATP1B1, OATP1B3, or MATE1		
Method	Measurement of uptake of tazemetostat into control MDCK-II cells and MDCK-II cells expressing OATP1B1, OATP1B3, or MATE1		
Assay / Analyte	LC-MS/MS / Tazemetostat		
Concentration	1, 3, and 10 µmol/L		
In Vitro Data for the Transport of Tazemetostat by OATP1B1, OATP1B3 and MATE1			
Transporter	**Test Conditions**	**Cellular Accumulation (Transporter Expressing Cell) (pmol/min/cm^2)**	**Cellular Accumulation (Control Cell) (pmol/min/cm^2)**
OATP1B1	1 µmol/L tazemetostat	6.21±0.450	4.59±1.07
	3 µmol/L tazemetostat	18.3±1.51	22.9±7.66
	10 µmol/L tazemetostat	77.8±3.20	76.9±6.27
	10 µmol/L tazemetostat + 100 µmol/L rifampicin	108±4.45	109±2.24
OATP1B3	1 µmol/L tazemetostat	6.36±1.37	4.23±0.381
	3 µmol/L tazemetostat	20.6±0.937	18.2±0.268
	10 µmol/L tazemetostat	77.3±10.4	84.7±16.4
	10 µmol/L tazemetostat + 100 µmol/L rifampicin	112±10.1	97.5±0.679
MATE1	1 µmol/L tazemetostat	1.31±0.243	0.883±0.0937
	3 µmol/L tazemetostat	6.98±0.451	4.63±0.878
	10 µmol/L tazemetostat	25.3±1.22	15.2±2.07
	10 µmol/L tazemetostat + 10 µmol/L cimetidine	24.0±2.18	18.5±4.67

Data are expressed as mean ±SD (n=3). Probe substrates were: OATP1B1; 2 µmol/L [^{3}H]estradiol 17β-glucuronide, OATP1B3; 2 µmol/L [^{3}H]CCK-8, and MATE1; 10 µmol/L [^{14}C]metformin. Selective inhibitors were: OATP1B1; 100 µmol/L rifampicin, OATP1B3; 100 µmol/L rifampicin, and MATE1; 10 µmol/L cimetidine.

CCK-8 = cholecystokinin octapeptide, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, MATE = multidrug and toxin extrusion, OATP = organic anion transporting polypeptide.

Additional Information: None.