2.6.4 薬物動態試験の概要文

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略号一覧

略号	省略していない表現（英）	省略していない表現（日）
ADME	absorption, distribution, metabolism and excretion	吸収・分布・代謝・排泄
AO	aldehyde oxidase	アルデヒドオキシダーゼ
AUC0-t	area under the drug plasma concentration-time curve (time 0 to t where t is a defined time point after administration)	血漿中薬物濃度-時間曲線下面積（0～t 時間）
AUC0-t, ss	area under the drug plasma concentration-time curve (time 0 to t where t is a defined time point after administration) at steady state	定常状態における血漿中薬物濃度-時間曲線下面積（0～t 時間）
AUCinf	area under the drug plasma concentration-time curve (time 0 to infinity)	血漿中薬物濃度-時間曲線下面積（0～無限大時間）
AUClast	area under the drug plasma concentration-time curve (time 0 to the last measurable concentration sampling time)	血漿中薬物濃度-時間曲線下面積（0～最終定量可能時点）
AUCtau, ss	area under the drug plasma concentration-time curve (time 0 to the end of the dosing interval) at steady state	定常状態における血漿中薬物濃度-時間曲線下面積（0～投与間隔時間）
BBB	blood-brain barrier	血液脳関門
CLblood	systemic blood clearance	全身血液クリアランス
CL/F	apparent clearance	見かけのクリアランス
CLplasma	systemic plasma clearance	全身血漿クリアランス
Cmax	maximal drug plasma concentration	最高血漿中薬物濃度
Cmax, ss	maximal drug plasma concentration at steady state	定常状態における最高血漿中薬物濃度
CSF	cerebrospinal fluid	脳脊髄液
CYP	cytochrome P450	チトクローム P450
F	-	生物学的利用率
HPLC	high performance liquid chromatography	高速液体クロマトグラフィー
HPLC-RA	high performance liquid chromatography coupled to radioactivity detection	放射能検出器を接続した高速液体クロマトグラフィー
HPLC-UV	high performance liquid chromatography coupled to ultraviolet absorbance detection	紫外線吸光度検出器を接続した高速液体クロマトグラフィー
IC50	half maximal (50%) inhibitory concentration	50%阻害濃度
LC-MS	liquid chromatography-mass spectrometry	液体クロマトグラフィー質量分析
LC-MS/MS	liquid chromatography-tandem mass spectrometry	液体クロマトグラフィータンデム質量分析
LLOQ	lower limit of quantification	定量下限
LSC	liquid scintillation counter	液体シンチレーションカウンター
MET	mesenchymal-epithelial transition factor	間葉上皮転換因子
MS	mass spectrometry	質量分析
NA	not applicable	該当なし
ND	not detected	検出されず
NMR	nuclear magnetic resonance	核磁気共鳴
NOAEL	no observed adverse effect level	無毒性量

略号	省略していない表現（英）	省略していない表現（日）
PXR	pregnane X receptor	-
QWBA	quantitative whole body autoradiography	定量的全身オートラジオグラフィー
T1/2	elimination half life	消失半減期
T1/2α	α-phase elimination half life	初期分布相の消失半減期
T1/2β	β-phase elimination half life	終末相の消失半減期
Tmax	time to reach the maximum drug plasma concentration following drug administration	最高血漿中薬物濃度到達時間
Vss	distribution volume at steady state	定常状態における分布容積
Vz/F	apparent distribution volume	見かけの分布容積
XO	xanthine oxidase	キサンチンオキシダーゼ

用語の定義一覧

用語	定義
X1101 試験	INC280X1101 試験は，本書では X1101 試験で表記した。
X2106 試験	INC280X2106 試験は，本書では X2106 試験で表記した。
A2201 試験	INC280A2201 試験は，本書では A2201 試験で表記した。

1 まとめ

マウス（CD1 albino），ラット［Hanover Wister（albino） / Sprague Dawley（albino） / Long Evans（partially pigmented）］，ウサギ，イヌ（Beagle）及びサル（Cynomolgus）における吸収，分布，代謝及び排泄（ADME）について，放射性標識（^{14}C）又は非標識カプマチニブを用いて *in vitro* 及び *in vivo* で検討した。Table 1-1 に薬物動態試験，Table 1-2 にトキシコキネティクス試験の一覧を示す。ラット及びサルについては，薬物動態試験と毒性試験とで同一の系統を用いた。

Table 1-1 薬物動態試験一覧

動物種	放射性標識	投与量 (mg/kg)	投与剤型	投与経路	投与期間	報告書番号
マウス	非標識	2.5 (free base)	溶液	静脈内	単回	INCYTE-DMB-08.124.1
ラット	非標識	5	溶液	静脈内	単回	INCYTE-DMB-08.128.1
		5	懸濁液	経口	単回	INCYTE-DMB-08.128.1
	非標識	0.25	溶液	静脈内	単回	INCYTE-DMB-08.129.1
	^{14}C	3	溶液	静脈内	単回	DMPK R1100027-01
		10	溶液	経口	単回	DMPK R1100027-01
	^{14}C	10	溶液	経口	単回	DMPK R1300834-01
	^{14}C	40	溶液	経口	単回 / 反復	DMPK R1600074-01
イヌ	非標識	2.5	溶液	静脈内	単回	INCYTE-DMB-08.134.1
		5	溶液	経口	単回	INCYTE-DMB-08.134.1
	非標識	50	カプセル / 錠剤	経口	単回	DMPK R1300725
サル	非標識	2.5	溶液	静脈内	単回	INCYTE-DMB-08.131.1
		2.5，10	溶液	経口	単回	INCYTE-DMB-08.131.1
	^{14}C	3	溶液	静脈内	単回	DMPK R1300820
		30	溶液	経口	単回	DMPK R1300820
	非標識	61.5	溶液	経口	単回	DMPK R1600337
ヒト	^{14}C	600	カプセル	経口	単回	CINC280X2106

Source: [Table 2.6.5.3A-INCYTE-DNB-08.124.1], [Table 2.6.5.3B-INCYTE-DNB-08.128.1], [Table 2.6.5.5A-INCYTE-DMB-08.129.1], [Table 2.6.5.3C- DMPK R1100027-01], [Table 2.6.5.5C- DMPK R1300834-01], [Table 2.6.5.4A- DMPK R1600074-01], [Table 2.6.5.3D-INCYTE-DMB-08.134.1], [Table 2.6.5.3E- DMPK R1300725], [Table 2.6.5.3F-INCYTE-DMB-08.131.1], [Table 2.6.5.3G- DMPK R1300820], [Table 2.6.5.3H- DMPK R1600337], [5.3.3.1-1-X2106 試験]

Table 1-2 トキシコキネティクス試験一覧

動物種	放射性標識	投与量 (mg/kg)	投与剤型	投与経路	投与期間	報告書番号
マウス	非標識	100，300，600	懸濁液	経口（強制）	単回	T07-11-12
	非標識	20，40，80	懸濁液	経口（強制）	反復（6 日間）	T08-02-16
	非標識	100，300，600	懸濁液	経口（強制）	反復（8 日間）	T07-12-02
ラット	非標識	20，40，80，200	懸濁液	経口（強制）	反復（9 日間）	T08-02-12
	非標識	雄: 20，60，120 雌: 10，30，60	懸濁液	経口（強制）	反復（4 週間）	T08-04-11
	非標識	60，90	懸濁液	経口（強制）	反復（6 週間）	1370733
	非標識	雄: 20，40，60，90 雌: 10，20，30，45	懸濁液	経口（強制）	反復（13 週間）	T10-02-02
	非標識	1，10，30	懸濁液	経口（強制）	反復（12 日間）	1170160

動物種	放射性標識	投与量 (mg/kg)	投与剤型	投与経路	投与期間	報告書番号
	非標識	雄: 20，60 雌: 10，30	懸濁液	経口（強制）	反復（4 週間）	1570059
	非標識	60，90	懸濁液	経口（強制）	反復（4 週間）	1170512
ウサギ	非標識	1，5，60	懸濁液	経口（強制）	反復（14 日間）	1170159
	非標識	5，20，60，120	懸濁液	経口（強制）	反復（14 日間）	1170158
サル	非標識	20，50，150，600	懸濁液	経口（経鼻強制）	単回	T07-11-13
	非標識	30，75，150	懸濁液	経口（経鼻強制）	反復（4 週間）	T08-01-08
	非標識	10，30，75	懸濁液	経口（強制）	反復（13 週間）	1070417

Source: [Table 2.6.7.5-T07-11-12], [Table 2.6.7.6-T08-02-16], [Table 2.6.7.6-T07-12-02], [Table 2.6.7.6A- T08-02-12], [Table 2.6.7.7A-T08-04-11], [Table 2.6.7.17C-1370733], [Table 2.6.7.7B-T10-02-02], [Table 2.6.7.13A-1170160], [Table 2.6.7.17E-1570059], [Table 2.6.7.17C-1170512], [Table 2.6.7.13B-1170159], [Table 2.6.7.11-1170158], [Table 2.6.7.5-T07-11-13], [Table 2.6.7.7C-T08-01-08], [Table 2.6.7.7D-1070417]

吸収

カプマチニブを単回又は反復経口投与したときの最高血漿中薬物濃度到達時間（Tmax）は，ラット，イヌ及びサルでは 0.25～7 時間，ヒトでは 1～2 時間であった。カプマチニブの吸収率は，ラットで 51.1%，サルではほぼ完全であった。ラット，イヌ及びサルにカプマチニブを静脈内又は経口投与したとき，経口バイオアベイラビリティは動物間又は試験間で変動が認められ，ラットで 66.2%～114%，イヌで 28%，サルで 24%～108%であった。マウス及びラットにおいては，カプマチニブの曝露量に性差が認められたが，サルやヒトにおいて性差は認められなかった。

分布

マウス，ラット，イヌ及びサルでの血漿中非結合型分率は 3.0%～17.8%であった。ヒトでの血漿中非結合型分率は 4.0%であり，濃度依存性は認められなかった。カプマチニブの血液／血漿分布比は，ラットで 1.1，サルで 1.4 と同程度であったが，イヌでは 7.9 であり，ラット及びサルと比較して高かった。ヒトでの血液／血漿分布比は 1.5 であったが，より高濃度では 0.9 に減少した。

マウス，ラット，イヌ，サルにおいて，カプマチニブ及び代謝物はすべての組織に広範囲かつ速やかに分布した。カプマチニブ関連物質は，眼の脈絡膜や毛様体といったメラニン含有組織に長時間残留した。また，ラット及びサルにおいて，カプマチニブ及び放射性標識成分は血液脳関門を通過する可能性があると示唆された。

代謝

カプマチニブをラット，サル及びヒトに経口投与したとき，血漿中ではいずれの動物種においても未変化体が最も多く，代謝物については，ラット及びヒトでは CMN288（M16），サルでは CMN290（M8）が最も多くみられた。

すべての動物種におけるカプマチニブの代謝は，主に *C*-酸化体［CNN019（M3），M4，M5，CMN290（M8）及び CMN288（M16）］，*N*-酸化体［CJH800（M21）］及びカルボン酸体［CMC583（M13）］の生成で特徴づけられた。水酸化体［CMN290（M8）］やイミダゾ-トリア

ジノン体（ラクタム）［CMN288（M16）］は，イヌを除くすべての動物種の肝細胞における主代謝物であった。アミド結合の加水分解及びカルボン酸体である CMC583（M13）の生成は，イヌにおいて主代謝経路であったが，マウス，ラット，サル及びヒトにおける寄与は低かった。水素化体（M26），カルビノールアミド体［CNJ292（M17）］及び *N*-脱アルキル体［CNJ294（M18）］は，ヒトでのみ生成された。カプマチニブの酸化的代謝にはチトクローム P450（CYP）3A4 が主に関与していること，CMN288（M16）及び CJK530（M19）は，ヒト肝細胞質の酵素であるアルデヒドオキシダーゼ（AO）及びキサンチンオキシダーゼ（XO）によって生成され，CMN288（M16）の生成には主に AO が関与していることが示された。

CMN290（M8）及び CNJ294（M18）は MET 阻害活性を有することが示されたが，CMN288（M16）では MET 阻害活性はみられなかった。全 MET 阻害活性に対するこれらの代謝物の寄与はごくわずかであった。

排泄

ラット，サル及びヒトに[^{14}C]カプマチニブを単回経口投与したとき，放射能の大部分は糞便中に排泄され，尿中への排泄はわずかであった。

胆管カニューレ挿入ラットに[^{14}C]カプマチニブを単回静脈内投与したとき，放射能の 66.3%が胆汁中に，12.1%が尿中に認められた。また，放射能の 9.23%が糞便中に認められたことから，カプマチニブ関連物質の直接の小腸分泌が示唆された。胆汁中に未変化体は認められず，代謝物の胆汁中排泄がラットにおける主排泄経路であると考えられた。投与量の 2.30%がカプマチニブとして糞便中に認められたことから，未変化体の小腸分泌も示唆された。

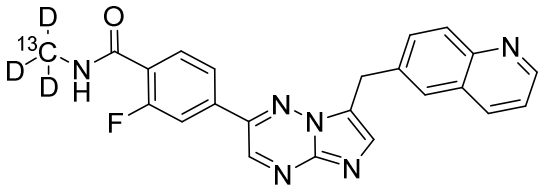
2 分析法

2.1 安定同位体及び放射性標識体

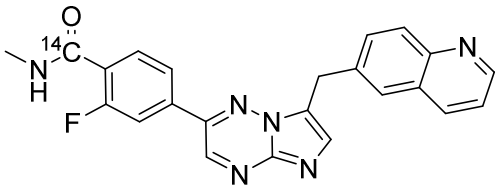
2.1.1 カプマチニブ

安定同位体標識体[$^{13}CD_3$]カプマチニブ及び放射性標識体[^{14}C]カプマチニブはノバルティス ファーマ社（スイス・バーゼル）で合成されたものを使用した。[$^{13}CD_3$]カプマチニブ及び[^{14}C]カプマチニブの化学構造式と標識位置を Figure 2-1 に示す。[$^{13}CD_3$]カプマチニブの化学的純度は 99.5%以上（紫外線吸光度検出器を接続した高速液体クロマトグラフィー，HPLC-UV），質量純度は 99%以上（質量分析法，MS）であった [Table 2.6.5.2A-DMPK R1000645 (SSE 200-1)]。^{14}C-カプマチニブの化学的純度は 99.4%以上（HPLC-UV），放射性純度は 99.0%以上（放射能検出器を接続した高速液体クロマトグラフィー，HPLC-RA）であった [Table 2.6.5.2B-DMPK R1000579 (RSE 493-1)]。

Figure 2-1 [$^{13}CD_3$]カプマチニブ及び[^{14}C]カプマチニブの構造式及び標識部位



[$^{13}CD_3$]カプマチニブ

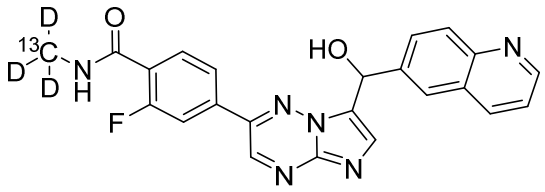


[^{14}C]カプマチニブ

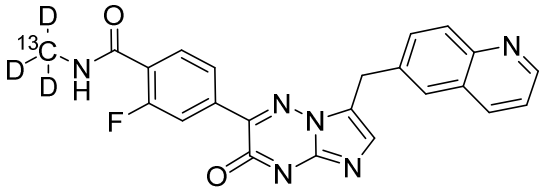
2.1.2 カプマチニブ代謝物

[$^{13}CD_3$]カプマチニブ代謝物の化学構造式と標識位置を Figure 2-2 に示す。[$^{13}CD_3$]カプマチニブ代謝物の化学的純度は 98.5%以上（HPLC-UV），質量純度は 99%以上（MS）であった [Table 2.6.5.2J-DMPK R1000646 (SSE 201-1)]，[Table 2.6.5.2K-DMPK R1400283 (SSE 270-1)]，[Table 2.6.5.2L-DMPK R1400841-01 (SSE 281-1)]，[Table 2.6.5.2M-DMPK R1400842 (SSE 282-1)]。これらの安定同位体カプマチニブ代謝物は，非臨床薬物動態試験の生物学的定量分析の内標準物質として用いた。[$^{13}CD_3$]CMN290（M8）及び[$^{13}CD_3$]CMN288（M16）については，臨床試験の生物学的定量分析の内標準物質としても用いられた。

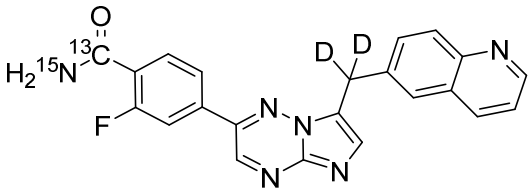
Figure 2-2 [$^{13}CD_3$]カマチニブ代謝物の構造式及び標識部位



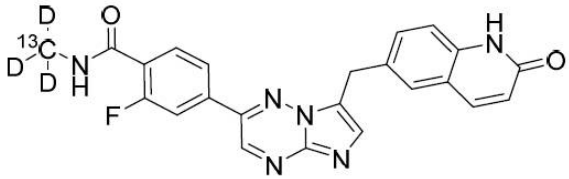
[$^{13}CD_3$]CMN290 (M8)



[$^{13}CD_3$]CMN288 (M16)



[$^{13}C^{15}ND_2$]CNJ294 (M18)



[$^{13}CD_3$]CJK530 (M19)

2.2 同位体標識体の分析

血液，血漿，胆汁，尿，糞便，死骸，ケージ洗浄液及び投与溶液の放射能は液体シンチレーションカウンター（LSC）で測定した。臓器及び組織の放射能は，定量的全身オートラジオグラフィ（QWBA）で測定し，比較定量法により定量した。

2.3 未変化体の分析

マウス，ラット，ウサギ，イヌ，サル及びヒトの血漿中カプマチニブ濃度は，液体クロマトグラフィータンデム質量分析（LC-MS/MS）を用いて定量した。[$^{13}CD_3$]カプマチニブは生物学的定量分析の内標準物質として用いた。各動物種における血漿中カプマチニブ濃度の定量法を Table 2-1 に示す。

Table 2-1 血漿中カプマチニブ濃度の定量法

動物種	定量法	定量下限（LLOQ）	長期安定性
マウス	LC-MS/MS	10.0 ng/mL	57 日間（−60°C 以下）
ラット	LC-MS/MS	4 ng/mL, 5 ng/mL	85 日間（−80°C 以下）
ウサギ	LC-MS/MS	1.00 ng/mL	69 日間（−60°C 以下）
イヌ	LC-MS/MS	1.00 ng/mL	40 日間（−70°C 以下）
サル	LC-MS/MS	8 ng/mL, 10 ng/mL	154 日間（−60°C 以下）

Source: [Table 2.6.5.2C-DMPK R1100266F], [Table 2.6.5.2D-INCYTE-DMB-08.119.1], [Table 2.6.5.2E -DMPK R1100266C], [Table 2.6.5.2F-DMPK R1100266D], [Table 2.6.5.2G-DMPK R1300899], [Table 2.6.5.2H-INCYTE-DMB-08.120.1], [Table 2.6.5.2I-DMPK R1100266]

2.4 代謝物の同定及び構造解析

ラット，サル及びヒト ADME 試験における血漿，尿，糞便及び胆汁中の代謝物濃度や代謝物パターンは，HPLC-RA を用いて測定した（Table 2.6.5.3C-DMPK R1100027-01, Table 2.6.5.3G-DMPK R1300820, 5.3.3.1-1-X2106 試験）。代謝物の構造決定には，液体クロマトグラフィー質量分析（LC-MS）又は LC-MS/MS を用いた。

代謝物の同定には，非標識体の標準品を用いた。代謝物 CNN019（M3），CMN290（M8），CMC583（M13），CMN288（M16），CNJ292（M17），CNJ294（M18），CJK530（M19）及び CJH800（M21）は HPLC，核磁気共鳴（NMR）及び MS を用いて同定された [Table 2.6.5.2N-DMPK R1400282 (USE 036-1)], [Table 2.6.5.2O-RD-2017-00400]。化学的純度は，HPLC-UV で評価した。

3 吸収

カプマチニブの吸収，バイオアベイラビリティ及び薬物動態に関する試験は，マウス，ラット，イヌ，サル及びヒトにおいて，単回静脈内又は経口投与で実施した。

3.1 吸収及びバイオアベイラビリティ

ラット，サル及びヒトに[^{14}C]カプマチニブを単回静脈内又は経口投与したときの血漿中総放射性標識成分の薬物動態パラメータを Table 3-1 に，ラット，イヌ，サル及びヒトにカプマチニブを単回又は反復経口投与したときのカプマチニブの薬物動態パラメータを Table 3-2 に示す。

単回経口投与したときの血漿中総放射能の Tmax は，いずれの動物種においても 0.25～2 時間であった。ラット，サル及びヒトにおける吸収率は，それぞれ 51.1%，100%及び 70%超（X2106

試験でのカプセル剤投与時の吸収率は 49.6%）と推定された（Table 3-1）。ヒトに経口投与したときの Tmax は，中央値で 2 時間であった。

静脈内及び経口投与の結果から，経口バイオアベイラビリティは，ラットで 66.2%～114%，イヌで 28%，サルで 24%～108%と，動物間又は試験間で変動が認められた。

Table 3-1 ラット，サル及びヒトに[^{14}C]カプマチニブを単回静脈内又は経口投与したときの血漿中総放射能の薬物動態パラメータ

動物種	ラット				サル		ヒト
投与経路	静脈内	経口	経口	経口	静脈内	経口	経口
投与量 (mg/kg) [a)]	3	10	40	40	3	30	8.57 [b)]
Tmax (h)	0.083	0.5 [c)]	1 [c)]	4 [c)]	0.083	2	2 [c)]
Cmax (µmol/L)	12.3	0.643	17.6	18.3	17.9	98.4	19
Cmax/dose (µmol/L/(mg/kg)) [d)]	3.92	0.0624	0.45	0.46	5.98	3.28	2.22
AUClast (µmol/L·h)	16.5	26.5	162	187	37.6	47.3	17.4
AUClast/dose (µmol/L·h/(mg/kg)) [d)]	5.05	2.58	4.11	4.70	12.5	1.58	2.03
T1/2 (h)	4.66	NA	3.78	4.75	NA	NA [e)]	10.6
吸収率 (%)	NA	51.1 (83.2) [f)]	NA	NA	NA	72 [g)]	>70 [h)]

Source: Table 2.6.5.3C-DMPK R1100027-01, Table 2.6.5.4A-DMPK R1600074-01, Table 2.6.5.3G-DMPK R1300820, 5.3.3.1-1-X2106 試験-Table 14.2-1.1

NA: 該当なし

平均を示した。

a) 単回投与及び反復投与時の 1 日投与量を遊離体換算（分子量: 412.43）で示した。

b) 体重 70 kg，投与量 600 mg に基づいて算出した。

c) 中央値

d) 正確な投与量に基づいて算出した。

e) 396 h（1 匹の個体かつ 168 時間までの観察期間から算出）

f) 異なる投与量を投与した場合

g) 総放射性標識成分の血漿 AUC より 139%と推定された。尿中及び糞便中から回収された放射能の合計より 72%と推定された。

h) 薬物が腸内細菌叢に対して安定であると仮定すると，INC280 の平均経口吸収は，尿中及び糞便中の放射能の排泄から推定できる。吸収率は 49.6 ± 20.9%（n = 6）を示したが，21.0%（症例番号 1000-00006）～81.7%（症例番号 10000-00015）と変動がみられた。錠剤とカプセルの製剤を比較したときや食事の影響試験での曝露量から INC280 の吸収率は 70%超であると推定された。

Table 3-2 ラット，イヌ，サル及びヒトにカプマチニブを単回又は反復経口投与したときのカプマチニブの薬物動態パラメータ

動物種	ラット			イヌ			サル				ヒト	
投与量 (mg/kg) [a)]	5	10	40	40 [b)]	5	5 [c)]	2.5	10	30	75	8.57 [d)]	11.4 [b, e)]
Tmax (h)	0.33	0.25 [g)]	NA	NA	0.38	1 [g)]	2.7 [h)]	7 [h)]	2	1.7	2 [g)]	1.09 [f)]
Cmax (ng/mL)	3134	850	3188	3765	242	36.3	920	2656	17700	14100	3670	4780 [f, i)]

動物種	ラット			イヌ			サル				ヒト	
Cmax/dose (ng/mL/(mg/kg))[j)]	627	82	80.9	94.6	48.3	7.26	368	266	590	188	428	418
AUClast (ng/mL·h)	7176[k)]	5898	28045	32582	403[k)]	96.9	4248[k)]	30850[k)]	72900	72800	14300	40400 [f, i)]
AUClast/dose (ng/mL·h/(mg/kg))[j)]	1435	590	712	819	80.6	19.38	1699	3085	2430	971	1669	3535
T1/2 (h)	2.9	NA	NA	NA	0.98	NA	4.6	4.4	NA[l)]	NA	7.84	6.54 [f, m)]
CL/F (L/h)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	45.5[f)]	NA[m)]
Vz/F (L)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	473 [f, n)]	NA[m)]
F (%)	66.2	114 (69) [o)]	NA	NA	28	NA	24	44	108	NA	NA	NA

Source: Table 2.6.5.3B-INCYTE-DMB-08.128.1, Table 2.6.5.3C-DMPK R1100027-01, Table 2.6.5.4A-DMPK R1600074-01, Table 2.6.5.3D-INCYTE-DMB-08.134.1, Table 2.6.5.3G-DMPK R1300820, Table 2.6.5.3F-INCYTE-DMB-08.131.1, Table 2.6.5.3H-DMPK R1600337, 5.3.3.1-1-X2106 試験-Table 14.2-1.1, 5.3.5.2-1-A2201 試験-Table 14.2-6.1, Table 14.2-6.2

NA: 該当なし

平均を示した。

a) 遊離体換算（分子量: 412.43）で示した。

b) 反復投与

c) 体重 10 kg，投与量 50 mg に基づいて算出した。

d) 体重 70 kg，投与量 600 mg に基づいて算出した。

e) 体重 70 kg，400 mg（錠剤）を 1 日 2 回投与に基づいて算出した。

f) 幾何平均

g) 中央値

h) 溶解度の律速による吸収を示したと考えられた。

i) サイクル 1 の 15 日目の定常状態の値（AUC は 0-24 h としたときの値）を示した。

j) 正確な投与量に基づいて算出した。

k) AUCinf

l) 61.7 h と算出されたが，静脈内投与後に二相性の消失を示した。

m) T1/2, eff: 6.54 h（蓄積比の幾何平均より算出）; CL/F: 26.9 L/h（サイクル 1 の Day 1 での幾何平均）; Vz/F: 84.1 L（サイクル 1 の Day 1 での幾何平均）

n) Vss/F: 164 L（母集団薬物動態解析）

o) 異なる投与量を投与した場合

3.2 カプマチニブの薬物動態

マウス，ラット，イヌ及びサルにカプマチニブを単回静脈内投与したときのカプマチニブの薬物動態パラメータを Table 3-3 に示す。カプマチニブの全身血漿クリアランス（CLplasma）は，雄マウスで 1.5 L/h/kg，雌マウスで 1.05 L/h/kg，ラットで 0.46～1.97 L/h/kg，イヌで 3.46 L/h/kg 及びサルで 0.15～0.45 L/h/kg であり，マウス，ラット及びサルで低～中程度であったが，イヌでは高かった。

マウス，ラット，イヌ及びサルでは，カプマチニブは，0.72～4.28 時間の消失半減期（T1/2）で全身循環から消失した。サルの ADME 試験において，カプマチニブの血漿中濃度は，二相性の指数関数的な低下を示した。初期分布相の消失半減期（T1/2α）は 0.66 時間と短かったのに対し，終末相の消失半減期（T1/2β）は 88 時間と長かったが，終末相の AUC は 2-コンパートメン

トモデル解析に基づく血漿中薬物濃度-時間曲線下面積（0～無限大時間）（AUCinf）の 27%のみで，サルのトキシコキネティクス試験において，カプマチニブの蓄積は観察されなかったことと対応した（3.4.3 項）。X1101 試験において，進行固形がん患者にカプマチニブを 1 日 1 回経口投与したときの T1/2 は 3.5～6.4 時間であった [5.3.5.2-3-X1101 試験-Table 11-6]。ヒト ADME 試験（X2106 試験）においても T1/2 は 7.8 時間と同程度であった [5.3.3.1-1-X2106 試験-Table 11-3]。

静脈内投与したときの全身血液クリアランス（CLblood）は，肝血流量（Davies and Morris, 1993）に対して，雄マウスで 28%，雌マウスで 19%，雄ラットで 13%～54%，イヌで 24%及びサルで 4%～12%と低～中程度であった。定常状態における分布容積（Vss）は検討した動物種において 0.27～1.73 L/kg であり，総体液量の約 0.5～2.6 倍であった。ヒトにおける見かけの分布容積（Vz/F）は 473 L であった（Table 3-2）。

マウス（3.4.1 項）及びラット（3.4.2 項）のトキシコキネティクス試験において，カプマチニブの曝露量に性差が認められたが，CYP や AO の発現の性差によるものと考えられた（Martignoni et al., 2006）（Garattini and Terao, 2012）。サルやヒトにおいては，カプマチニブの曝露量に性差は認められなかった。

Table 3-3　マウス，ラット，イヌ及びサルにカプマチニブを単回静脈内投与したときのカプマチニブの薬物動態パラメータ

動物種	マウス	ラット		イヌ	サル	
投与量 (mg/kg) [a)]	2.5	5	3	2.5	2.5	3
AUClast (ng/mL·h)	NA	10855 [b)]	1580	NA	17734 [b)]	6720
AUClast/dose (ng/mL·h/(mg/kg))	NA	2171 [b)]	494	NA	7094 [b)]	2240
T1/2 (h)	雄: 0.66 雌: 0.76	3.6	1.42 [c)]	0.72	4.28	0.66 / 88 [d)]
CLplasma (L/h/kg)	雄: 1.5 雌: 1.05	0.46	1.97	3.46	0.15	0.45
CLblood (L/h/kg) [e)]	雄: 1.5 雌: 1.05	0.42	1.79	0.44	0.11	0.32
Vdss (L/kg)	雄: 0.98 雌: 0.77	0.61	1.73	0.308	0.27	1.47

Source: Table 2.6.5.3A-INCYTE-DMB-08.124.1, Table 2.6.5.3B-INCYTE-DMB-08.128.1, Table 2.6.5.3C-DMPK R1100027-01, Table 2.6.5.3D-INCYTE-DMB-08.134.1, Table 2.6.5.3F-INCYTE-DMB-08.131.1, Table 2.6.5.3G-DMPK R1300820

NA: 該当なし

平均を示した。

a) 遊離体換算（分子量 412.43）で示した。

b) AUCinf 及び AUCinf/dose の値を示した。

c) 8 時間までのデータを用いて算出した。

d) T1/2α 及び T1/2β の値を示した。

e) 血液／血漿分布比を用いて算出（4.1 項）。マウスの場合，濃度比は 1 と仮定した。

3.3 カプマチニブ代謝物の薬物動態

3.3.1 CMN288（M16）の薬物動態

サル及びヒトにカプマチニブを単回又は反復経口投与したときの CMN288（M16）の薬物動態パラメータを Table 4-1 に示す。

サルにカプマチニブ 75 mg/kg を単回経口投与したとき，血漿中 CMN288（M16）は投与後 2 時間に最高血漿中薬物濃度（Cmax）を示し，投与後 30 時間まで検出された。

A2201 試験において，ヒトにカプマチニブ（錠剤）400 mg を 1 日 2 回反復経口投与したとき，血漿中 CMN288（M16）が検出された。T1/2 は 3.05 時間であり，カプマチニブの T1/2 と同程度であった。カプマチニブの反復投与による CMN288（M16）の蓄積は認められなかった。

カプマチニブ単回又は反復経口投与後の CMN288（M16）とカプマチニブの AUC 比は，サルで 0.32～0.61，ヒトで 0.269～0.398 であった。ラット及びサルの 28 日間及び 13 週間の毒性試験での無毒性量（NOAEL）における CMN288（M16）のヒトに対する曝露量比は，それぞれの動物種で 3.5～5.3 及び 0.7～2.2 であった（5.2.4 項）。

Table 3-4 サル及びヒトにカプマチニブを単回又は反復経口投与したときの CMN288（M16）の薬物動態パラメータ

動物種	サル	ヒト
投与量 (mg/kg) [a)]	75（単回）	11.4（反復） [b)]
Tmax (h)	1.7	NA
Cmax (ng/mL)	8300	1200 [c)]
AUClast (ng/mL·h)	44200	11600 [d)]
T1/2 (h)	NA [e)]	3.06
Cmax ratio（CMN288/カプマチニブ） [f)]	0.58	0.242
AUC ratio（CMN288/カプマチニブ） [f)]	0.61	0.269

Source: Table 2.6.5.3H-DMPK R1600337, 5.3.5.2-1-A2201 試験-Table 14.2-6.4, Table 14.2-6.5

NA: 該当なし

平均（Cmax 及び AUClast は幾何平均）を示した。

a) 遊離体換算（分子量 428.43）で示した。

b) 体重 70 kg，400 mg（錠剤）1 日 2 回を 14 日間投与に基づいて算出した。

c) Cmax, ss

d) AUCtau, ss, 0-24 h

e) 2 匹のサルから推定された平均半減期は 9 h。

f) 同試験中での CMN288（M16）及びカプマチニブの Cmax，AUClast（サル）及び AUCtau, ss（ヒト）を用いて算出した。

3.4 トキシコキネティクス

マウス，ラット，ウサギ及びサルにカプマチニブを経口投与したときのトキシコキネティクスについて，毒性試験の一部として評価した。曝露量の詳細は，[Table 2.6.7.3-トキシコキネティクス試験成績一覧表]に記載した。

3.4.1 マウス

マウスにカプマチニブ 20～600 mg/kg を経口投与したとき，カプマチニブの曝露量は投与量とともに増加したが，用量比例性は一定の傾向を示さなかった。カプマチニブの曝露量には性差が認められた。同量のカプマチニブと投与したとき，雄マウスの AUC は，雌マウスの AUC の約 30%～60%であった。マウスにおいて 1 日 1 回反復経口投与したときの曝露量は，単回経口投与したときの曝露量と同程度であった。

3.4.2 ラット

ラットにカプマチニブ 1～200 mg/kg を経口投与したとき，Tmax は 0.5～1.5 時間であり，速やかに吸収された。カプマチニブの曝露量は投与量とともに増加したが，用量比例性は一定の傾向を示さなかった。カプマチニブを 1 日 1 回経口投与したときの蓄積は，すべての投与量で 2 倍以下であった。カプマチニブの曝露量には性差が認められた。同量のカプマチニブと投与したとき，雄ラットの曝露量は，雌ラットの曝露量の 1/2～1/3 倍であった。雄ラットにおけるカプマチニブ代謝物 CJK530（M19）及び CMC583（M13）の曝露量は，それぞれカプマチニブの曝露量の約 1%及び約 2%であった。

3.4.3 サル

サルにカプマチニブ 10～600 mg/kg を経口投与したとき，速やかに吸収された。カプマチニブの曝露量は投与量とともに増加したが，用量比例性は一定の傾向を示さなかった。カプマチニブの曝露量に性差は認められなかった。サルにおいて 1 日 1 回反復経口投与したとき，すべての投与量及びいずれの性別においても蓄積は認められなかった。

3.4.4 ラット及びウサギでの胚-胎児発生への影響に関する毒性試験

雌ラット及び雌ウサギにカプマチニブを経口投与したとき，いずれの投与量においても投与後 0.5 時間に Cmax を示した。カプマチニブの曝露量は，ラットでは，1～30 mg/kg/day の投与量範囲で概ね投与量比例的に増加，ウサギでは，1～60 mg/kg/day の投与量範囲で用量比を上回って増加した。

4 分布

4.1 血液／血漿分布及び血漿タンパク結合

マウス，ラット，イヌ及びサルでの血漿中カプマチニブの *in vitro* での非結合型分率は，それぞれ 4.5%，4.5%，17.8%及び 3.0%であり，血漿タンパク結合率は中程度～高度であった [Table 2.6.5.6A-INCYTE-DMB-08.122.1]。ヒトでの血漿非結合型分率は 4.0%であり，濃度範囲 100～10000 ng/mL で濃度依存性は認められなかった [5.3.2.1-1-DMPK R1400051]。

カプマチニブの血液／血漿分布比は，ラットで 1.1，サルで 1.4 と同程度であったが，イヌでは 7.9 であり，ラット及びサルと比較して高かった [Table 2.6.5.6B-INCYTE-DMB-08.123.1]。ヒトで

の血液／血漿分布比は，濃度範囲 10～1000 ng/mL で 1.5 であったが，高濃度 10000 ng/mL では 0.9 に低下したことから，血球への分布が飽和したと考えられた（5.3.2.1-1-DMPK R1400051）。

ラット，サル及びヒトでの，カプマチニブの主代謝物である CMN288（M16）の非結合型分率は，それぞれ 0.356%，1.57%及び 0.466%であり，血漿タンパク結合率は高かった [Table 2.6.5.6C-DMPK R1600760]。

4.2 組織分布

アルビノ及び有色ラットでの[^{14}C]カプマチニブ由来の放射能活性の臓器及び組織分布に関する試験を実施した（Table 2.6.5.5B-DMPK R1100027-01，Table 2.6.5.5C-DMPK R1300834-01，Table 2.6.5.5D-DMPK R1600074-01）。放射能活性は，QWBA で測定した。

雄のアルビノ及び有色ラットに[^{14}C]カプマチニブ 10 mg/kg を単回経口投与したとき，総放射性標識成分は，血管外の全身に速やかに分布した（Table 2.6.5.5B-DMPK R1100027-01，Table 2.6.5.5C-DMPK R1300834-01）。多くの組織で，Cmax は投与後 0.25～4 時間であった。検討した組織の半分で，血液よりも高い濃度の総放射性標識成分が検出された。総放射性標識成分の Cmax 及び血漿中薬物濃度-時間曲線下面積（0～最終定量可能時点）(AUClast）が最も高かったのは，眼（脈絡膜及び毛様体）等のメラニン含有組織であった。多くの組織では，総放射性標識成分の濃度は，投与後 4 時間で低下したが，眼（脈絡叢及び毛様体）のようにメラニン含有組織を含むいくつかの組織では，投与後 168 時間以降においても定量可能であった（Table 2.6.5.5B-DMPK R1100027-01，Table 2.6.5.5C-DMPK R1300834-01）。これらの組織への総放射性標識成分の分布は，少なくとも部分的に可逆的であった。

アルビノラットに[^{14}C]カプマチニブ 40 mg/kg を単回投与時及び 1 日 1 回反復経口投与時の放射能の組織分布のパターンや Cmax は類似していた（Table 2.6.5.5D-DMPK R1600074-01）。総放射性標識成分の Cmax 及び AUClast が最も高かったのは，包皮腺，肝臓，胃（腺及び腺以外），腸壁（小腸），腎臓（皮髄境界部及び皮質）及び血管壁であった。単回投与時と反復投与時の AUClast 比は，眼（水晶体）で 41.6，副腎（髄質）で 9.01 であり，高い蓄積が認められた。副腎（皮質及び髄質），腎臓（髄質），涙腺，肝臓，包皮腺，唾液腺（顎下腺），精嚢腺壁及び歯（歯髄）では，AUClast 比が 2.57～3.44 であった。他の組織では，AUClast 比が 2.5 より小さかったため，蓄積は小さいと考えられた。

脳組織への分布

カプマチニブは，わずかではあるが，血液脳関門（BBB）を通過する可能性がある。ラット（Table 2.6.7.7A-T08-04-11）及びサル（Table 2.6.7.7C-T08-01-08）での 28 日間反復投与毒性試験における脳脊髄液（CSF）中カプマチニブ濃度は，いずれの投与量，性別及び採血ポイント（Day 28 の投与後 4 及び 24 時間後）でも，ラットで非結合型血漿中カプマチニブ濃度の約 33.5%及びサルで 89.8%であった（Table 4-1）。ラットでの 4 週間反復投与試験における脳組織中

カプマチニブ濃度は，血液中濃度の約 9%であり，予想される最大の血管コンタミネーションの最大値（8%）に近い値であった [Table 2.6.5.16A-DMPK R0101302]。

ラットに[^{14}C]カプマチニブを投与したとき，脳／血液の放射能濃度比は，血管コンタミネーションの限界値に比べてわずかに高かった（Table 2.6.5.5B-DMPK R1100027-01，Table 2.6.5.5C-DMPK R1300834-01）。放射性標識成分は，脳組織の領域によらず，BBB をわずかに通過した。反復投与後においても脳組織での放射能の蓄積は認められなかった。単回投与したときの脳組織と血液の AUClast 比は 0.1～0.422 の範囲であった（Table 4-2）。

Table 4-1　カプマチニブの脳脊髄液（CSF）及び脳への分布

動物種	ラット			サル
投与量 (mg/kg)	20, 60, 120（経口）	0.25（静脈内）	90（経口）	30, 75, 150（経口）
採取ポイント	Day 28 投与後 4，24 時間	4 時間注入後	Day 1, 3, 7, 14, 28 投与後 3 時間	Day 28 投与後 23 時間
脳脊髄液／血漿				
非結合型	0.335 ± 0.19	0.362 ± 0.060	NA	0.898 ± 0.53
総濃度	0.0188 ± 0.0109	0.204 ± 0.0320	NA	0.0305 ± 0.0180
脳／血漿				
非結合型	NA	0.173 ± 0.042	0.0940 ± 0.00337	NA
総濃度	NA	0.157 ± 0.038 [a)]	0.0855 ± 0.00306 [a)]	NA

Source: Table 2.6.7.7A-T08-04-11, Table 2.6.5.16B-INCYTE-DMB-09.01.1, Table 2.6.5.5A-INCYTE-DMB-08.129.1, Table 2.6.7.17C-Study 1170512, Table 2.6.7.7C-T08-01-08, Table 2.6.5.16C-INCYTE-DMB-09.02.1

NA: 該当なし

a) 血液／血漿比 1.1 を用いて，算出した。

Table 4-2　放射能の脳組織での分布（ラット）

投与量 (mg/kg)	組織	薬物動態パラメータ			
		Cmax (nmol/g)	Cmax 比（組織／血液）	AUClast (nmol/g·h)	AUClast 比（組織／血液）
10（単回経口）	脳	0.922 (0.0922) [a)]	0.120	2.24 (0.224) [a)]	0.114
10（単回経口）	脳	0.812 (0.0812) [a)]	0.159	2.32 (0.232) [a)]	0.154
40（単回経口）	脳	1.73 (0.0433) [a)]	0.107	10.5 (0.263) [a)]	0.110
	小脳	1.87	0.115	11.3	0.118
	脈絡叢	10.8	0.667	40.4	0.422
	皮質	1.56	0.0963	9.80	0.102
	延髄	2.27	1.140	12.9	0.135
	嗅球	1.75	0.108	10.5	0.110
	視床	1.82	0.112	9.20	0.0962
40（反復経口）	脳	1.48 (0.037) [a)]	0.107	8.27 (0.206) [a)]	0.111
	小脳	1.56	0.113	8.52	0.115
	脈絡叢	10.3	0.746	44.2	0.596
	皮質	1.76	0.128	8.27	0.111

投与量 (mg/kg)	組織	薬物動態パラメータ			
		Cmax (nmol/g)	Cmax 比（組織／血液）	AUClast (nmol/g·h)	AUClast 比（組織／血液）
	延髄	1.52	0.110	8.27	0.111
	嗅球	1.92	0.139	10.0	0.135
	視床	1.37	0.0993	7.83	0.105

Source: Table 2.6.5.5B-DMPK R1100027-01, Table 2.6.5.5C-DMPK R1300834-01, Table 2.6.5.5D-DMPK R1600074-01
a) 投与量(mg/kg)で標準化した値。

5 代謝

マウス，ラット，イヌ，サル及びヒト肝細胞及びヒト肝ミクロソームを用いて，カプマチニブの代謝に関する *in vitro* 試験を実施した。また，ラット，サル及びヒトにおいて *in vivo* 試験を実施した。

5.1 *In vitro* 代謝

マウス，ラット，イヌ，サル及びヒト肝細胞及びヒト肝ミクロソームを用いて，[^{14}C]カプマチニブの代謝について検討した [Table 2.6.5.10A-DMPK R1000705]。検討した動物種における推定代謝経路を Figure 5-1 に示す。

ヒト肝ミクロソームを用いた検討において，[^{14}C]カプマチニブは，M4，M5，CMN290（M8），CNJ292（M17）及び CJH800（M21）の 5 つの主代謝物に代謝された。ヒト肝ミクロソームにおいて，カプマチニブの酸化的代謝には CYP3A4 が主に関与していることが示唆された [5.3.2.2-1-DMPK R1100191]。

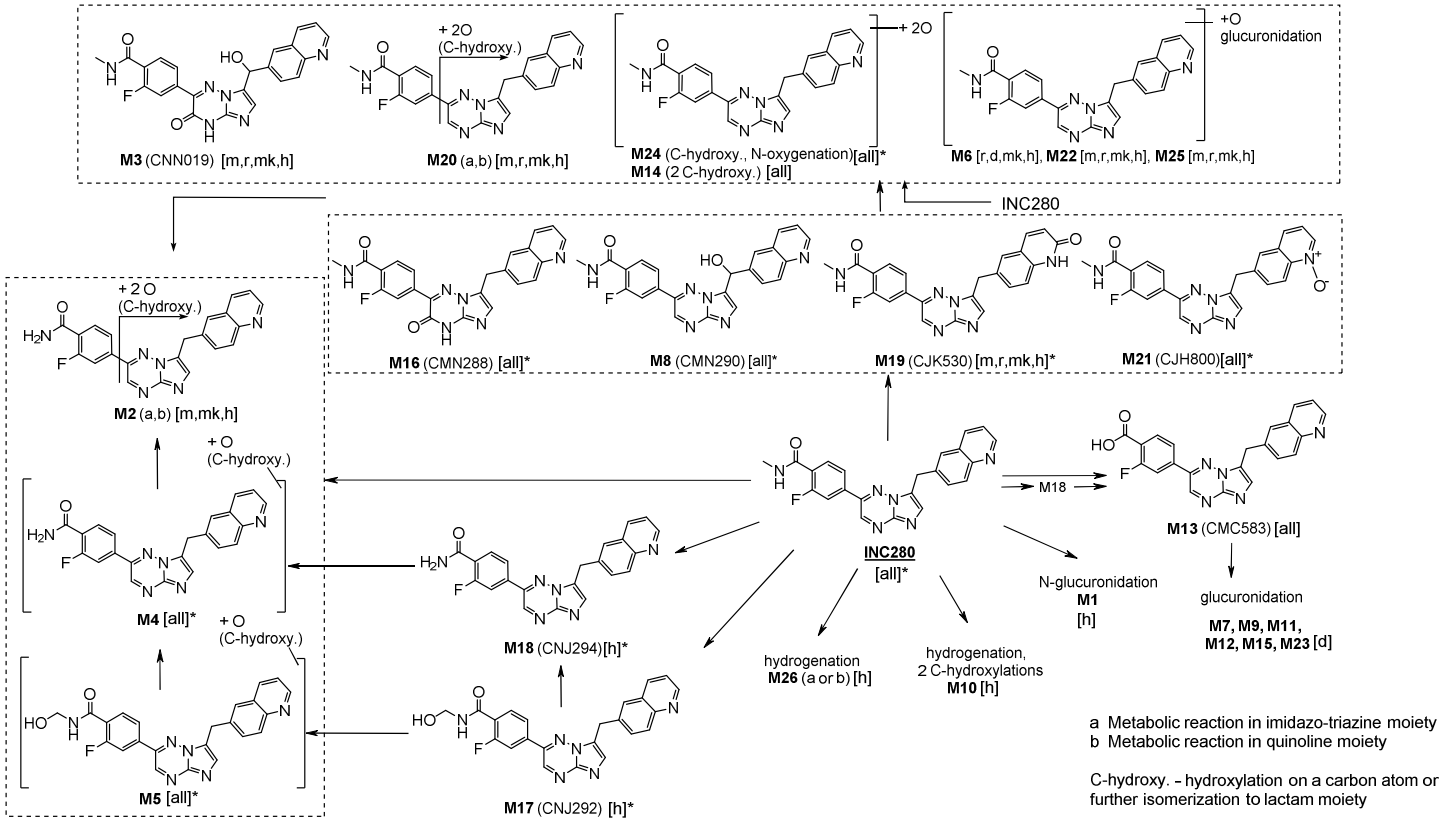
さらに，CMN288（M16）及び CJK530（M19）の生成におけるヒト代謝酵素の関与を検討した [5.3.2.2-2-DMPK R1400185] ところ，CMN288（M16）及び CJK530（M19）は，ヒト肝細胞質の酵素である AO 及び XO によって生成され，CMN288（M16）の生成には主に AO が関与していると考えられた。カプマチニブの AO 代謝物がげっ歯類，ヒト以外の霊長類及びヒトでは生成されるが，イヌでは生成されないという点については，これまでに AO で代謝される基質についての報告と一致していた（Garattini and Terao, 2012）。

これらの検討結果から，イヌを除くマウス，ラット，サル及びヒトでの *in vitro* 推定代謝経路は種間で類似していると考えられた（Figure 5-1）。

すべての動物種におけるカプマチニブの代謝は，主に *C*-酸化体［CNN019（M3），M4，M5，CMN290（M8）及び CMN288（M16）］，*N*-酸化体［CJH800（M21）］及びカルボン酸体［CMC583（M13）］の生成で特徴づけられた。水酸化体［CMN290（M8）］やイミダゾ-トリアジノン体（ラクタム）［CMN288（M16）］は，イヌを除くすべての動物種の肝細胞における主代謝物であった。アミド結合の加水分解及びカルボン酸体である CMC583（M13）の生成は，イヌにおいて主代謝経路であったが，マウス，ラット，サル及びヒトにおける寄与は低かった。水

素化体（M26），カルビノールアミド体［CNJ292（M17）］及び *N*-脱アルキル体［CNJ294（M18）］は，ヒトでのみ生成された。

Figure 5-1　　推定代謝経路（*in vitro* 試験：マウス，ラット，イヌ，サル及びヒト肝細胞及びヒト肝ミクロソーム）



Source: Table 2.6.5.11A-薬物動態試験：推定代謝経路／*in vitro*（マウス，ラット，イヌ，サル及びヒト）

m: mouse hepaote; r: rat hepatocyte; d: dog hepatocyte; mk: monkey hepatocyte; h: human hepatocyte; all: all species hepatocyte

*: human liver microsome

5.2 *In vivo* 代謝

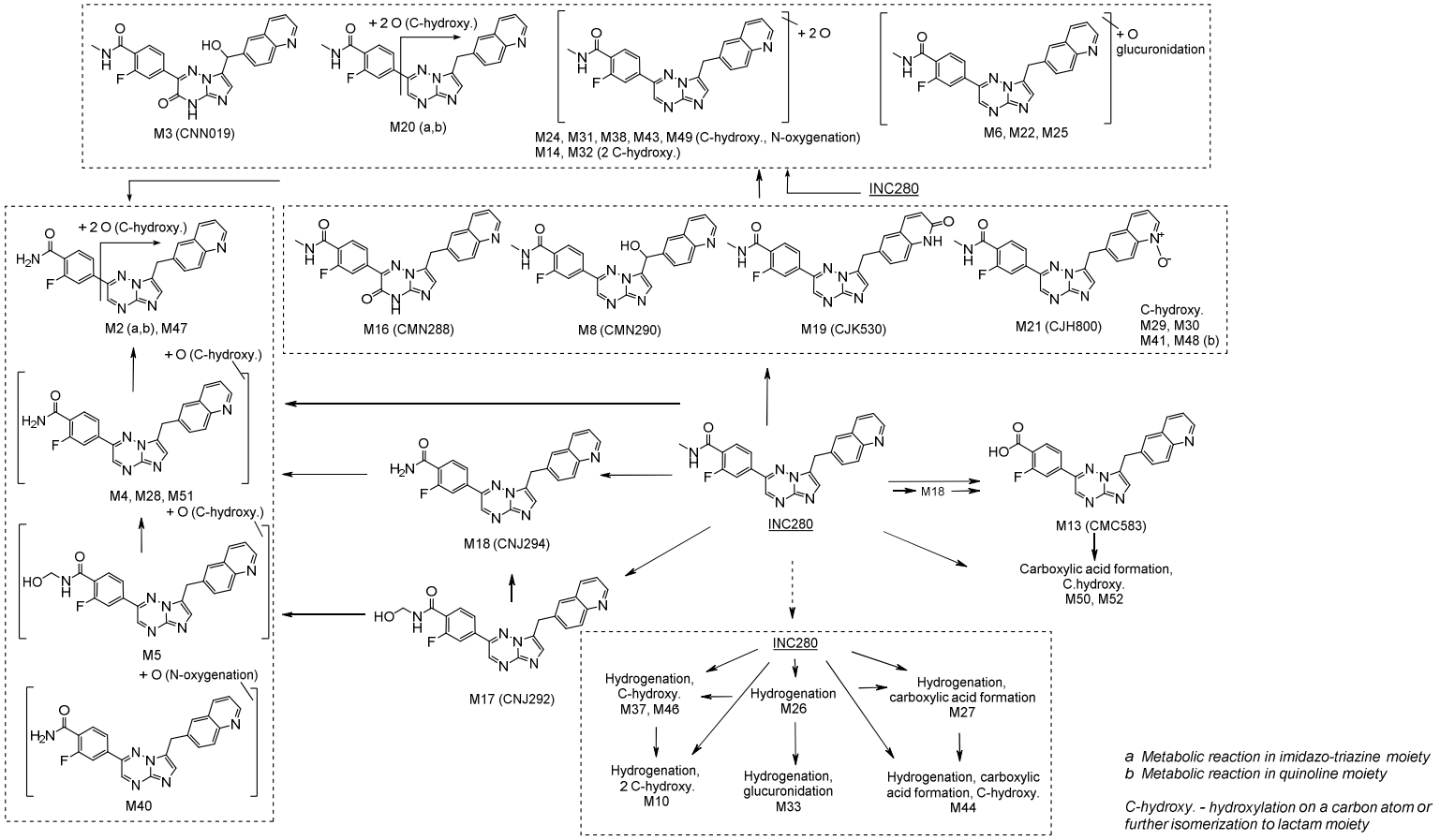
カプマチニブの *in vivo* 代謝について，ラット（Table 2.6.5.9A-DMPK R1100027-01，Table 2.6.5.9B-DMPK R1600074-01），サル（Table 2.6.5.9C-DMPK R1300820）及びヒト（5.3.3.1-1-X2106 試験）で検討した。検討した動物種における推定代謝経路を Figure 5-2 に示す。

カプマチニブの代謝において，*C*-水酸化，ラクタム形成，*N*-酸化，*N*-脱アルキル化，カルボン酸形成及びこれらの組合せの第 I 相反応が認められた。続いて，酸化代謝物のグルクロン酸抱合が第 II 相反応として認められた。

ラット，サル及びヒトにカプマチニブを経口投与したとき，血漿中では[^{14}C]カプマチニブの未変化体が主に検出され，主代謝物は CMN290（M8），CMN288（M16）及び M28 であった（Table 2.6.5.9A-DMPK R1100027-01，Table 2.6.5.9C-DMPK R1300820，5.3.3.1-1-X2106 試験）。糞便中に排泄された主な代謝物は，CMN290（M8），CMC583（M13），CMN288（M16），M20 及び M26 であり，最も多く排泄されたのは CMN288（M16）であった。尿中には多くの代謝物が排泄されたが，未変化体については，ラットでは検出されず，サル及びヒトにおいてはわずかに排泄された。

胆管カニューレ挿入ラットにカプマチニブを静脈内投与したとき，胆汁中には代謝物として CMC583（M13），CMN288（M16），M22，M24 及び M25 が排泄されたが，未変化体は検出されなかった。

Figure 5-2　　推定代謝経路（*in vivo* 試験：ラット，サル及びヒト）



Source: Table 2.6.5.11B-薬物動態試験：推定代謝経路／*in vivo*（ラット，サル及びヒト）

5.2.1 ラットにおける *in vivo* 代謝

ラットにおいて，[^{14}C]カプマチニブを，単回静脈内投与（3 mg/kg），単回経口投与（10 mg/kg）及び単回又は反復経口投与（40 mg/kg/day）したときの代謝を検討した（Table 2.6.5.9A-DMPK R1100027-01，Table 2.6.5.9B-DMPK R1600074-01）。カプマチニブの代謝は，*C*-水酸化，ラクタム形成，*N*-酸化，*N*-脱アルキル化，水素化，カルボン酸形成及びこれらの組合せの第 I 相反応が認められた。続いて，酸化代謝物のグルクロン酸抱合が第 II 相反応として認められた [Table 2.6.5.11C-薬物動態試験：推定代謝経路／*in vivo*（ラット）]。

[^{14}C]カプマチニブを静脈内投与又は経口投与したときの代謝物のプロファイルを定性的及び定量的に検討した。血漿中では，未変化体由来の放射性標識成分が最も多く検出され，静脈内投与時においては，総血漿中放射性標識成分の AUC0-8h に対して 50.6%，経口投与時においては，総血漿中放射性標識成分の AUC0-24h に対して 33.4%の割合であった。主代謝物は，CMN290（M8）及び CMN288（M16）であり，静脈内投与時ではそれぞれ総放射活性の 8.54%及び 23.2%，経口投与時ではそれぞれ総放射活性の 8.09%及び 33.1%であった。糞便中では，CMN290（M8），CMC583（M13）及び CMN288（M16）が主に検出され，総放射活性に対する 3 代謝物の合計の割合は，静脈内投与時で 48.9%，経口投与時で 44.3%であった。尿中においては，CMN290（M8）及び CMN288（M16）が主代謝物として総放射活性の 1.8%程度検出されたが，未変化体は検出されなかった。胆汁中においては，主代謝物として CMC583（M13），CMN288（M16），M22，M24 及び M25 が主代謝物として総放射活性の 36.5%が排泄されたが，未変化体は検出されなかった。

ラットにカプマチニブを単回又は反復経口投与したときの結果より，未変化体及び代謝物は，血漿中への蓄積は認められず，糞便中及び胆汁中排泄により体内から消失することが示された。

5.2.2 サルにおける *in vivo* 代謝

サルにおいて，[^{14}C]カプマチニブを単回静脈内投与（3 mg/kg）及び単回経口投与（30 mg/kg）したときの代謝を検討した（Table 2.6.5.9C-DMPK R1300820）。カプマチニブの代謝は，*C*-水酸化，ラクタム形成，*N*-酸化，*N*-脱アルキル化，カルボン酸形成及びこれらの組合せの第 I 相反応が認められた。続いて，酸化代謝物のグルクロン酸抱合が第 II 相反応として認められた [Table 2.6.5.11D-薬物動態試験：推定代謝経路／*in vivo*（サル）]。

[^{14}C]カプマチニブを経口投与又は静脈内投与したときの代謝物のプロファイルを定性的及び定量的に検討した。血漿中では，未変化体由来の放射性標識成分が最も多く検出され，静脈内投与時においては，総血漿中放射性標識成分の AUC0-7h に対して 54.1%，経口投与時においては，総血漿中放射性標識成分の AUC0-10h に対して 42.5%の割合であった。主代謝物は，CMN290（M8）及び CMN288（M16）であり，静脈内投与時ではそれぞれ総放射活性の 13.7%及び 13.4%，経口投与時ではそれぞれ総放射活性の 22.8%及び 13.5%であった。尿及び糞便中では，CMN290（M8）及び CMN288（M16）が主に検出され，総放射活性に対する CMN290（M8）の割合は，

静脈内投与時で 6.7%，経口投与時で 13.0%，CMN288（M16）の割合は，静脈内投与時で 25.9%，経口投与時で 20.7%であった。未変化体については，主に糞便中で検出され，総放射活性に対する割合は，静脈投与時で 5.30%，経口投与時で 6.64%であった。

サルにカプマチニブを単回投与したときの結果より，カプマチニブは糞便中及び胆汁中排泄により体内から消失することが示された。

5.2.3 ヒトにおける *in vivo* 代謝

ヒトにおいて，[^{14}C]カプマチニブ 600 mg を単回経口投与したときの代謝を検討した（5.3.3.1-1-X2106 試験）。カプマチニブの代謝は，ラクタム形成，水酸化，*N*-脱アルキル化，カルボン酸形成，水素化，*N*-酸素化，グルクロン酸抱合及びこれらの組合せの反応が認められた [Table 2.6.5.11E-薬物動態試験：推定代謝経路／*in vivo*（ヒト）]。

血漿中では，未変化体由来の放射性標識成分が最も多く検出され，血漿中の総放射能の AUC0-12h に対して 42.9 ± 2.9%の割合であった。主代謝物は CMN288（M16）であり，血漿中の総放射能の AUC0-12h に対して 21.5 ± 2.1%であった。糞便中では，総放射能の 69.9 ± 10.9%（範囲 59.4%～84.8%）が投与後 96 時間以内に排泄された。未変化体の総放射能に対する割合は，42.1 ± 23.0%（範囲 9.3%～72.6%）であり，個体間差が大きかった。主な代謝物である CMN288（M16）の総放射能に対する割合は，5.1 ± 2.1%であった。未変化体及び代謝物の糞便中排泄率は，投与量の 65.9%以上であった。尿中では，総放射能の 21.7 ± 8.4%（範囲 8.8%～31.3%）が投与後 96 時間以内に排泄された。主代謝物として CMN288（M16）が 2.9 ± 1.2%の割合で検出されたが，未変化体の割合はわずか（0.07 ± 0.03%）であった。未変化体及び代謝物の尿中排泄率は，投与量の 19.2%以上であった。

ヒトにカプマチニブを単回投与したときの結果より，カプマチニブ及び代謝物は糞便中及び胆汁中排泄により体内から消失することが示された。

AO 及び XO による消失経路の評価

ヒト肝細胞を用いて，カプマチニブの代謝におけるモリブデン含有水酸化酵素である AO 及び XO の関与を検討した（5.3.2.2-2-DMPK R1400185），[5.3.2.2-3-DMPK R1500757]。M2，CNN019（M3），M10，M14，CMN288（M16），CJK530（M19），M20，M28 及び M49 の生成には，部分的に AO 及び XO が関与していることが示唆された。ヒトの排泄物中のこれらの代謝物の割合は，39.7 ± 2.2%を占めていた。

5.2.4 ヒトにおける主代謝物：CMN288（M16）

ラット，サル及びヒトにおける CMN288（M16）について，ラット ADME 試験（[^{14}C]カプマチニブ 10 mg/kg 単回経口投与），サル ADME 試験（[^{14}C]カプマチニブ 30 mg/kg 単回経口投与），サルでの単回経口投与試験（カプマチニブ 75 mg/kg 単回経口投与）及び A2201 試験でがん患者にカプマチニブ 400 mg（錠剤）を 1 日 2 回投与したときの曝露量を比較した（Table 5-1）。ラッ

ト及びサルのトキシコキネティクス試験での NOAEL において，ヒト AUC0-24h, ss との比は，それぞれ 3.5～5.3 及び 0.7～2.2 であった。

Table 5-1　　ラット，サル及びヒトにおける CMN288（M16）の曝露量の比較

動物種	NOAEL (mg/kg/day)	性別	カプマチニブ AUC0-24h (μM·h)	CMN288（M16） AUC0-24h (μM·h) [a)]	ヒト AUC0-24h,ss との比 [b)]
ラット [c)]	30	雌	145	143.7	5.32
	60	雄	143	141.7	5.25
ラット [d)]	20	雌	94.4	93.6	3.46
	40	雄	118	116.9	4.33
サル [c)]	30	雌	111	35.7	1.32
	30	雄	96.7	31.1	1.15
サル [d)]	30	雌	56.7	18.3	0.68
	30	雄	102.6	33.0	1.22

Source: Table 2.6.5.9A-DMPK R1100027-01, Table 2.6.5.9C-DMPK R1300820

a) ラット ADME 試験（[^{14}C]カプマチニブ 10 mg/kg 単回経口投与）（Table 2.6.5.9A-DMPK R1100027-01）又はサル ADME 試験（[^{14}C]カプマチニブ 30 mg/kg 単回経口投与）（Table 2.6.5.9C-DMPK R1300820）で得られたカプマチニブの AUCinf に対する CMN288（M16）の AUCinf の割合を基に算出

b) がん患者にカプマチニブ 400 mg（錠剤）を 1 日 2 回投与したときのサイクル 1 の 15 日目の AUC0-24h,ss（27.0 μM·h）を用いて算出（5.3.5.2-1-A2201 試験-Table 14.2-6.4）

c) ラット（Table 2.6.7.17E-1570059）及びサル（Table 2.6.7.7C-T08-01-08）での 28 日間反復毒性試験

d) ラット（Table 2.6.7.7.B-T10-02-02）及びサル（Table 2.6.7.7D-1070417）での 13 週間反復毒性試験

5.2.5　　ヒトにおける代謝物の薬理学的活性

CMN290（M8），CMN288（M16）及び CNJ294（M18）の代謝物について，キナーゼアッセイ及び細胞アッセイにおける MET 阻害活性を検討し，カプマチニブの MET 阻害活性と比較した（Table 5-2）。検討した代謝物の中では，CJN294（M18）が最も高い阻害活性を示したが，カプマチニブの活性より低かった。また，CMN288（M16）の MET 阻害活性は，10 μM までの検討濃度では認められなかった。

ヒトにカプマチニブ 400 mg（錠剤）を 1 日 2 回投与したときのカプマチニブの血漿への曝露量とこれら 3 つの代謝物の推定曝露量から，ヒトにおける総 MET 阻害活性に対するこれら 3 つの代謝物の寄与は低い（< 4%）と考えられた。

Table 5-2　　カプマチニブの代謝物の薬理学的活性

	キナーゼアッセイ		細胞アッセイ	
	IC50 (nM)	相対活性 [a)]	IC50 (nM)	相対活性 [a)]
カプマチニブ	1.7	1	3.5	1
CMN290（M8）	36.5	22	181	52
CMN288（M16）	> 10000	NA	> 10000	NA
CNJ294（M18）	13	8	8.6	2.5

Source: Table 2.6.3.2-RD-2014-00427

NA: 該当なし

a) 相対活性は，各代謝物の平均 50%阻害濃度（IC50）値をカプマチニブの平均 IC50 値で除して算出した。CMN288（M16）については，活性代謝物でなかったため，相対活性は算出できなかった。

6 排泄

6.1 尿及び糞便中への排泄

ラット，サル及びヒトに[^{14}C]カプマチニブを単回投与したときのカプマチニブ及びカプマチニブ関連放射性標識成分の尿及び糞便中排泄の結果を Table 6-1 に示す。ラット及びサルに[^{14}C]カプマチニブ 3 mg/kg を静脈内投与したとき，放射能の 77%～89%が糞便中に，6%～10%が尿中に認められた。また，ヒトに[^{14}C]カプマチニブ 600 mg を単回経口投与したとき，放射能の 77.9%が糞便中に，21.8%が尿中に認められた。いずれの動物種においても，糞便中排泄が主な消失経路であった。

ラット，サル（10 mg/kg）及びヒト（600 mg）に[^{14}C]カプマチニブを単回経口投与したとき，それぞれ投与後 48 時間，168 時間及び 72 時間以内に放射能の 80%超が排泄された。放射能の排泄は，検討した観察期間内でほぼ完全～完全であり，ラットで 95.5%，サルで 84.6%及びヒトで 99.7%であった。

いずれの動物種においても，未変化体の尿中排泄は認められないか，わずかに認められる程度であった。

Table 6-1 ラット，サル及びヒトに[^{14}C]カプマチニブを単回静脈内又は経口投与したときのカプマチニブ及びカプマチニブ関連放射性標識成分の排泄

動物種	ラット		サル		ヒト
性別／例数	雄／3	雄／4	雄／2	雄／3	男／6
投与経路	静脈内	経口	静脈内	経口	経口
投与量 (mg base/kg) [a)]	3	10	3	30	8.57
尿中排泄					
放射活性 (% of dose)	0-168 h: 5.71	0-168 h: 7.82	0-168 h: 7.92	0-168 h: 9.67	0-168 h: 21.8
カプマチニブ (% of dose)	0-48 h: ND	0-48 h: ND	0-72 h: 微量	0-72 h: 微量	0-96 h: 0.07
糞便中排泄					
放射活性 (% of dose)	0-168 h: 88.6	0-168 h: 86.4	0-168 h: 77.4	0-168 h: 72.0	0-168 h: 77.9
カプマチニブ (% of dose)	0-48 h: 8.52	0-48 h: 11.7	0-72 h: 5.28	0-72 h: 6.59	0-96 h: 42.13

Source: Table 2.6.5.13A-DMPK R1100027-01, Table 2.6.5.13B-DMPK R1300820, 5.3.3.1-1-X2106 試験-Table 11-5

ND: 検出されず

a) 投与量は，遊離体換算（分子量 412.4）した値を示した。ラットにはカプマチニブ二塩酸塩（分子量 485.35），サル及びヒトにはカプマチニブに塩酸塩一水和物（分子量 503.4）を投与した。

6.2 胆汁中への排泄

胆管カニューレ挿入ラットに[^{14}C]カプマチニブ 3 mg/kg を単回静脈内投与したときのカプマチニブ及びカプマチニブ関連放射性標識成分の尿，糞便及び胆汁中排泄の結果を Table 6-2 に示す。

放射能の 66.3%が胆汁中に，12.1%が尿中に認められた。また，放射能の 9.23%が糞便中に認められたことから，カプマチニブ関連物質の直接の小腸分泌が示唆された。

胆汁中に未変化体は認められず，代謝物の胆汁中排泄がラットにおける主排泄経路であると考えられた。投与量の 2.30%がカプマチニブとして糞便中に認められたことから，未変化体の小腸分泌も示唆された。

カプマチニブは，代謝及び代謝物の胆汁中排泄によって主に体内より消失することが示され，小腸分泌を介した糞便中排泄により消失する経路の寄与も認められた。尿中排泄は認められないか，ごくわずかであった。

Table 6-2 胆管カニューレ挿入ラットに[^{14}C]カプマチニブを単回静脈内投与したときのカプマチニブ及びカプマチニブ関連放射性標識成分の排泄

動物種	ラット
性別／例数	雄／4
投与経路	静脈内
投与量 (mg base/kg) [a)]	3
尿中排泄	
放射活性 (% of dose)	0-24 h: 12.1
カプマチニブ (% of dose)	0-24 h: ND
糞便中排泄	
放射活性 (% of dose)	0-24 h: 9.23
カプマチニブ (% of dose)	0-24 h: 2.30
胆汁中排泄	
放射活性 (% of dose)	0-24 h: 66.3
カプマチニブ (% of dose)	0-24 h: ND

Source: Table 2.6.5.14A-DMPK R1100027-01

ND: 検出されず

a) 投与量は，遊離体換算（分子量 412.4）した値を示した。ラットにはカプマチニブ二塩酸塩四水和物（分子量 557.41）を投与した。

7 薬物動態学的薬物相互作用

ラット及びヒト核内受容体 PXR レポーター遺伝子アッセイを用いて，カプマチニブが *in vitro* で CYP3A を誘導する可能性を評価した。10 μM カプマチニブによる PXR の誘導はみられず，臨床試験で用いられている用法用量で CYP3A を誘導する可能性は低いと考えられた [Table 2.6.5.12A-INCYTE-DMB-08.135.1]。

In vitro 及び *in vivo* の薬物相互作用試験の結果は 2.7.2 臨床薬理試験に記載した。

8 その他の薬物動態試験

動物におけるその他の薬物動態試験は実施していない。

9 考察及び結論

カプマチニブの薬物動態について，マウス，ラット，イヌ，サル及びヒトにおいて検討した。

カプマチニブを経口投与後の Tmax は，検討した動物種において 0.25～7 時間の範囲であった。カプマチニブの吸収率は，ラットで 51.1%，サルではほぼ完全であった。ラット，イヌ及びサルにカプマチニブを静脈内又は経口投与したとき，経口バイオアベイラビリティは動物間又は試験間で変動が認められ，ラットで 66.2%～114%，イヌで 28%，サルで 24%～108%であった。マウス及びラットにおいては，カプマチニブの曝露量に性差が認められたが，サルやヒトにおいて性差は認められなかった。

マウス，ラット，イヌ及びサルでの血漿中非結合型分率は 3.0%～17.8%であった。ヒトでの血漿中非結合型分率は 4.0%であり，濃度依存性は認められなかった。カプマチニブの血液／血漿分布比は，ラット，サル及びイヌでそれぞれ 1.1，1.4 及び 7.9 であった。ヒトでは 10～1000 ng/mL の濃度で 1.5 であったが，10000 ng/mL では 0.9 に低下し，血球への分布は飽和する可能性が考えられた。

アルビノ及び有色ラットに[^{14}C]カプマチニブを投与したとき，放射能は広範囲に分布し，大部分の組織から比較的速やかに排泄された。有色ラットにおいて，眼の脈絡膜や毛様体といったメラニン含有組織に放射能が可逆的に分布し，長時間残留した。また，放射能は，BBB を通過し脳組織内にわずかに移行したが，反復投与後においても蓄積は認められなかった。

ラット，サル及びヒトにカプマチニブを経口投与したとき，血漿中ではいずれの動物種においても未変化体が最も多く，代謝物については，ラット及びヒトでは CMN288（M16），サルでは CMN290（M8）が最も多くみられた。すべての動物種においてカプマチニブの代謝は，*C*-酸化体，*N*-酸化体及びカルボン酸体の生成で特徴づけられ，水酸化体 CMN290（M8）及びイミダゾ-トリアジノン体（ラクタム）CMN288（M16）は，イヌを除くすべての動物種の肝細胞における主代謝物であった。アミド結合の加水分解及びカルボン酸体である CMC583（M13）の生成は，イヌにおいて主代謝経路であったが，マウス，ラット，サル及びヒトにおける寄与は低かった。水素化体（M26），カルビノールアミド体 CNJ292（M17）及び *N*-脱アルキル体（M18）は，ヒトでのみ生成された。カプマチニブの酸化的代謝には CYP3A4 が主に関与していること，CMN288（M16）及び CJK530（M19）は，ヒト肝細胞質の酵素である AO 及び XO によって生成され，CMN288（M16）の生成には主に AO が関与していることが示された。

CMN290（M8）及び CNJ294（M18）は MET 阻害活性を有することが示されたが，CMN288（M16）では MET 阻害活性はみられなかった。全 MET 阻害活性に対するこれらの代謝物の寄与はごくわずかであった。

ラット，サル及びヒトに[^{14}C]カプマチニブを単回経口投与したとき，いずれの動物種においても放射能の大部分は糞便中に排泄され，尿中への排泄はわずかであった。

胆管カニューレ挿入ラットに[^{14}C]カプマチニブを単回静脈内投与したとき，放射能の 66.3%が胆汁中に，12.1%が尿中に認められた。また，放射能の 9.23%が糞便中に認められたことから，

カプマチニブ関連物質の直接の小腸分泌が示唆された。胆汁中に未変化体は認められず，代謝物の胆汁中排泄がラットにおける主排泄経路であると考えられた。投与量の 2.30%がカプマチニブとして糞便中に認められたことから，未変化体の小腸分泌も示唆された。

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2.6.5 薬物動態試験概要表

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略号一覧

略号	省略していない表現（英）	省略していない表現（日）
AUCinf	area under the drug plasma concentration-time curve (time 0 to infinity)	血漿中薬物濃度-時間曲線下面積（0～無限大時間）
AUClast	area under the drug plasma concentration-time curve (time 0 to the last measurable concentration sampling time)	血漿中薬物濃度-時間曲線下面積（0～最終定量可能時点）
BLQ	below limit of quantitation	定量限界未満
CLplasma	systemic plasma clearance	全身血漿クリアランス
Cmax	maximal drug plasma concentration	最高血漿中薬物濃度
CSF	cerebrospinal fluid	脳脊髄液
CV	coefficient of variation	変動係数
DMF	dimethylformamide	ジメチルホルムアミド
ESI	electrospray ionization	エレクトロスプレーイオン化
fb	Fraction bound	結合型画分
fu	fraction unbound	非結合型画分
GIT	gastrointestinal tract	胃腸組織
GLP	good laboratory practice	医薬品の安全性に関する非臨床試験の実施の基準
HPLC	high performance liquid chromatography	高速液体クロマトグラフィー
HPLC-RA	high performance liquid chromatography coupled to radioactivity detection	放射能検出器を接続した高速液体クロマトグラフィー
HPLC-UV	high performance liquid chromatography coupled to ultraviolet absorbance detection	紫外線検出器を接続した高速液体クロマトグラフィー
i.v.	intravenous	静脈内
LC-MS	liquid chromatography-mass spectrometry	液体クロマトグラフィー質量分析
LC-MS/MS	liquid chromatography-tandem mass spectrometry	液体クロマトグラフィータンデム質量分析
LLOQ	lower limit of quantification	定量下限
LOD	limit of detection	検出限界
LOQ	limit of quantification	定量限界
LSC	liquid scintillation counter	液体シンチレーションカウンター
MCPBA	3-chloroperbenzoic acid	メタクロロ過安息香酸
MRM	multiple reaction monitoring	多重反応モニタリング
MS	mass spectrometry	質量分析
MTBE	methyl t-butyl ether	メチル tert-ブチルエーテル
NA	not applicable	該当なし
NC	not calculated	計算されず
ND	not detected	検出されず
NM	not measurable	測定されず
NMR	nuclear magnetic resonance	核磁気共鳴
NS	not sectioned	分割されず
PCN	pregnenolone 16α-carbonitrile	プレグネノロン-16α-カルボニトリル
p.o.	per os	経口

略号	省略していない表現（英）	省略していない表現（日）
PXR	pregnane X receptor	-
PyBOP	(Benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate	ベンゾトリアゾール-1-イルオキシトリピロリジノホスホ二ウム ヘキサフルオロリン酸
QWBA	quantitative whole-body autoradiography	定量的全身オートラジオグラフィー
RA	radioactivity	放射能
RSQ	Coefficient of determination, R^2	決定係数
SD	standard deviation	標準偏差
T1/2	elimination half life	消失半減期
TFA	trifluoroacetic acid	トリフルオロ酢酸
THF	tetrahydrofuran	テトラヒドロフラン
Tlast	time of last quantifiable concentration	最終定量可能時点
Tmax	time to reach the maximum drug plasma concentration following drug administration	最高血漿中薬物濃度到達時間
UK	United Kingdom of Great Britain and Northern Ireland	英国
ULOQ	upper limit of quantification	定量上限
US	the United States of America	米国
UV	ultraviolet	紫外線
Vss	distribution volume at steady state	定常状態における分布容積

2.6.5.1 薬物動態試験：一覧表

Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
2.6.5.2 Analytical methods and validation								
2.6.5.2A	Synthesis and release analysis	SSE 200-1	NA	[$^{13}CD_3$]INC280 ([M+4]INC280)	Not required	Novartis, Swiss	DMPK R1000645 (SSE 200-1)	4.2.2.1-1
2.6.5.2B	Synthesis and release analysis	RSE 493-1	NA	[^{14}C]INC280	Not required	Novartis, Swiss	DMPK R1000579 (RSE 493-1)	4.2.2.1-2
2.6.5.2C	Plasma of mouse	spiked samples	NA	INC280, [M+4]INC280 10-10000 ng/mL	Not required	Novartis, US	DMPK R1100266F	4.2.2.1-3
2.6.5.2D	Plasma of rat	spiked samples	NA	INCB028060, INCB027868 0.01-20 µM	Not required	Incyte Corp., US	INCYTE-DMB-08.119.1	4.2.2.1-4
2.6.5.2E	Plasma of rat	spiked samples	NA	INC280, [M+4]INC280 5-5000 ng/mL	Not required	Novartis, US	DMPK R1100266C	4.2.2.1-5
2.6.5.2F	Plasma of rabbit	spiked samples	NA	INC280, [M+4]INC280 1-1000 ng/mL and 50-50000 ng/mL (cross validation)	Not required	Novartis, US	DMPK R1100266D	4.2.2.1-6
2.6.5.2G	Plasma of dog	spiked samples	NA	INC280, [M+4]INC280 1-1000 ng/mL	Not required	[redacted] China	DMPK R1300899	4.2.2.1-7
2.6.5.2H	Plasma of monkey	spiked samples	NA	INCB028060, INCB027868 0.01-20 µM	Not required	Incyte Corp., US	INCYTE-DMB-08.120.1	4.2.2.1-8
2.6.5.2I	Plasma of monkey	spiked samples	NA	INC280, [M+4]INC280 10-10000 ng/mL	Not required	Novartis, US	DMPK R1100266	4.2.2.1-9

Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
2.6.5.2J	Synthesis and release analysis	SSE 201-1	NA	CJK530	Not required	Novartis, Swiss	DMPK R1000646 (SSE 201-1)	4.2.2.1-10
2.6.5.2K	Synthesis and release analysis	SSE 270-1	NA	CMN288	Not required	Novartis, Swiss	DMPK R1400283 (SSE 270-1)	4.2.2.1-11
2.6.5.2L	Synthesis and release analysis	SSE 281-1	NA	CMN290	Not required	Novartis, Swiss	DMPK R1400841-01 (SSE 281-1)	4.2.2.1-12
2.6.5.2M	Synthesis and release analysis	SSE 282-1	NA	CNJ294	Not required	Novartis, Swiss	DMPK R1400842 (SSE 282-1)	4.2.2.1-13
2.6.5.2N	Synthesis and release analysis	USE 036-1	NA	CMN288	Not required	Novartis, Swiss	DMPK R1400282 (USE 036-1)	4.2.2.1-14
2.6.5.2O	Synthesis and release analysis	Zschore 1-001-Exp008	NA	CJH800, CMN290 CNJ292, CNJ294 CNJ296, CNN019 CMN288	Not required	Novartis, Swiss	RD-2017-00400	4.2.2.1-15
2.6.5.3 Pharmacokinetics: Absorption after a single dose								
2.6.5.3A	Mouse (CD-1, male & female)	i.v.	Single	INC280 free base i.v.: 2.5 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-08.124.1 INCYTE-DMB-08.118.1	4.2.2.2-1 4.2.2.2-2
2.6.5.3B	Rat (Sprague-Dawley, male	i.v. and p.o.	Single	INC280 TFA salt i.v.: 5 mg/kg p.o.: 5 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-08.128.1 INCYTE-DMB-08.118.1	4.2.2.2-3 4.2.2.2-2
2.6.5.3C	Rat (Hannover Wister, male), water and food *ad libitum*	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg p.o.: 10 mg/kg	Not required	Novartis, US Novartis, Swiss	DMPK R1100027-01 DMPK R1100027a	4.2.2.2-4 4.2.2.2-5
2.6.5.3D	Dog (Beagle, male)	i.v. and p.o.	Single	INC280 HCl salt i.v.: 2.5 mg/kg p.o.: 5 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-08.134.1 INCYTE-DMB-08.118.1	4.2.2.2-6 4.2.2.2-2

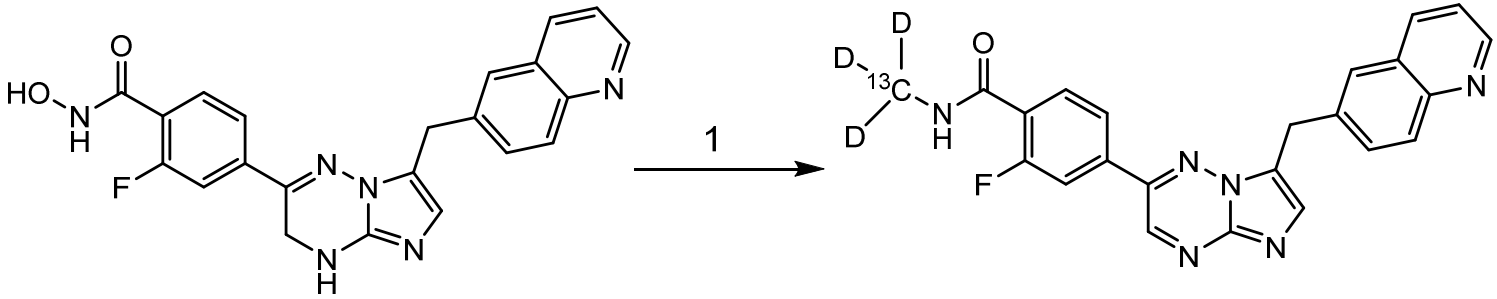
Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
2.6.5.3E	Dog (Beagle, male), fasted overnight, water *ad libitum*	p.o.	Single	INC280 HCl salt p.o.: 50 mg/kg	Not required	Novartis, Swiss [redacted] China	DMPK R1300725 DMPK R1300725a	4.2.2.2-7 4.2.2.2-8
2.6.5.3F	Monkey (Cynomolgus, male)	i.v. and p.o.	Single	INC280 HCl salt i.v.: 2.5 mg/kg p.o.: 2.5 mg/kg p.o.: 10 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-08.131.1 INCYTE-DMB-08.118.1	4.2.2.2-9 4.2.2.2-2
2.6.5.3G	Monkey (Cynomolgus, male), food once daily, water *ad libitum*	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg p.o.: 30 mg/kg	Not required	Novartis, US Novartis, Swiss	DMPK R1300820 DMPK R1300820a	4.2.2.2-10 4.2.2.2-11
2.6.5.3H	Monkey (Cynomolgus, male), food and water *ad libitum*	p.o.	Single	INC280 HCl salt p.o.: 75 mg/kg	Not required	Novartis, US	DMPK R1600337 DMPK R1600337a	4.2.2.2-12 4.2.2.2-13
2.6.5.4 Pharmacokinetics: Absorption after a repeated doses								
2.6.5.4A	Rat (Sprague-Dawley, male), water and food *ad libitum*	p.o.	Single Multiple	[^{14}C]INC280 HCl salt p.o.: 40 mg/kg	Not required	Novartis, Swiss	DMPK R1600074-01	4.2.2.2-14
2.6.5.5 Pharmacokinetics: Organ distribution								
2.6.5.5A	Rat (Sprague-Dawley, male), fasted	i.v.	Single	INC280 HCl salt i.v.: 0.25 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-08.129.1 INCYTE-DMB-08.118.1	4.2.2.3-1 4.2.2.2-2
2.6.5.5B	Rat (Sprague-Dawley, male), water and food *ad libitum*	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg	Not required	Novartis, US Novartis, Swiss [redacted]	DMPK R1100027-01 DMPK R1100027b	4.2.2.2-4 4.2.2.3-2

Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
				p.o.: 10 mg/kg		[redacted] UK		
2.6.5.5C	Rat (Long Evans, pigmented, male), water and food *ad libitum*	p.o.	Single	[^{14}C]INC280 HCl salt p.o.: 10 mg/kg	Not required	Novartis, Swiss	DMPK R1300834-01	4.2.2.3-3
2.6.5.5D	Rat (Sprague-Dawley, male), water and food *ad libitum*	p.o.	Single Multiple	[^{14}C]INC280 HCl salt p.o.: 40 mg/kg	Not required	Novartis, Swiss	DMPK R1600074-01	4.2.2.2-14
2.6.5.6 Plasma protein binding								
2.6.5.6A	Mouse (CD-1), rat (Sprague-Dawley), dog (Beagle), monkey (Cynomolgus), and human	*In vitro* plasma and serum protein binding and *ex vivo* protein binding	NA	INC280 salt	Not required	Incyte Corp., US	INCYTE-DMB-08.122.1 INCYTE-DMB-08.118.1	4.2.2.3-4 4.2.2.2-2
2.6.5.6B	Rat (strain not mentioned), dog (Beagle), monkey (Cynomolgus), and human	Blood to plasma ratio	NA	INC280 HCL salt	Not required	Incyte Corp., US	INCYTE-DMB-08.123.1	4.2.2.3-5
2.6.5.6C	Rat (Sprague-Dawley), monkey (cynomolgus), and human	*In vitro* plasma protein binding	NA	CMN288	Not required	[redacted] UK	DMPK R1600760	4.2.2.3-6
2.6.5.7 Study in pregnant or nursing animals								
NA								
2.6.5.8 Other distribution study								
NA								
2.6.5.9 Metabolism *in vivo*								
2.6.5.9A	Rat (Honnover	i.v. and p.o.	Single	[^{14}C]INC280 HCl	Not required	Novartis, US	DMPK R1100027-01	4.2.2.2-4

Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
	Wistar, male), food and water *ad libitum*			salt i.v.: 3 mg/kg p.o.: 10 mg/kg		Novartis, Swiss		
2.6.5.9B	Rat (Sprague-Dawley, male), food and water *ad libitum*	p.o.	Single Multiple	[^{14}C]INC280 HCl salt p.o.: 40 mg/kg	Not required	Novartis, Swiss	DMPK R1600074-01	4.2.2.2-14
2.6.5.9C	Monkey (Cynomolgus, male), food and water *ad libitum*	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg p.o.: 30 mg/kg	Not required	Novartis, US Novartis, Swiss	DMPK R1300820	4.2.2.2-10
2.6.5.10 Metabolism *in vitro*								
2.6.5.10A	Mouse, rat, dog, monkey, and human hepatocytes; human liver microsomes	*in vitro*	NA	[^{14}C]INC280 HCl salt 5 µM for microsomes 10 µM for hepatocytes	Not required	Novartis, Swiss	DMPK R1000705	4.2.2.4-1
2.6.5.11 Possible metabolic pathways								
2.6.5.11A	Pharmacokinetics: Metabolic pathways *in vitro* in mouse, rat, monkey and human							
2.6.5.11B	Pharmacokinetics: Metabolic pathways *in vivo* in rat, monkey and human							
2.6.5.11C	Pharmacokinetics: Possible metabolic pathways *in vivo* in rat							
2.6.5.11D	Pharmacokinetics: PossiblemMetabolic athways *in vivo* in monkey							
2.6.5.11E	Pharmacokinetics: Possible metabolic pathways *in vivo* in human							
2.6.5.12 Induction / inhibition of drug-metabolizing enzymes								
2.6.5.12A	Rat and human HepG2 cells	*in vitro*	NA	INC280 HCl salt 10 µM	Not required	Incyte Corp., US	INCYTE-DMB-08.135.1	4.2.2.6-1
2.6.5.13 Excretion								
2.6.5.13A	Rat (Hannover Wistar-male),	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt	Not required	Novartis, US	DMPK R1100027-01	4.2.2.2-4

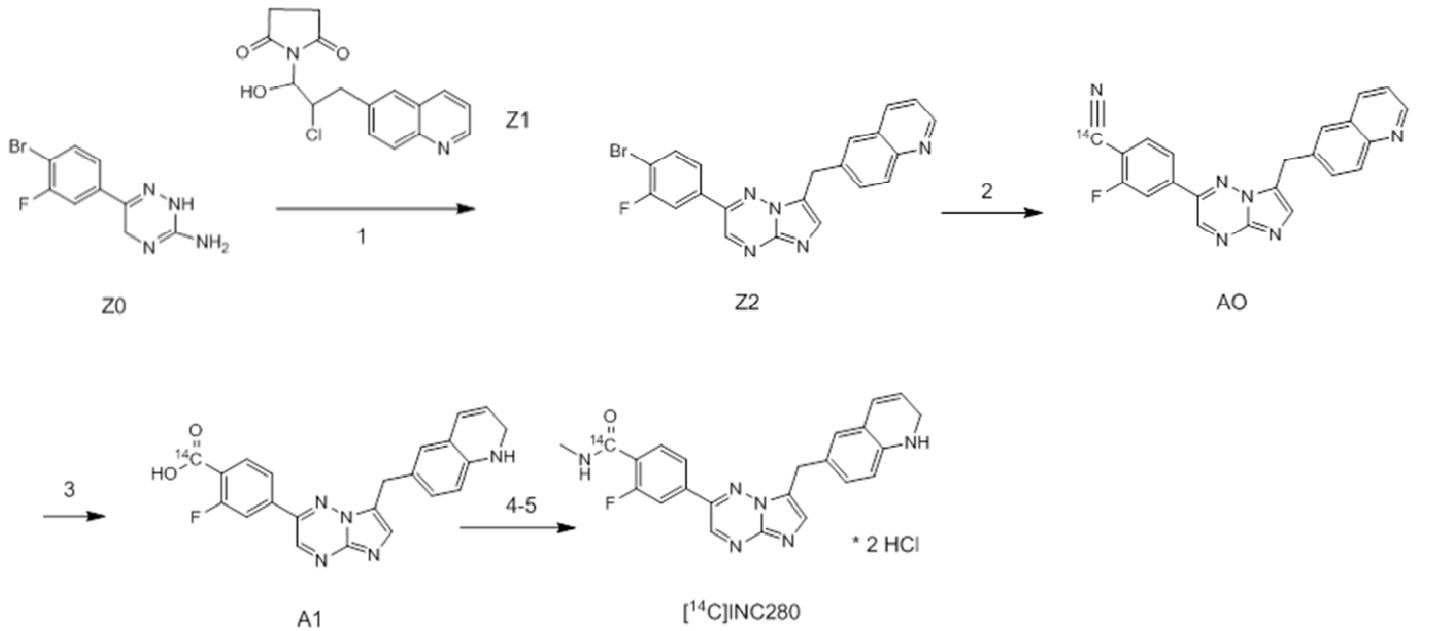
Type of study	Test system(s), Species, Strain, Sex, Feeding	Administration, Sample(s), Batch(es)	Duration of dosing	Test Compound(s), Dose(s), Concentrations	GLP compliance	Testing facility	Study number	Location in CTD
	food and water *ad libitum*			i.v.: 3 mg/kg p.o.: 10 mg/kg		Novartis, Swiss	DMPK R1100027a	4.2.2.2-5
2.6.5.13B	Monkey (Cynomolgus-male), food once daily and water *ad libitum*	i.v. and p.o.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg p.o.: 30 mg/kg	Not required	Novartis, US Novartis, Swiss	DMPK R1300820	4.2.2.2-10
2.6.5.14 Excretion in to bile								
2.6.5.14A	Rat (Hannover Wistar-male), food and water *ad libitum*	i.v.	Single	[^{14}C]INC280 HCl salt i.v.: 3 mg/kg (free base)	Not required	Novartis, US Novartis, Swiss	DMPK R1100027-01 DMPK R1100027a	4.2.2.2-4 4.2.2.2-5
2.6.5.15 Drug-drug interaction								
NA								
2.6.5.16 Other								
2.6.5.16A	Rat (Hanover Wister-male), fasted	i.v.	Single	[^{14}C]Inulin i.v.: 10 mg/kg	Not required	Novartis, Swiss	DMPK R0101302	4.2.2.7-1
2.6.5.16B	Rat (Spraque Dawley-male and female)	p.o.	Multiple	INC280 salt Male: 20, 60, 120 mg/kg Female: 10, 30, 60 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-09.01.1 INCYTE-DMB-08.119.1	4.2.2.7-2 4.2.2.1-4
2.6.5.16C	Monkey (Cynomolgus-male and female)	p.o.	Multiple	INC280 salt 30, 75, 150 mg/kg	Not required	Incyte Corp., US	INCYTE-DMB-09.02.1 INCYTE-DMB-08.120.1	4.2.2.7-3 4.2.2.1-8

2.6.5.2A 薬物動態試験：分析方法

Study title:	[$^{13}CD_3$]INC280 Synthesis and release analysis	Study No. DMPK R1000645 (SEE 200-1)
Location in CTD:	4.2.2.1-1	
GLP compliance:	Not required	
Test articles:	[$^{13}CD_3$]INC280 free base	
Formula (weight):	$^{12}C_{22}{}^{13}C_1H_{14}D_3FN_6O$ (416.44 g/mol)	
Synthesis batch number:	SEE 200-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV	
Synthesis scheme:	 Z0 [$^{13}CD_3$]INC280	
	Reaction conditions: 1. [$^{13}CD_3$]$MeNH_2$ HCl, PyBOP, Et_3N, DMF	
Synthesis information:	Coupling of the acid derivative Z0 with the stable labeled methylamine A0 was performed in the presence of PyBOP. The final product [$^{13}CD_3$]INC280 was obtained after purification.	
Results:	Identity:	Corresponds to structure
	Degree of labeling:	M+4
	Mass purity:	> 99%
	Chemical purity:	> 99.5% (HPLC-UV)

2.6.5.2B 薬物動態試験：分析方法

Study title:	[^{14}C]INC280 Synthesis and release analysis	Study No. DMPK R1000579 (RSE 493-1)
Location in CTD:	4.2.2.1-2	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 dihydrochloride	
Formula (weight):	$C_{23}H_{17}FN_6O \cdot 2HCl$ (485.35 g/mol)	
Synthesis batch number:	RSE 493-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV, HPLC-RA, LSC	
Synthesis scheme:		



Reaction conditions: 1. nBuOH, reflux; 2. [^{14}C]Zn(CN)$_2$, Tris (dibenzylidenacetone) dipalladium, 1,1-Bis (diphenylphosphino) ferrocene, DMF, 110°C; 3. HCl con., H_2O, reflux; 4. $MeNH_2$ 2M THF, PyBOP, Et_3N, DMF, 5. HCl 6M, H_2O, MeCN

Study title:	[^{14}C]INC280 Synthesis and release analysis		Study No. DMPK R1000579 (RSE 493-1)
Synthesis information:	Thermal condensation of compound Z0 (provided by the external supplier Pharmaron) and Z1 (provided by Chemical and Analytical Development (CHAD) at Novartis) provided bromide derivative Z2. The palladium coupling catalyzed reaction of C-14 zinc cyanide with bromide Z2 gave the corresponding labeled cyanide derivative A0. Hydrolysis of cyanide A0 followed by amide coupling reaction between the resulting acid A1 and methylamine promoted by PyBOP gave [^{14}C]INC280 as free base. Final salt formation by treatment with aqueous hydrochloride acid in water/acetonitrile afforded [^{14}C]INC280 dihydrochloride product.		
Results:	Identity:	Corresponds to reference	
	Specific activity:	1.762 GBq/mmol; 3.630 MBq/mg	
	Radiochemical purity:	99.0% (HPLC-RA)	
	Chemical purity:	99.4% (HPLC-UV)	

2.6.5.2C 薬物動態試験：分析方法

Study title:	Quantitative determination of INC280 in mouse plasma by LC-MS/MS	Study No. DMPK R1100266F
Location in CTD:	4.2.2.1-3	
GLP compliance:	Not required	
Test articles:	INC280	
Species / matrix:	Mouse / plasma	
Method:	The method for a 50 µL plasma sample consists of addition of 25 µL internal standard working solution, protein precipitation with 200 µL of acetonitrile, centrifugation, evaporation of solvent, reconstitution of the sample residues with 200 µL of 20/80 (v/v) acetonitrile/water, injection of 5-7 µL into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INC280	
Internal standard:	[M+4]INC280	

Results:		
	Selectivity:	Interference of INC280 ≤ 20% of analytical response at the LLOQ
		Interference of [M+4]INC280 ≤ 5% of analytical response at the working concentration
	Stability:	Stable in post-preparative extracts for 5 days at 5°C
		Stable in spiked mouse plasma after 4 freeze-thaw cycles with storage at ≤ −60°C
		Stable in spiked mouse plasma for 24 h at room temperature
		Stable in spiked mouse plasma for 57 days at ≤ −60°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 10.0 ng/mL; ULOQ: 10000 ng/mL using 50 µL of mouse plasma
	Recovery:	Mean recovery of INC280 at 3 concentration levels: 101% (96.9%-106%)
		Mean recovery of [M+4]INC280 at the working concentration: 98.8%
		Mean [M+4]INC280 normalized recovery of INC280 at 3 concentration levels: 102% (98.9% to 107%)
	Matrix effect:	Range of matrix factor for INC280 at 3 concentration levels: 1.03 to 1.09
		Range of matrix factor for [M+4]INC280 at the working concentration: 1.04 to 1.10
		[M+4]INC280 normalized matrix factor for INC280 at 3 concentration levels: 0.998 (0.987 to 1.01)
	Carryover:	Response after injection of one blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for INC280

Study title:	Quantitative determination of INC280 in mouse plasma by LC-MS/MS	Study No. DMPK R1100266F
	Response after injection of one blank sample following injection of the ULOQ < 5% of the response observed for the working concentration for [M+4]INC280	
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%
	Special issues:	None

2.6.5.2D 薬物動態試験：分析方法

Study title:	INCB028060: Method validation for the quantitation of INCB028060 in rat plasma by turbo ion spray LC-MS/MS	Study No. INCYTE-DMB-08.119.1
Location in CTD:	4.2.2.1-4	
GLP compliance:	Not required	
Test articles:	INCB028060	
Species / matrix:	Rat / plasma	
Method:	The method for a 50 µL plasma sample consists of addition of 50 µL internal standard working solution, condition with a 100 µL of 0.1M $NaHCO_3$, liquid-liquid extraction with 800 µL of methyl t-butyl ether (MTBE), vortex-mixing and centrifugation, evaporation of MTBE layer, reconstitution of the sample residue with 300 µL of 25/75 (v/v) acetonitrile/water, injection of 2 µL of the reconstituted sample extract into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INCB028060	
Internal standard:	INCB0027868 (N-ethyl-2-fluoro-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide)	
Results:	Validation in plasma	
	Selectivity:	Interference of INCB028060 ≤ 20% of analytical response at the LLOQ
	Stability:	Stable in stock solutions for 106 days at ≤ 2-8°C
		Stable in post-preparative extracts for 11 days at room temperature
		Stable after 3 freeze-thaw cycles with storage at ≤ −80°C
		Stable in spiked rat plasma for 24 h at room temperature
		Stable in rat plasma for 85 days at ≤ −80°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 0.01 µM; ULOQ: 20 µM using 50 µL of rat plasma
	Recovery:	Mean recovery of INCB028060 at 3 concentration levels: 47.9% (45.1% to 50.2%)
		Mean recovery of INCB027868 at the working concentration: 49.0% (45.1% to 52.1%)
	Matrix effect:	Mean matrix factor for INCB028060 at 3 concentration levels: 0.914 (0.864 to 0.955)
		Mean matrix factor for INCB027868 at the working concentration: 0.947 (0.935 to 0.960)
	Carryover:	Response after injection of 1 blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for

Study title:	INCB028060: Method validation for the quantitation of INCB028060 in rat plasma by turbo ion spray LC-MS/MS	Study No. INCYTE-DMB-08.119.1
		INCB028060
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%
	Special issues:	None

2.6.5.2E 薬物動態試験：分析方法

Study title:	Quantitative determination of INC280 in rat plasma by LC-MS/MS	Study No. DMPK R1100266C
Location in CTD:	4.2.2.1-5	
GLP compliance:	Not required	
Test articles:	INC280	
Species / matrix:	Rat / plasma	
Method:	The method for a 50 µL plasma sample consists of protein precipitation with 200 µL of acetonitrile containing internal standard, centrifugation, evaporation of supernatant, reconstitution of sample residue with 50/50 (v/v) acetonitrile/water, injection of 5 µL into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INC280	
Internal standard:	[M+4]INC280	
Results:	Validation in plasma	
	Specificity:	Interference of INC280 ≤ 20% of analytical response at the LLOQ
		Interference of [M+4]INC280 ≤ 5% of analytical response at the working concentration
	Stability:	Stable in stock solutions for 50 days at ≤ −15°C
		Stable in post-preparative extracts for 24 h at room temperature
		Stable after 3 freeze-thaw cycles with storage at ≤ −60°C
		Stable in spiked rat plasma for 24 h at room temperature
		Stable in rat plasma for 33 days at ≤ −60°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 5.00 ng/mL; ULOQ: 5000 ng/mL using 50 µL of rat plasma
	Recovery:	Mean recovery of INC280 at 3 concentration levels: 94.9% (88.4% to 107%)
		Mean recovery of [M+4]INC280 at the working concentration: 101%
		Mean M+4]INC280 normalized recovery of INC280 at 3 concentration levels: 101%
	Matrix effect:	Mean matrix factor for INC280 at 3 concentration levels: 0.998
		Mean matrix factor for [M+4]INC280 at the working concentration: 1.04
	Carryover:	Response after injection of one blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for

Study title:	Quantitative determination of INC280 in rat plasma by LC-MS/MS		Study No. DMPK R1100266C
		INC280	
		Response after injection of one blank sample following injection of the ULOQ < 5% of the response observed for the working concentration for [M+4]INC280	
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels	
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%	
	Special issues:	None	

2.6.5.2F 薬物動態試験：分析方法

Study title:	Quantitative determination of INC280 in rabbit plasma by LC-MS/MS	Study No. DMPK R1100266D
Location in CTD:	4.2.2.1-6	
GLP compliance:	Not required	
Test articles:	INC280	
Species / matrix:	Rabbit / plasma	
Method:	The method for a 50 µL plasma sample consists of addition of 25 µL internal standard working solution, protein precipitation with 200 µL of acetonitrile, centrifugation, evaporation of the supernatant, reconstitution of the sample residue with 150 µL of 20/80 (v/v) acetonitrile/water, injection of 3 to 5 µL into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INC280	
Internal standard:	[M+4]INC280	
Results:	Validation in plasma	
	Specificity:	Interference of INC280 ≤ 20% of analytical response at the LLOQ
		Interference of [M+4]INC280 ≤ 5% of analytical response at the working concentration
	Stability:	Stable in stock solutions for 50 days at ≤ −15°C, 21 hours at room temperature
		Stable in post-preparative extracts for 7 days at 2-8°C
		Stable after 4 freeze-thaw cycles with storage at ≤ −60°C
		Stable in spiked rabbit plasma for 24 h at room temperature
		Stable in rabbit plasma for 69 days at ≤ −60°C
		Stable in incurred rabbit plasma for 31 days at ≤ −60°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 1.00 ng/mL; ULOQ: 1000 ng/mL using 50 µL of rabbit plasma
	Recovery:	Mean recovery of INC280 at 3 concentration levels: 101% (93.1% to 107%)
		Mean recovery of [M+4]INC280 at the working concentration: 102%
	Matrix effect:	Mean matrix factor for INC280 at 3 concentration levels: 1.15
		Mean matrix factor for [M+4]INC280 at the working concentration: 1.12
	Carryover:	Response after injection of one blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for

Study title:	Quantitative determination of INC280 in rabbit plasma by LC-MS/MS		Study No. DMPK R1100266D
		INC280	
		Response after injection of one blank sample following injection of the ULOQ < 5% of the response observed for the working concentration for [M+4]INC280	
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels	
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%	
	Special issues:	None	
	<u>Cross validation in plasma (50.0-50000 ng/mL)</u>		
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values	
		Precision of ≤ 15% (≤ 20% at the LLOQ)	
	Dynamic range:	LLOQ: 50.0 ng/mL; ULOQ: 50000 ng/mL using 50 µL of rabbit plasma	
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels	
	Special issues:	None	

2.6.5.2G 薬物動態試験：分析方法

Study title:	Quantitative determination of INC280 in dog plasma by LC-MS/MS	Study No. DMPK R1300899
Location in CTD:	4.2.2.1-7	
GLP compliance:	Not required	
Test articles:	INC280	
Species / matrix:	Dog / plasma	
Method:	The method for a 100 µL plasma sample consists of addition of 50 µL internal standard working solution, condition with 300 µL of 0.5% ammonium hydroxide in water, solid phase extraction with 3M Empore™ C_{18} 96-well plate (10 mg/well), elution with methanol, evaporation of the eluent, reconstitution of the sample residue with 300 µL of 20/80 (v/v) acetonitrile/water, injection of 10 µL of the reconstituted sample extract into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INC280	
Internal standard:	[M+4]INC280	
Results:	Validation in plasma	
	Specificity:	Interference of INC280 ≤ 20% of analytical response at the LLOQ
		Interference of [M+4]INC280 ≤ 5% of analytical response at the working concentration
	Stability:	Stable in post-preparative extracts for 84 hours at 8°C
		Stable after 5 freeze-thaw cycles with storage at ≤ −15°C and ≤ −70°C
		Stable in spiked dog plasma for 24 h at room temperature
		Stable in dog plasma for 40 days at ≤ −15°C and ≤ −70°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 1.00 ng/mL; ULOQ: 1000 ng/mL using 100 µL of dog plasma
	Recovery:	Mean recovery of INC280 at 3 concentration levels: 82.7% (80.0% to 84.7%)
		Mean recovery of [M+4]INC280 at the working concentration: 82.5%
	Matrix effect:	Mean matrix factor for INC280 at 3 concentration levels: 1.11 (1.03 to 1.18)
		Mean matrix factor for [M+4]INC280 at the working concentration: 1.03 (1.02 to 1.04)
	Carryover:	Response after injection of 1 blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for INC280.

Study title:	Quantitative determination of INC280 in dog plasma by LC-MS/MS	Study No. DMPK R1300899
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 20-fold. Precision ≤ 15%
	Special issues:	The unfulfilled carryover assessment may have been due to column aging. Therefore, the possible impact due to carryover shall be evaluated in study sample analysis.

2.6.5.2H 薬物動態試験：分析方法

Study title:	INCB028060: Method validation for the quantitation of INCB028060 in cynomolgus monkey plasma by turbo ion spray LC-MS/MS	Study No. INCYTE-DMB-08.120.1
Location in CTD:	4.2.2.1-8	
GLP compliance:	Not required	
Test articles:	INCB0280060	
Species / matrix:	Cynomolgus monkey / plasma	
Method:	The method for a 50 µL plasma sample consists of addition of 50 µL internal standard working solution, condition with 100 µL of 0.1M $NaHCO_3$, liquid-liquid extraction with 800 µL MTBE, vortex-mixing and centrifugation, evaporation of MTBE layer, reconstitution of the sample residue with 300 µL of 25/75 (v/v) acetonitrile/water, injection of 2 µL into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INCB028060	
Internal standard:	INCB0027868	
Results:	Validation in plasma	
	Specificity:	Interference of INCB028060 ≤ 20% of analytical response at the LLOQ
	Stability:	Stable in stock solutions for 106 days at ≤ 2-8°C
		Stable in post-preparative extracts for 10 days at room temperature
		Stable after 3 freeze-thaw cycles with storage at ≤ −80°C
		Stable in spiked monkey plasma for 24 h at room temperature
		Stable in monkey plasma for 102 days at ≤ −80°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 0.02 µM; ULOQ: 20 µM using 50 µL of monkey plasma
	Recovery:	Mean recovery of INCB028060 at 3 concentration levels: 39.9% (33.9 to 45.4%)
		Mean recovery of INCB027868 at the working concentration: 44.7% (40.1% to 50.3%)
	Matrix effect:	Mean matrix factor for INCB028060 at 3 concentration levels: 0.973 (0.886 to 1.08)
		Mean matrix factor for INCB027868 at the working concentration: 0.976 (0.898 to 1.11)
	Carryover:	Response after injection of one blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for INCB028060

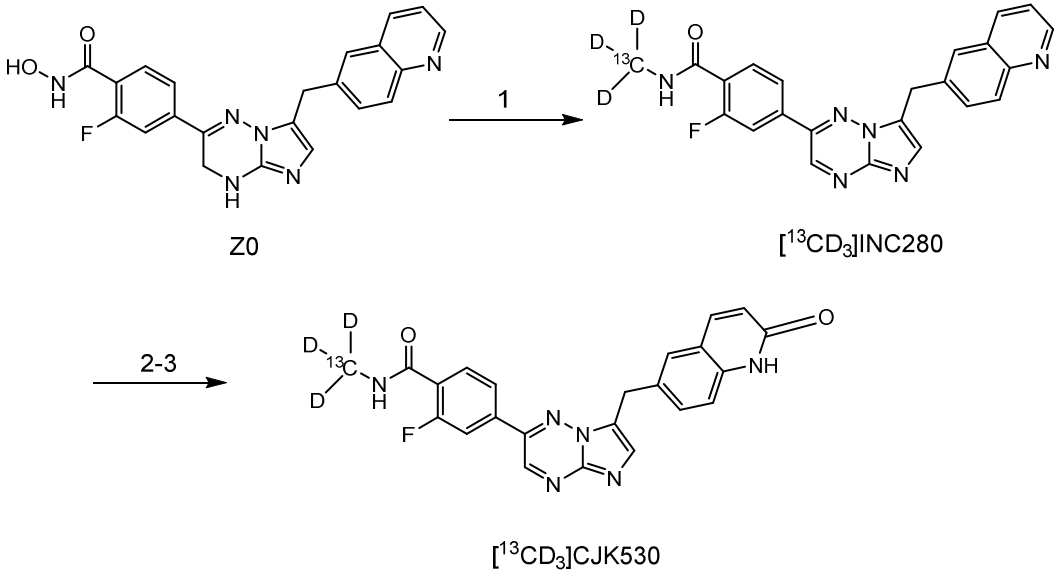
Study title:	INCB028060: Method validation for the quantitation of INCB028060 in cynomolgus monkey plasma by turbo ion spray LC-MS/MS		Study No. INCYTE-DMB-08.120.1
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels	
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%	
	Special issues:	None	

2.6.5.2I 薬物動態試験：分析方法

Study title:	Quantitative determination of INC280 in monkey plasma by LC-MS/MS	Study No. DMPK R1100266
Location in CTD:	4.2.2.1-9	
GLP compliance:	Not required	
Test articles:	INC280	
Species / matrix:	Monkey / plasma	
Method:	The method for a 50 µL plasma sample consists of addition of 25 µL internal standard working solution, protein precipitation with 200 µL of acetonitrile, centrifugation, dilution of the supernatant with 20/80 (v/v) acetonitrile/water, injection of 5 µL into an LC-MS/MS system and measurement in MRM mode using ESI positive as the ionization method.	
Substance analyzed:	INC280	
Internal standard:	[M+4]INC280	
Results:	Validation in plasma	
	Selectivity:	Interference of INC280 ≤ 20% of analytical response at the LLOQ
		Interference of [M+4]INC280 ≤ 5% of analytical response at the working concentration
	Stability:	Stable in stock solutions for 50 days at ≤ −15°C
		Stable in post-preparative extracts for 5 days at 5°C
		Stable after 3 freeze-thaw cycles with storage at ≤ −60°C
		Stable in spiked monkey plasma for 24 h at room temperature
		Stable in monkey plasma for 154 days at ≤ −60°C
	Intra-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Inter-day accuracy and precision:	Mean bias within ±15% (±20% at the LLOQ) of the nominal values
		Precision of ≤ 15% (≤ 20% at the LLOQ)
	Dynamic range:	LLOQ: 10.0 ng/mL; ULOQ: 10000 ng/mL using 50 µL of monkey plasma
	Recovery:	Mean recovery of INC280 at 3 concentration levels: 106% (88.0% to 129%)
		Mean recovery of [M+4]INC280 at the working concentration: 103%
		[M+4]INC280 normalized recovery of INC280 at 3 concentration levels: 101% (99.9% to 102%)
	Matrix effect:	Range of matrix factor for INC280 at 3 concentration levels: 0.669 to 0.881
		Range of matrix factor for [M+4]INC280 at the working concentration: 0.626 to 0.853
		[M+4]INC280 normalized matrix factor for INC280 at 3 concentration levels: 1.06 (1.03 to 1.13)

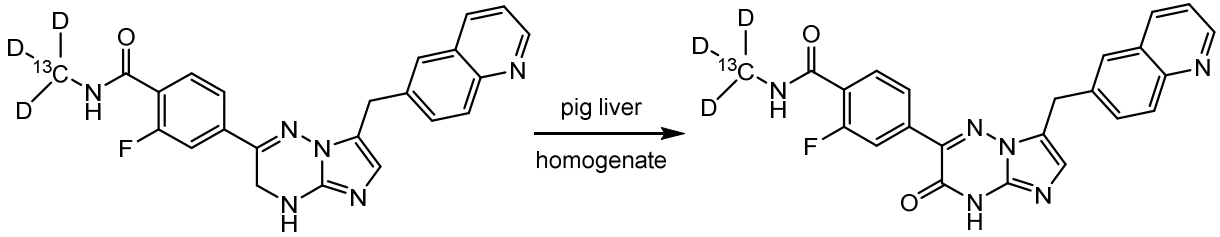
Study title:	Quantitative determination of INC280 in monkey plasma by LC-MS/MS	Study No. DMPK R1100266
	Carryover:	Response after injection of one blank sample following injection of the ULOQ < 20% of the response observed for the LLOQ for INC280
		Response after injection of one blank sample following injection of the ULOQ < 5% of the response observed for the working concentration for [M+4]INC280
	Calibration:	Deviation of ±15% (±20% at the LLOQ) for 75% of the calibration standards from the nominal values at a minimum of 6 different levels
	Dilutions:	Bias within ±15% of the nominal concentration for samples diluted up to 10-fold. Precision ≤ 15%
	Special issues:	The coefficient of variation (CV) (%) values measured for some of the matrix factor and recovery evaluations for the analyte and/or the internal standard did not meet the acceptance criteria (≤ 15%). However, the CV% values for the internal standard normalized matrix factor and recovery values were all less than 15% for the analyte. The results were accepted and reported.

2.6.5.2J 薬物動態試験：分析方法

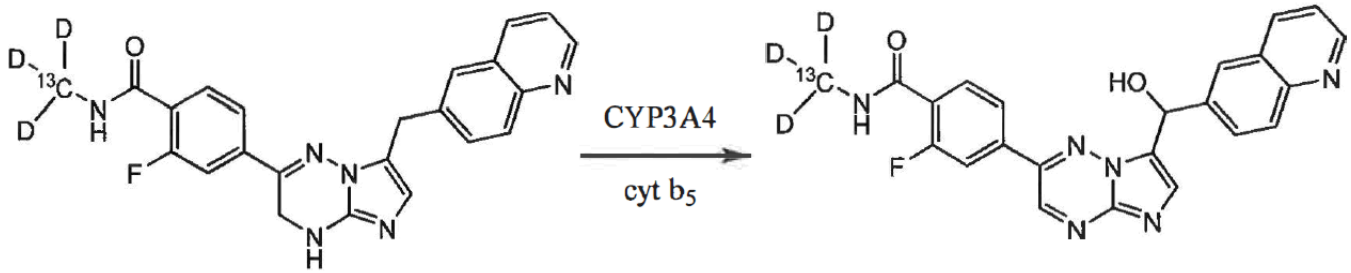
Study title:	[$^{13}CD_3$]CJN530 (metabolite of INC280) Synthesis and release analysis	Study No. DMPK R1000646 (SSE 201-1)
Location in CTD:	4.2.2.1-10	
GLP compliance:	Not required	
Test articles:	[$^{13}CD_3$]CJK530 free base	
Formula (weight):	$^{12}C_{22}{}^{13}C_1H_{14}D_3FN_6O_2$ (432.44 g/mol)	
Isotope label:	^{13}C, Deuterium	
Synthesis batch number:	SSE 201-1	
Analytical methods (Identity, Mass and Chemical Purity):	HPLC-UV, ^{1}H-NMR, MS	
Synthesis scheme:	 Z0 → [$^{13}CD_3$]INC280 → [$^{13}CD_3$]CJK530 Reaction conditions: 1. [$^{13}CD_3$]MeNH$_2$.HCl, PyBOP, Et$_3$N, DMF; 2. MCPBA, CHCl$_3$; 3. toluenesulfonyl chloride, K_2CO_3, H_2O, CH_2Cl_2.	
Synthesis information:	Coupling of the acid derivative Z0 with the stable labeled methylamine A0 was performed in the presence of PyBOP to afford [$^{13}CD_3$]INC280. N-oxidation of the quinoline residue with MCPBA followed by treatment of the resulting N-oxide with toluensulfonylchloride gave the final product	

Study title:	[$^{13}CD_3$]CJN530 (metabolite of INC280) Synthesis and release analysis		Study No. DMPK R1000646 (SSE 201-1)
	[$^{13}CD_3$]CJK530.		
Results:	Identity:	Corresponds to structure	
	Degree of labeling:	M+4	
	Mass purity:	> 99% (MS)	
	Chemical purity:	99% (HPLC-UV)	

2.6.5.2K 薬物動態試験：分析方法

Study title:	[$^{13}CD_3$]CMN288 Synthesis and release analysis	Study No. DMPK R1400283 (SSE 270-1)
Location in CTD:	4.2.2.1-11	
GLP compliance:	Not required	
Test articles:	[$^{13}CD_3$]CMN288 free base	
Formula (weight):	$^{12}C_{22}{}^{13}C_1H_{14}D_3FN_6O_2$ (432.43 g/mol)	
Isotope label:	^{13}C, Deuterium	
Synthesis batch number:	SSE 270-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV	
Synthesis scheme:	 [$^{13}CD_3$]INC280 → [$^{13}CD_3$]CMN288	
Synthesis information:	The starting precursor [$^{13}CD_3$]INC280 was prepared via a chemical synthesis route. [$^{13}CD_3$]INC280 was biochemically oxidized using pig liver homogenate to the hydroxylated [$^{13}CD_3$]CMN288 product following the same procedures for unlabeled CMN288.	
Results:	Identity:	Corresponds to reference
	Degree of labeling:	M + 4
	Mass purity:	> 99% (MS)
	Chemical purity:	98.9% (HPLC-UV)

2.6.5.2L 薬物動態試験：分析方法

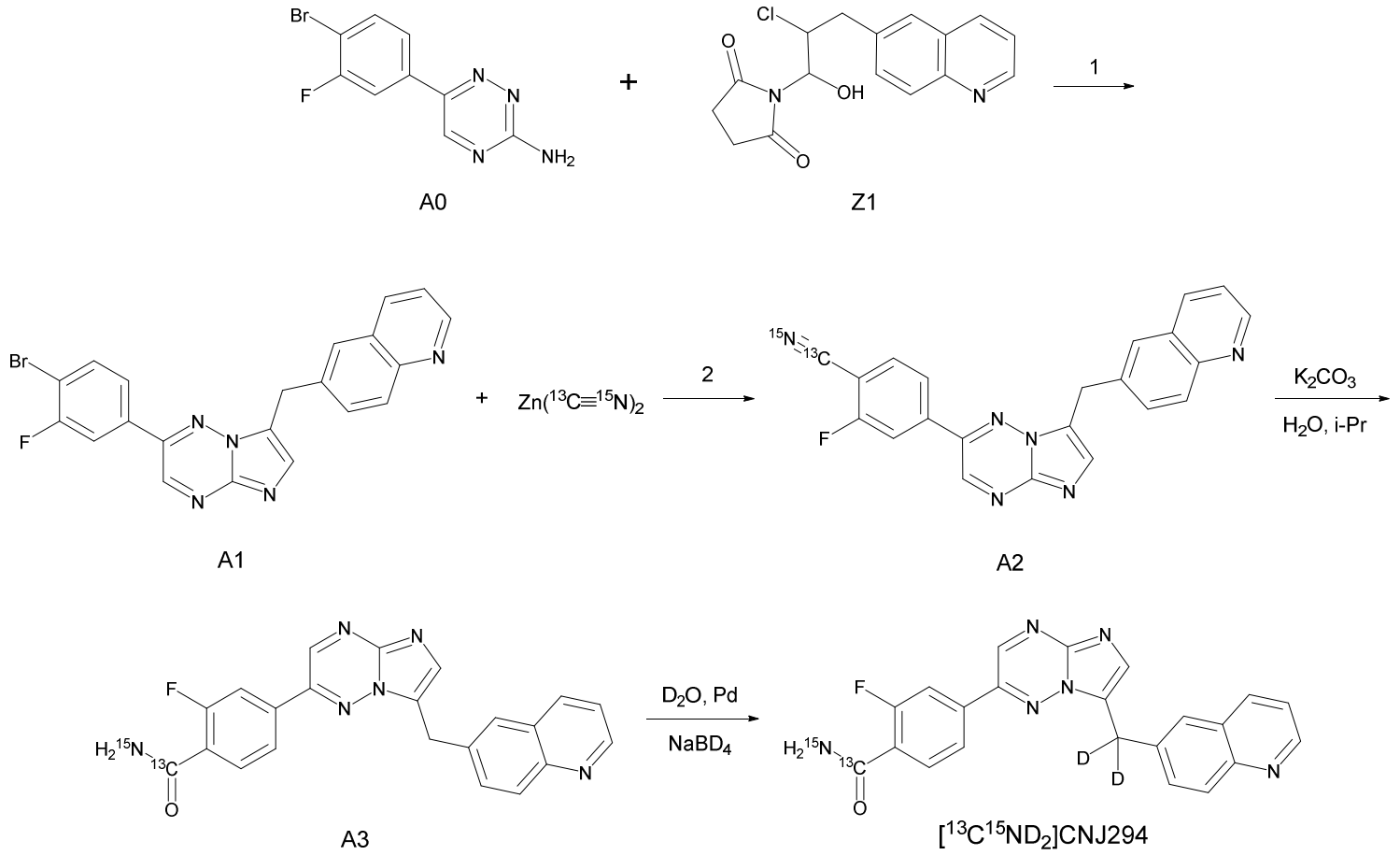
Study title:	[$^{13}CD_3$]CMN290 Synthesis and release analysis	Study No. DMPK R1400841-01 (SSE 281-1)
Location in CTD:	4.2.2.1-12	
GLP compliance:	Not required	
Test articles:	[$^{13}CD_3$]CMN290 free base	
Formula (weight):	$^{12}C_{22}{}^{13}C_1H_{14}D_3FN_6O_2$ (432.44 g/mol)	
Isotope label:	^{13}C, Deuterium	
Synthesis batch number:	SSE 281-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV	
Synthesis scheme:		
Synthesis information:	The starting stable labeled precursor [$^{13}CD_3$]INC280 was prepared via a chemical synthesis route. [$^{13}CD_3$]INC280 was oxidized using CYP3A4 to the hydroxylated [$^{13}CD_3$]CMN290 product in a similar manner to the non-labeled CMN290 as described in 4.2.2.1-15-RD-2017-00400.	
Results:	Identity:	Corresponds to reference
	Degree of labeling:	M+4
	Mass purity:	> 99% (MS)
	Chemical purity:	98.5% (HPLC-UV)

2.6.5.2M 薬物動態試験：分析方法

Study title:	[$^{13}C^{15}ND_2$]CNJ294 Synthesis and release analysis	Study No. DMPK R1400842 (SSE 282-1)
Location in CTD:	4.2.2.1-13	
GLP compliance:	Not required	
Test articles:	[$^{13}C^{15}ND_2$]CNJ294 free base	
Formula (weight):	$^{12}C_{21}{}^{13}CH_{13}D_2F^{15}N_1N_5O$ (402.39 g/mol)	
Isotope label:	^{13}C, Deuterium, ^{15}N	
Synthesis batch number:	SSE 282-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV	

Study title:	[$^{13}C^{15}ND_2$]CNJ294 Synthesis and release analysis	Study No. DMPK R1400842 (SSE 282-1)

Synthesis scheme:

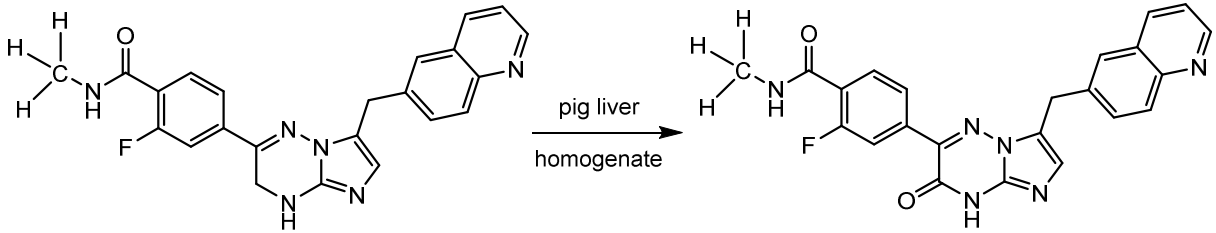


Reaction conditions: 1. 1-Butanol, 110°C, 12 h, $NaHCO_3$, $MgSO_4$; 2. $Zn(^{13}C{\equiv}^{15}N)_2$, DMF, 1,1'- Bis(diphenylphosphino)ferrocene, tris (dibenzylideneacetone) dipalladium (0), 120°C, 12 h, $NaHCO_3$, EtOAc, $MgSO_4$.

Synthesis information: The starting precursor A0 was coupled to Z1 to form A1. Intermediate A1 was subsequently coupled with Zn ($^{13}C{\equiv}^{15}N)_2$ under palladium catalytic conditions to obtain A2. Subsequent nitrile hydrolysis of A2 gave the subsequent amide A3. To obtain the final labeled [$^{13}C^{15}ND_2$]CNJ294 product, the

Study title:	[$^{13}C^{15}ND_2$]CNJ294 Synthesis and release analysis		Study No. DMPK R1400842 (SSE 282-1)
	two deuterium labels were reductively introduced in intermediate A3 using $NaBD_4$, Pd and D_2O.		
Results:	Identity:	Corresponds to structure	
	Degree of labeling:	M+4	
	Mass purity:	> 99% (MS)	
	Chemical purity:	99.1% (HPLC-UV)	

2.6.5.2N 薬物動態試験：分析方法

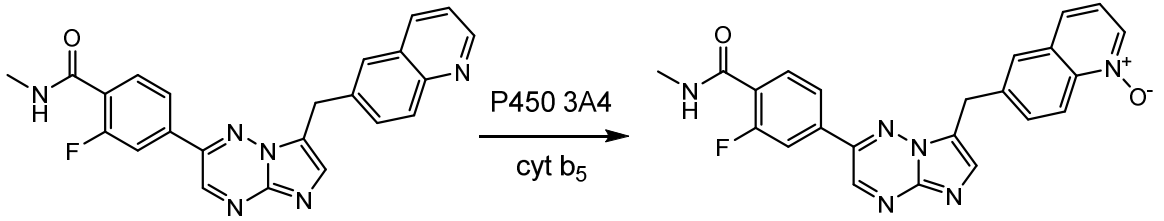
Study title:	CMN288 Synthesis and release analysis	Study No. DMPK R1400282 (USE 036-1)
Location in CTD:	4.2.2.1-14	
GLP compliance:	Not required	
Test articles:	CNM288 free base	
Formula (weight):	$C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
Isotope label:	NA	
Synthesis batch number:	USE 036-1	
Analytical methods (Identity, Mass and Chemical Purity):	^{1}H-NMR, MS, HPLC-UV	
Synthesis scheme:		
	INC280 CMN288	
Synthesis information:	INC280 was biochemically oxidized using pig liver homogenate to the hydroxylated CMN288 product using as described in 4.2.2.1-15-RD-2017-00400.	
Results:	Identity:	Corresponds to structure
	Degree of labeling:	NA
	Mass purity:	> 99% (MS)
	Chemical purity:	95% (HPLC-UV)

2.6.5.2O 薬物動態試験：分析方法

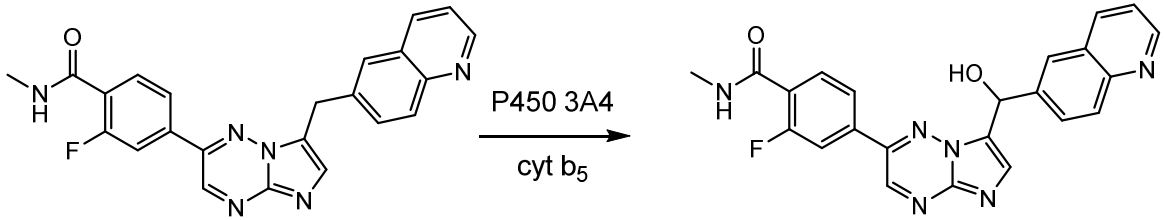
Study title:	Biocatalytic syntheses of NVP-INC280 metabolites	Study No. RD-2017-00400
Location in CTD:	4.2.2.1-15	
GLP compliance:	Not required	
Test articles:	CJH800, CMN290, CNJ292, CNJ294, CNJ296, CNN019 and CMN288	
Formula (weight):	CJH800: $C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
	CNM290: $C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
	CNJ292: $C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
	CNJ294: $C_{22}H_{15}FN_6O$ (398.40 g/mol)	
	CNJ296: $C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
	CNN019: $C_{23}H_{17}FN_6O_3$ (444.43 g/mol)	
	CMN288: $C_{23}H_{17}FN_6O_2$ (428.43 g/mol)	
Isotope label:	NA	
Synthesis batch number:	CJH800: NVP-CJH800-NX-3	
	CNM290: NVP-CMN290-NX-1 and NVP-CMN290-NX-2	
	CNJ292: NVP-CNJ292-NX-1	
	CNJ294: NVP-CNJ294-NX-1	
	CNJ296: NVP-CNJ296-NX-1	
	CNN019:NVP-CNN019-NX-1	
	CMN288: NVP-CMN288-NX-1, NVP-CMN288-NX-3, NVP-CMN288-NX-4, NVP-CMN288-NX-5 and NVP-CMN288-NX-6	
Analytical methods (Identity, Mass and Chemical Purity):	HPLC-UV, ^{1}H-NMR, HPLC-MS	

Study title:	Biocatalytic syntheses of NVP-INC280 metabolites	Study No. RD-2017-00400

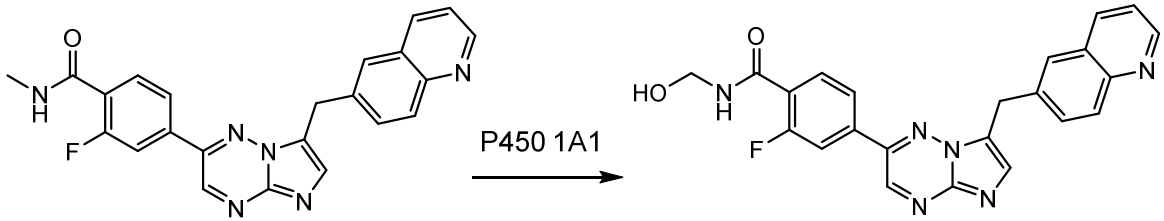
Synthesis scheme:



INC280 CJH800

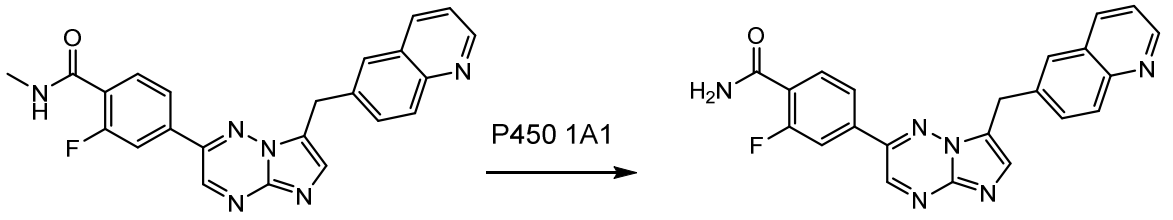


INC280 CMN290

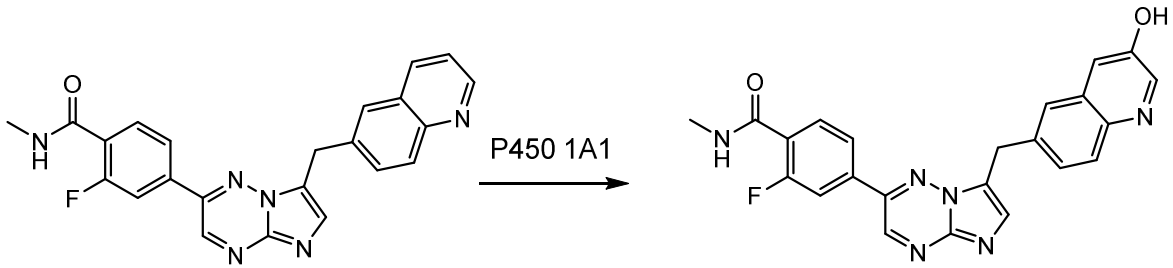


INC280 CNJ292

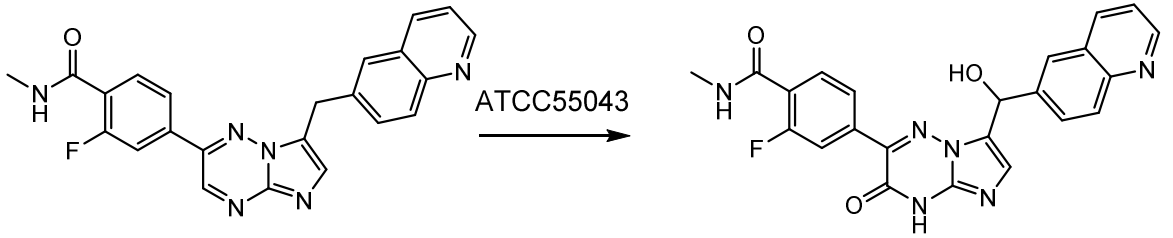
Study title:	Biocatalytic syntheses of NVP-INC280 metabolites	Study No. RD-2017-00400



INC280　　CNJ294

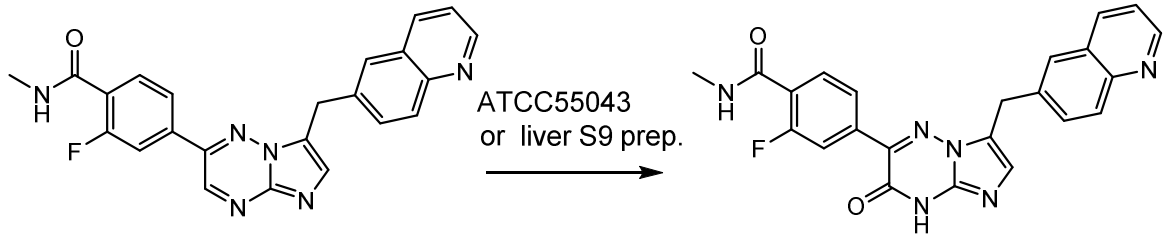


INC280　　CNJ296



INC280　　CNN019

Study title:	Biocatalytic syntheses of NVP-INC280 metabolites	Study No. RD-2017-00400



INC280 CMN288

Synthesis information:	The biocatalytic synthesis of the metabolites NVP-CJH800 and NVP-CMN290 were carried out applying *E. coli* whole cell biocatalysts co-expressing human CYP 3A4 together with human CYP reductase and human cytochrome b_5. The biocatalytic synthesis of the metabolites NVP-CNJ292, NVP-CNJ294 and NVP-CNJ296 were carried out applying *E. coli* whole cell biocatalysts co-expressing human CYP 1A1 together with human CYP reductase. The metabolite NVP-CMN288 and NVP-CNN019 were synthesized by biotransformation of NVP-INC280 with the microbial strain ATCC55043 (*Streptomyces sp.*). In addition several batches of NVP-CMN288 were all obtained by using pig or foal liver S9 preparation	
Results:	Identity:	Corresponds to structure
	Degree of labeling:	NA
	Chemical purity:	94%-99% (HPLC-UV)

2.6.5.3A 薬物動態試験：単回投与後の吸収（マウス）

Study title:	The pharmacokinetics of INCB028060 in mice		Study No. INCYTE-DMB-08.124.1
Location in CTD:	4.2.2.2-1		
GLP compliance:	Not required		
Test articles:	INC280 (synonym: INCB028060) (Lot 4392-90, free base)		
Species / Strain:	Mouse /CD-1		
Gender / No. of animals:	Male/27, Female/27 (3 per collection time)		
Feeding condition:	Not reported		
Vehicle / Formulation:	5% dimethylacetamide, 10% propylene glycol in saline		
Route of dosing:	i.v.		
Dose:	2.5 mg/kg		
Samples:	Plasma		
Sample times:	Pre-dose, 0.083, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h post-dose		
Analyte:	INC280		
Analytical methods:	LC-MS/MS (details in INCYTE-DMB-08.118.1)		
Results:	PK parameters [a)]	Male (2.5 mg/kg)	Female (2.5 mg/kg)
	CLplasma (L//h/kg)	1.50	1.05
	Vss (L/kg)	0.98	0.77
	T1/2 (h)	0.66	0.76

a) Values are given as mean; no SD reported

2.6.5.3B 薬物動態試験：単回投与後の吸収（ラット）

Study title:	The pharmacokinetics of INCB028060 in rat		Study No. INCYTE-DMB-08.128.1
Location in CTD:	4.2.2.2-3		
GLP compliance:	Not required		
Test articles:	INC280 (synonym: INCB028060) (Lot 2, trifluoroacetic acid salt)		
Species / Strain:	Rat / Sprague-Dawley		
Gender / No. of animals:	Male / 6 (3 for i.v., 3 for p.o.)		
Feeding condition:	Not reported		
Vehicle / Formulation:	i.v.: 5% dimethylacetamide, 40% propylene glycol in saline		
	p.o.: 5% dimethylacetamide in 0.5% aqueous methylcellulose		
Route of dosing:	i.v. and p.o.		
Dose:	5 mg/kg		
Samples:	Plasma		
Sample times:	Pre-dose, 0.083, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h post-dose		
Analyte:	INC280		
Analytical methods:	LC-MS/MS (details in 4.2.2.2-2-INCYTE-DMB-08.118.1)		
Results:	PK parameters [a)]	i.v. (5 mg/kg)	p.o. (5 mg/kg)
	Tmax (h)	-	0.33 ± 0.14
	Cmax (μM)	-	7.60 ± 2.08
	AUCinf (μM·h)	26.32 ± 1.36	17.4 ± 1.0
	CLplasma (L/h/kg)	0.46 ± 0.02	-
	Vss (L/kg)	0.61 ± 0.07	-
	T1/2 (h)	3.6 ± 1.3	2.9 ± 0.9
	Bioavailability	-	66.2 ± 3.8
Conclusion:	Following intravenous administration, the mean systemic plasma clearance (CLplasma) of INC280 was approximately 14% of hepatic blood flow in rats. The mean volume of distribution (Vss) was similar to the total volume of body water in rats, suggesting limited distribution beyond body water. The mean half-life (T1/2) for INC280 was 3.6 ± 1.3 h. Following oral administration in rats, the mean peak plasma concentration (Cmax) and AUC values of INC280 were 7.60 ± 2.08 μM and 17.4 ± 1.0 μM*h, respectively, and the mean Tmax value was 0.33 ± 0.14 h. The apparent terminal half-life (T1/2) for INC280 was with 2.9 ± 0.9 h similar to that observed after i.v. dosing. The mean oral bioavailability of INC280 in rats was (66.2 ± 3.8%).		

a) Values are given as mean ± SD of n=3.

2.6.5.3C 薬物動態試験：単回投与後の吸収（ラット）

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No. 1 — Study No. DMPK R1100027-01
Location in CTD:	4.2.2.2-4
GLP compliance:	Not required
Test articles:	[^{14}C]INC280 (dihydrochrolide)
Species / Strain:	Rat / Hanover Wistar (albino)
Gender / No. of animals:	Male / 13 (3 for i.v. [Group 1], 3 for p.o. [Group 2], 3 for i.v. [Group 3], 4 for p.o. [Group 4])
Feeding condition:	Water and food *ad libitum*
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 300 / 80% aqueous glucose solution (5%) p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80
Route of dosing:	i.v. (bolus), p.o. (gavage)
Dose:	i.v.: 3 mg/kg, p.o.: 10 mg/kg (doses referring to the free base)
Samples:	Plasma
Sample times:	Group 1: 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48 and 72 h post-dose. Group 2: 0.25, 0.5, 1, 2, 4, 8, 24, 30, 48 and 72 h post-dose Group 3: 0.083, 0.5, 1, 4, 8, 24 and 48 h post-dose Group 4: 0.25, 0.5, 1, 4, 8, 24 and 48 h post-dose
Analyte:	[^{14}C]INC280
Analytical methods:	Radioactivity: LSC INC280: LC-MS/MS using ESI, LLOQ: 0.00242 µM or 1 ng/mL (details in 4.2.2.2-5-DMPK R1100027a)

Results:

PK parameters [a)]	Group 1 (i.v., 3 mg/kg, actual dose 3.12 ± 0.0153)			
	^{14}C	INC280	CJK530 (M19)	CMC583 (M13)
Cmax (µM)	12.3 ± 0.493	6.61 ± 0.0897	0.0376 ± 0.00991	0.178 ± 0.0165
Tmax	-	-	0.25 [0.25-0.25]	0.083 [0.083-0.25]
AUClast (µM·h)	16.5 ± 2.34	3.83 ± 0.269	0.0422 ± 0.0100	0.162 ± 0.0128
AUClast/dose (µM·h/[mg/kg])	5.05 ± 0.673	1.23 ± 0.0808	-	-
AUCinf (µM·h)	16.6 ± 2.32	3.86 ± 0.262	-	-
T1/2 (h)	4.66 ± 0.526	1.42 ± 0.0929	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No. 1		Study No. DMPK R1100027-01	
CLplasma (L/h/kg)	-	1.97 ± 0.128	-	-
Vdss (L/kg)	-	1.73 ± 0.203	-	-
Absorption (%)	-	-	-	-
Bioavailability (%)	-	-	-	-

PK parameters [a)]	Group 2 (p.o., 10 mg/kg, actual dose: 10.3 ± 0.100)			
	^{14}C	INC280	CJK530 (M19)	CMC583 (M13)
Cmax (µM)	3.95 ± 0.946	2.06 ± 0.420	0.0129 ± 0.00634	0.0990 ± 0.0114
Tmax	0.5 [0.25-0.5]	0.25 [0.25-0.5]	1 [0.5-8]	0.5 [0.25-0.5]
AUClast (µM·h)	26.5 ± 9.05	14.3 ± 3.64	0.0712 ± 0.0362	0.599 ± 0.227
AUClast/dose (µM·h/[mg/kg))	2.58 ± 0.907	1.40 ± 0.360	-	-
AUCinf (µM·h)	-	-	-	-
T1/2 (h)	-	-	-	-
CLplasma (L/h/kg)	-	-	-	-
Vss (L/kg)	-	-	-	-
Absorption (%)	51.1 [b)]	-	-	-
Bioavailability (%)	-	114 [c)]	-	-

PK parameters [a)]	Group 3 (i.v., 3 mg/kg, actual dose: 2.64 ± 0.151 mg/kg)	Group 4 (p.o., 10 mg/kg, actual dose: 10.4 ± 0.344 mg/kg)
	^{14}C	^{14}C
Cmax (µM)	10.0 ± 1.08	6.04 ± 1.22
Tmax	NC	0.5 [0.25-1]
AUClast (µM·h)	13.7 ± 0.557	46.6 ± 2.20
AUClast/dose (µM·h/[mg/kg])	5.19 ± 0.0850	4.32 ± 0.421
AUCinf (µM·h)	-	-
T1/2 (h)	-	-
CLplasma (L/h/kg)	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No. 1		Study No. DMPK R1100027-01
	Vss (L/kg)	-	-
	Absorption (%)	-	-
	Bioavailability (%)	-	-
Conclusion:	The rate of absorption of INC280 after oral dosing was fast (median Tmax: 0.5 h for radioactivity and 0.25 h for INC280)		
	For the kinetic Groups 1 and 2, the fraction absorbed calculated from total radioactivity was 51.1% and was lower than the absolute bioavailability at 114%. Based on metabolism data of Groups 3 and 4, the absorption was 83.2% and was higher than the oral bioavailability at 69%.		
	The apparent terminal elimination T1/2 value of INC280 was 1.42 ± 0.0929 h, which might be biased towards shorter values due to the short observation period up to 8 h.		
	The plasma clearance of INC280 was 1.97 L/h/kg and the volume of distribution 1.73 L/kg.		

a) Values are given as mean ± SD of n=3. Tmax values are given as median [range].

b) Absorption calculated from the metabolism groups 3 and 4 was 83.2%

c) Bioavailability calculated from the metabolism Groups 3 and 4 was 69% (metabolism data are presented in 2.6.5.9 Metabolism *in vivo*.)

2.6.5.3D 薬物動態試験：単回投与後の吸収（イヌ）

Study title:	The pharmacokinetics of INCB028060 in beagle dogs		Study No. INCYTE-DMB-08.134.1
Location in CTD:	4.2.2.2-6		
GLP compliance:	Not required		
Test articles:	INC280 (synonym: INCB028060) (Lot 4, hydrochloride salt)		
Species / Strain:	Dog / Beagle		
Gender / No. of animals:	Male / 4 (2 for i.v., 2 for p.o.)		
Feeding condition:	Not reported		
Vehicle / Formulation:	i.v.: 5% dimethylacetamide, 40% propylene glycol in saline		
	p.o.: 5% dimethylacetamide in 0.5% aqueous methylcellulose		
Route of dosing:	i.v. and p.o.		
Dose:	i.v.: 2.5 mg/kg, p.o.: 5 mg/kg (referring to free base)		
Samples:	Plasma		
Sample times:	i.v.: Pre-dose, 0.0333, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h post-dose		
	p.o.: Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h post-dose		
Analyte:	INC280		
Analytical methods:	LC-MS/MS (details in 4.2.2.2-2-INCYTE-DMB-08.118.1)		
Results:	PK parameters [a)]	i.v., 2.5 mg/kg	p.o., 5 mg/kg
	Cmax (μM)	-	0.586
	Tmax (h)	-	0.38
	CLplasma (L/h/kg)	3.46	-
	AUCinf (μM·h)	1.77	0.977 [b)]
	Vss (L/kg)	2.43	-
	T1/2 (h)	0.72	0.98 [b)]
	Bioavailability (%)	-	28 [b)]
Conclusion:	Following intravenous administration, the high mean systemic plasma clearance (CLplasma) of INC280 (3.46 L/h/kg). The mean blood volume of distribution (Vss) is 2.43 L/kg, indicating that INC280 was not distributed beyond the total volume of body water. The short mean T1/2 of 0.72 h was observed for INC280.		
	Following oral administration in Beagle dogs, the Cmax and Tmax values for INC280 were 0.586 μM and 0.38 h, respectively. The plasma concentrations from 8 to 24 h were all near the lower limit of quantitation; consequently, the 12 and 24 h time point data were not used in the pharmacokinetic analysis.		

Study title:	The pharmacokinetics of INCB028060 in beagle dogs	Study No. INCYTE-DMB-08.134.1
	The apparent terminal half-life for INC280 was 0.98 h.	

a) Values are given as mean of n = 2.

b) 12 and 24 h time points not included in pharmacokinetic analysis.

2.6.5.3E 薬物動態試験：単回投与後の吸収（イヌ）

Study title:	Pharmacokinetic profiles of INC280 in dogs following administration of three oral formulations Study No. DMPK R1300725			
Location in CTD:	4.2.2.2-7			
GLP compliance:	Not required			
Test articles:	INC280 (dihydrochloride)			
Species / Strain:	Dog / Beagle			
Gender / No. of animals:	Male / 4			
Feeding condition:	Fasted overnight, water *ad libitum*			
Vehicle / Formulation:	50 mg hard gelatin capsule with 19.6% drug load (Form A: reference; fine particles, Form B: variant 1; coarse particles), 50 mg tablet with 35.1% drug load (From C: variant 2, fine particles)			
Route of dosing:	p.o. (deep throat deposition)			
Dose:	50 mg/kg (referring to free base)			
Samples:	Blood, Plasma			
Sample times:	Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post-dose			
Analyte:	INC280 (dihydrochloride)			
Analytical methods:	LC-MS/MS, LLOQ: 1.00 ng/mL (details in DMPK R1300725a)			
Results:	PK parameters [a]	p.o., 50 mg/kg		
		Form A (reference, capsule)	Form B (variant 1, capsule)	Form C (variant 2, tablet)
	Cmax (ng/mL)	36.3 ± 29.3	116 ± 108	18.3 ± 11.2
	Tmax (h)	1.0 [1.0-2.0]	1.0 [0.5-2.0]	1.0 [0.25-1.0]
	AUClast (ng/mL·h)	96.9 ± 102	267 ± 184	41.6 ± 21.9
Conclusion:	The observed inter-animal variability (Cmax: CV ≥ 61%) was considered to be high for the three formulations tested. In general, Form B (variant 1, capsule with 'coarse' particle) led to significantly higher plasma concentrations and exposure to INC280 than Forms A (reference capsule with 'fine' particle and similar drug load) and C (variant 2 tablet with 'fine' particle and higher drug load). No statistical difference was observed between PK profiles of Form C and A.			

a) Values are given as mean ± SD of n=4. Tmax values are given as median [range].

2.6.5.3F 薬物動態試験：単回投与後の吸収（サル）

Study title:	The pharmacokinetics of INCB028060 in cynomolgus monkeys		Study No. INCYTE-DMB-08.131.1
Location in CTD:	4.2.2.2-9		
GLP compliance:	Not required		
Test articles:	INC280 (synonym: INCB028060) (Lot 4, hydrochloride salt: for i.v. (2.5 mg/kg) and p.o. (10 mg/kg) dosing; Lot 12, dihydrochloride salt): for p.o. (2.5 mg/kg) dosing)		
Species / Strain:	Monkey / Cynomolgus		
Gender / No. of animals:	Male / 7 (2 for i.v., 2 for p.o. (10 mg/kg), 3 for p.o. (2.5 mg/kg))		
Feeding condition:	Not reported		
Vehicle / Formulation:	i.v. (2.5 mg/kg): 5% dimethylacetamide, 40% propylene glycol in saline		
	p.o. (2.5 mg/kg): suspended in 0.5% methylcellulose and adjusted to pH 2.1 using hydrochloric acid		
	p.o. (10 mg/kg): 5% dimethylacetamide in 0.5% methylcellulose		
Route of dosing:	i.v. (no additional information)		
	p.o. (no additional information)		
Dose:	i.v.: 2.5 mg/kg (assumed to refer to free base)		
	p.o.: 2.5 and 10 mg/kg (assumed to refer to free base)		
Samples:	Blood, plasma, urine		
Sample times:	i.v.: Pre-dose, 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose		
	p.o.: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose		
Analyte:	INC280		
Analytical methods:	LC-MS/MS (details in INCYTE-DMB-08.118.1)		

Results:	PK parameters [a)]	i.v., 2.5 mg/kg	p.o., 2.5 mg/kg	p.o., 10 mg/kg
	Cmax (μM)	-	2.23 ± 1.30	6.44
	Tmax (h)	-	2.7 ± 1.5	7.0
	CLplasma (L/h/kg)	0.150	-	-
	AUCinf (μM·h)	43.0	10.3 ± 1.9	74.8
	Vss (L/kg)	0.27	-	-
	T1/2 (h)	4.28	4.6 ± 1.5	4.4
	Bioavailability (%)	-	24 ± 5	44

Study title:	The pharmacokinetics of INCB028060 in cynomolgus monkeys	Study No. INCYTE-DMB-08.131.1
Conclusion:	Following an intravenous dose of 2.5 mg/kg, the mean systemic plasma clearance (CLplasma) of INC280 was considered to be low, representing approximately 6% of hepatic blood flow in cynomolgus monkeys. The mean volume of distribution (Vss) was 0.27 L/kg, indicating that INC280 was not distributed beyond the total volume of body water (0.7 L/kg) in cynomolgus monkeys. The mean terminal half-life (T1/2) was 4.28 h. After intravenous dosing of INC280, less than 1% of the administered dose was excreted in the urine as parent compound by 24 h post dose, indicating that the renal clearance of INC280 was insignificant (no urine data are reported). Following an oral dose of 10 mg/kg of INC280, the mean Cmax and AUC values were 6.44 µM and 74.8 µM·h, respectively. The mean Tmax value was 7.0 h. The mean peak plasma concentration (Cmax) and AUC values were 2.23 ± 1.30 µM and 10.3 ± 1.9 µM·h, respectively, and the apparent terminal half-life was 4.6 ± 1.5 h. The mean Tmax value was 2.7 h.	

a) Values are given as mean of n = 2 (no SD calculated) or as mean ± SD of n = 3.

2.6.5.3G 薬物動態試験：単回投与後の吸収（サル）

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280	Study No. DMPK R1300820
Location in CTD:	4.2.2.2-10	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 (dihydrochloride)	
Species / Strain:	Monkey / Cynomolgus	
Gender / No. of animals:	Male / 5 (2 for i.v., 3 for p.o.)	
Feeding condition:	Water *ad libitum*, food once daily (normal diet)	
Vehicle / Formulation:	i.v.: 20% propylene glycol 200 / 80% aqueous glucose solution (5%)	
	p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	i.v. bolus (into saphenous vein)	
	p.o. (gavage)	
Dose:	i.v.: 3 mg/kg (doses referring to free base)	
	p.o.: 30 mg/kg (doses referring to free base)	
Samples:	Blood / analysis in blood (radioactivity only) and plasma (radioactivity and INC280)	
Sample times:	i.v.: Pre-dose, 0.083, 0.25, 0.5, 1, 2, 4, 7, 10, 24, 48, 72, 96 and 168 h post-dose	
	p.o.: Pre-dose, 0.25, 0.5, 1, 2, 4, 7, 10, 24, 26, 48, 72, 96 and 168 h post-dose	
Analyte:	INC280	
Analytical methods:	Radioactivity: LSC	
	INC280: LC-MS/MS analysis using positive ESI, LLOQ: 0.1 ng/mL and 10 ng/mL for the low curve (0.1-100 ng/mL) and the high curve (10-10000 ng/mL) assay method. (details in 4.2.2.2-11-DMPK R1300820a)	

Results:

	i.v., 3 mg/kg			p.o., 30 mg/kg (nominal) [a]		
PK parameters [a]	^{14}C in blood	^{14}C in plasma	INC280 in plasma	^{14}C in blood	^{14}C in plasma	INC280 in plasma
Cmax (ngEq/mL)	5690	7400	-	23000	40600	-
Cmax (ng/mL)	-	-	6370 [15500 nM]	-	-	17700 [42900 nM]
Tmax (h)	0.083 [b]	0.167	0.083 [b]	2	2	2
AUClast (ngEq/mL·h)	14600	15500	-	168500	215000	-
AUClast (ng/mL·h)	-	-	6720	-	-	72900

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280				Study No. DMPK R1300820		
				[16300 nM]			[177000 nM]
	AUCinf_obs (ngEq/mL·h)	23200	24800	-	224000	260000	-
	AUCinf_obs (ng/mL·h)	-	-	6750 [16400 nM]	-	-	73000 [177000 nM]
	AUC, λ1 (%)	-	-	73	-	-	-
	AUC, λ2 (%)	-	-	27	-	-	-
	T1/2, λ1 (h)	-	-	0.66	-	-	-
	T1/2, λ2 (h)	-	-	88	-	-	-
	T1/2 (h)	-	-	88.3	-	-	61.7
	CL_obs (mL/min/kg)	-	-	7.45	-	-	NA
	Vss_obs (L/kg)	-	-	1.47	-	-	NA
	Bioavailability (%)	-	-	-	-	-	108
	Absorption (%) [c)]	-	-	-	-	-	139
Conclusion:	Following a 3 mg/kg [^{14}C]INC280 intravenous dose in monkeys, the systemic plasma clearance was estimated to be 7.45 mL/min/kg. The volume of distribution at steady state (Vss) was calculated to be 1.47 L/kg. The initial phase half-life (T1/2, λ1) was 0.66 h and the terminal phase half-life (T1/2, λ2) was 88.3 h. The initial phase contributed a large proportion (73%) of the total AUCinf, whereas the terminal phase contributed only a small proportion (27%). Following a 30 mg base/kg [^{14}C]INC280 oral dose in monkeys, absorption appeared to be fast with Tmax of total radiolabeled compounds and INC280 occurring at 2 h in blood and plasma. Bioavailability for INC280 was calculated to be complete (108%) in monkeys. Oral absorption of INC280 in monkey was complete, suggesting a minimum first-pass effect in monkeys.						
Additional information	To obtain concentrations in molar units, divide the concentrations in ngEq (equal to ng-eq) or ng by 412.4 g/mol.						

NA: not applicable

a) Mean value of parameters was calculated using the data from two monkeys since one monkey in the oral group had emesis after the oral dosing.

b) first sampling time point

c) calculated from AUClast of plasma radioactivity

2.6.5.3H 薬物動態試験：単回投与後の吸収（サル）

Study title:	Pharmacokinetics of INC280, M16 (CMN288) and M18 (CNJ294) in the monkey following an oral dose of 75 mg/kg				Study No. DMPK R1600337	
Location in CTD:	4.2.2.2-12					
GLP compliance:	Not required					
Test articles:	INC280 (dihydrochloride monohydrate salt)					
Species / Strain:	Monkey / Cynomolgus					
Gender / No. of animals:	Male / 3					
Feeding condition:	Water and food *ad libitum*					
Vehicle / Formulation:	Aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80					
Route of dosing:	p.o. (gavage)					
Dose:	61.5 mg/kg (referring to the free base)					
Samples:	Blood / analysis in plasma					
Sample times:	Pre-dose, 0.25, 0.5, 1, 2, 4, 7, 24 and 30 h post-dose					
Analyte:	INC280, metabolites CMN288 and CNJ294					
Analytical methods:	INC280, CMN288 and CNJ294: Method of analysis not mentioned in the report (samples were sent to DMPK-DMBA, East Hanover) (details in 4.2.2.2-13-DMPK R1600337a)					
Results:	PK parameters [a]	INC280 in plasma	CMN288 in plasma	CMN288: metabolite exposure relative to INC280 (%)	CNJ294 in plasma	CMN288: metabolite exposure relative to INC280 (%)
	Tmax (h)	1.7 ± 0.58	1.7 ± 0.58	-	1.7 ± 0.58	-
	Cmax (ng/mL)	14100 ± 7330	8300 ± 8980	56	507 ± 227	4
	AUClast (ng/mL·h)	72800 ± 19800	44200 ± 44600	58	3050 ± 158	4
Conclusion:	Based on both Cmax and AUC the relative plasma exposure of CNJ294 was 4% of the INC280 exposure. For CMN288, the plasma Cmax was 56% of the INC280 Cmax, and the exposure 58% of the INC280 based on AUC.					
Additional information	To obtain concentrations in molar units, divide the concentrations in ngEq (equal to ng-eq) or ng by 412.4 g/mol.					

a) Values are given as mean ± SD of n=3

2.6.5.4A 薬物動態試験：反復投与後の吸収（ラット）

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No. 1 — Study No. DMPK R1600074-01
Location in CTD:	4.2.2.2-14
GLP compliance:	Not required
Test articles:	[^{14}C]INC280 (dihydrochloride monohydrate)
Species / Strain:	Rat / Sprague-Dawley (Crl:CD® [SD], albino)
Gender / No. of animals:	Male / 8 (3 in Group 3, 5 in Group 4)
Feeding condition:	Water and food *ad libitum*
Vehicle / Formulation:	Aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80
Route of dosing:	p.o. (gavage) / single and repeated dosing (10 days)
Dose:	40 mg/kg (doses referring to the free base)
Samples:	Blood / analysis in plasma
Sample times:	0.25, 1, 4, 8, 24, and 72 h post-dose
Analyte:	[^{14}C]INC280
Specific radioactivity:	0.134 MBq/mg (referring to the free base)
Analytical methods:	Radioactivity: LSC; limit of detection: 0.141 - 0.185 µM INC280: HPLC-RA

Results:

PK parameters [a)]	Group 3 (Single dose 40 mg/kg)		Group 4 (Repeated doses 40 mg/kg/day [10 days])	
	[^{14}C] in plasma	INC280 in plasma	[^{14}C] in plasma	INC280 in plasma
Cmax (µM)	17.6 ± 4.21	7.73	18.3 ± 4.49	9.13
Tmax (h)	1.0 [0.25 - 4.0]	-	4.0 [0.25 – 8.0]	-
Tlast (h)	24.0 [24.0 - 24.0]	-	24.0 [24.0 – 24.0]	-
AUC0-24h (µM·h)	-	68.0	NC	79.0
AUClast (µM·h)	162 ± 22.2	-	197 ± 63.8	-
AUCinf (µM·h)	164 ± 21.6	-	203 ± 58.0	-
T1/2 (h)	3.78 ± 0.795	-	4.75 ± 2.75	-
T1/2 range (h)	[4.0 – 24.0]	-	[4.0 – 24.0]	-

Conclusion: Exposure of total radiolabeled components in plasma after multiple oral dosing was comparable to the exposure observed after single oral dosing. Thus, no accumulation was observed in plasma, neither for total radiolabeled components nor for parent compound.

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No. 1	Study No. DMPK R1600074-01
	The mean AUC0-24h of INC280 after single dose (68.0 µM·h) and repeated dose (79.0 µM·h) administration represented approximately 42.0% and 40.1%, respectively, of the AUC0-24h of total radiolabeled components indicating that INC280 was the main component in plasma after both single and repeated dose regimen.	

a) Values are given as mean ± SD of n = 3 for Group 3 and mean ± SD of n = 5 for Group 4. Tmax and Tlast values are given as median [range].

2.6.5.5A 薬物動態試験：組織分布（ラット）

Study title:	Brain and cerebrospinal fluid (CSF) concentrations of INCB028060 in rats		Study No. INCYTE DMB-08.129.1
Location in CTD:	4.2.2.3-1		
GLP compliance:	Not required		
Test articles:	INC280 (synonym: INCB028060) (Lot 15, dihydrochloride salt)		
Species / Strain:	Rat / Sprague-Dawley		
Gender / No. of animals:	Male / 3		
Feeding condition:	Not reported		
Vehicle / Formulation:	5% dimethylacetamide and 10% 1,2-propanediol in saline		
Route of dosing:	Bolus intravenous followed by intravenous infusion for 4 h		
Dose:	0.25 mg/kg (bolus and infusion dose)		
Samples:	Blood, CSF and brain		
Sample times:	Blood: 2 and 4 h post-dose, CSF: 4 h post-dose, Brain: 4 h post-dose		
Analyte:	INC280		
Analytical methods:	LC-MS/MS (details in 4.2.2.2-2-INCYTE-DMB-08.118.1)		
Results:	Tissue / matrix [a)]	i.v. infusion, 0.25 mg/kg for 4 h	
		2 h	4 h
	Plasma total (μM)	0.810 ± 0.069	0.865 ± 0.092
	Plasma free (μM)	-	0.0484 ± 0.0052
	Brain (μM)	-	0.147 ± 0.020
	Ratio brain : plasma total (%)	-	17.3 ± 4.2
	CSF (μM)	-	0.0175 ± 0.029
	Ratio CSF: plasma free (%)	-	36.2 ± 6.0
Conclusion:	The mean plasma concentrations of INC280 were 0.810 and 0.865 μM at 2 and 4 h from the start of infusion, respectively. The mean brain homogenate concentration of INC280 was 0.147 μM or 17.3% of the mean plasma concentration at 4 h. The concentration of INCB028060 in the brain was above the level expected from vascular contribution (7%). The mean CSF concentration of INC280 was 0.0175 μM or 36.2% of the corresponding estimated free plasma concentration at 4 h.		
Additional information	*Ex vivo* fraction unbound = 5.6%, as determined in 4.2.2.3-4-INCYTE-DMB-08.122.1.		

a) Values are given as mean ± SD of n = 3

2.6.5.5B 薬物動態試験：組織分布（ラット）

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01
	[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280	DMPK R1100027b
Location in CTD:	4.2.2.2-4 (DMPK R1100027-01), 4.2.2.3-2 (DMPK R1100027b)	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 (dihydrochloride)	
Species / Strain:	Rat / Long Evans, pigmented; Hanover Wistar, albino	
Gender / No. of animals:	Male / 10 (2 albino rats: i.v. (Group 7); 2 albino rats: p.o. (Group 8); 6 pigmented rats: p.o. (Group 6)	
Feeding condition:	Water and food *ad libitum*	
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 300 / 80% aqueous glucose solution (5%)	
	p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	i.v. bolus (into vena femoralis) / single dose	
	p.o. (gavage) / single dose	
Dose:	i.v. : 3 mg/kg (referring to the free base)	
	p.o.: 10 mg/kg (referring to the free base)	
Sample times:	1 rat per time point:	
	i.v., albino rats: 24 and 168 h after the last dosing	
	p.o., albino rats: 24 and 168 h after the last dosing	
	p.o., pigmented rats: 0.25, 1, 4, 24, 72 and 168 h after the last dosing	
Analyte:	[^{14}C]INC280	
Analytical methods:	Concentration of total radiolabeled components: LSC	
	INC280: radioactivity / quantitative whole body autoradiography (QWBA) (nmol/g). Lower limit of quantification (LOQ): 133 nmol/g (i.v., albino), 480 nmol/g (p.o., albino) and 477 nmol/g (p.o., pigmented).	

Results: <u>i.v., 3 mg/kg (albino rat)</u>

Tissues / organs	Concentration (nmol/g)		Tissue : Blood concentration ratio		Percentage of the dose in carcass (inclusive and exclusive of the gastrointestinal tract)	
	24 h	168 h	24 h	168 h	24 h	168 h

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01
	[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280	DMPK R1100027b

	Rat #1	Rat #2	Rat #1	Rat #2	Rat #1	Rat #2
Blood LSC	ND	ND	NC	NC	-	-
Blood QWBA	BLQ	BLQ	NC	NC	-	-
Adrenal cortex	0.0734	0.0421	NC	NC	-	-
Adrenal medulla	0.157	BLQ	NC	NC	-	-
Aortic wall	BLQ	BLQ	NC	NC	-	-
Bile ducts	BLQ	BLQ	NC	NC	-	-
Bone marrow	BLQ	BLQ	NC	NC	-	-
Bone surface	BLQ	BLQ	NC	NC	-	-
Brain	BLQ	BLQ	NC	NC	-	-
Brown fat	BLQ	BLQ	NC	NC	-	-
Bulbo-urethral gland	BLQ	BLQ	NC	NC	-	-
Caecum mucosa	0.222	BLQ	NC	NC	-	-
Carcass (excluding gastrointestinal tract)	0.0929	BLQ	NC	NC	-	-
Carcass	1.22	BLQ	NC	NC	-	-
Cartilage	BLQ	BLQ	NC	NC	-	-
Choroid plexus	BLQ	BLQ	NC	NC	-	-
Coagulating gland	BLQ	BLQ	NC	NC	-	-
Epididymis	BLQ	BLQ	NC	NC	-	-
Epithelial tongue	0.140	BLQ	NC	NC	-	-
Exorbital lachrymal gland	0.0461	BLQ	NC	NC	-	-
Eye choroid	0.0357	BLQ	NC	NC	-	-
Eye lens	BLQ	BLQ	NC	NC	-	-
Harderian gland	BLQ	BLQ	NC	NC	-	-
Intra-orbital lachrymal gland	BLQ	BLQ	NC	NC	-	-
Kidney cortex-medulla junction	0.296	BLQ	NC	NC	-	-
Kidney cortex inner	0.564	BLQ	NC	NC	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b		
	Kidney cortex outer	0.259	BLQ	NC	NC	-	-
	Kidney medulla	0.0463	BLQ	NC	NC	-	-
	Large intestine mucosa	0.349	BLQ	NC	NC	-	-
	Liver	0.744	0.115	NC	NC	-	-
	Lung	BLQ	BLQ	NC	NC	-	-
	Mandibular lymph nodes	BLQ	BLQ	NC	NC	-	-
	Meibomium glands	0.0351	BLQ	NC	NC	-	-
	Meninges	BLQ	BLQ	NC	NC	-	-
	Mucus gland	BLQ	BLQ	NC	NC	-	-
	Muscle	BLQ	BLQ	NC	NC	-	-
	Myocardium	BLQ	BLQ	NC	NC	-	-
	Nasal mucosa	0.0433	BLQ	NC	NC	-	-
	Oesophageal wall	0.0517	BLQ	NC	NC	-	-
	Pancreas	0.0368	BLQ	NC	NC	-	-
	Penis	0.0484	BLQ	NC	NC	-	-
	Periodontal membrane	BLQ	BLQ	NC	NC	-	-
	Pineal body	BLQ	BLQ	NC	NC	-	-
	Pituitary	BLQ	BLQ	NC	NC	-	-
	Preputial gland	0.657	BLQ	NC	NC	-	-
	Prostate	0.0447	BLQ	NC	NC	-	-
	Rectum mucosa	0.111	BLQ	NC	NC	-	-
	Salivary glands	BLQ	BLQ	NC	NC	-	-
	Seminal vesicles	BLQ	BLQ	NC	NC	-	-
	Skin (non-pigmented)	BLQ	0.0464	NC	NC	-	-
	Skin (subcutis)	BLQ	BLQ	NC	NC	-	-
	Small intestine mucosa	0.316	BLQ	NC	NC	-	-
	Spinal cord	BLQ	BLQ	NC	NC	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b	
	Spleen	0.0444	BLQ	NC	NC	-	-
	Stomach mucosa (fundic)	0.0884	BLQ	NC	NC	-	-
	Stomach (non-fundic)	0.104	0.0592	NC	NC	-	-
	Testis	BLQ	BLQ	NC	NC	-	-
	Thymus	BLQ	BLQ	NC	NC	-	-
	Thyroid	0.0513	BLQ	NC	NC	-	-
	Tongue	BLQ	BLQ	NC	NC	-	-
	Tooth pulp	0.111	BLQ	NC	NC	-	-
	Trachea	BLQ	BLQ	NC	NC	-	-
	Urinary bladder wall	0.0463	BLQ	NC	NC	-	-
	Urine	0.138	BLQ	NC	NC	-	-
	Uveal tract/retina	0.0396	BLQ	NC	NC	-	-
	Vitreous humour	BLQ	BLQ	NC	NC	-	-
	White fat	BLQ	BLQ	NC	NC	-	-
	Total dose (nmol/rat)	-	-	-	-	1500	1550
	Animal weight (g)	-	-	-	-	230	223
	Carcass (nmol/g)	-	-	-	-	1.22	BLQ
	Carcass exclusive GIT (nmol/g)	-	-	-	-	0.0929	BLQ
	Total in carcass (nmol)	-	-	-	-	281	NA
	Total in carcass exclusive GIT (nmol)	-	-	-	-	21.4	NA
	% dose in carcass	-	-	-	-	18.7	NA
	% dose in carcass exclusive GIT	-	-	-	-	1.42	NA

p.o., 10 mg/kg (albino rat)

Tissues / organs	Concentration (nmol/g)	Tissue : Blood concentration ratio	Percentage of the dose in carcass (inclusive and exclusive of the gastrointestinal tract)

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01
	[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280	DMPK R1100027b

	24 h	168 h	24 h	168 h	24 h	168 h
	Rat #1	Rat #2	Rat #1	Rat #2	Rat #1	Rat #2
Blood LSC	ND	ND	NC	NC	-	-
Blood QWBA	BLQ	BLQ	NC	NC	-	-
Adrenal cortex	BLQ	BLQ	NC	NC	-	-
Adrenal medulla	0.428	0.220	NC	NC	-	-
Aortic wall	BLQ	BLQ	NC	NC	-	-
Bile ducts	BLQ	BLQ	NC	NC	-	-
Bone marrow	BLQ	BLQ	NC	NC	-	-
Bone surface	BLQ	BLQ	NC	NC	-	-
Brain	BLQ	BLQ	NC	NC	-	-
Brown fat	BLQ	BLQ	NC	NC	-	-
Bulbo-urethral gland	BLQ	BLQ	NC	NC	-	-
Caecum mucosa	0.525	BLQ	NC	NC	-	-
Carcass (excluding gastrointestinal tract)	0.154	BLQ	NC	NC	-	-
Carcass	1.04	BLQ	NC	NC	-	-
Cartilage	BLQ	BLQ	NC	NC	-	-
Choroid plexus	BLQ	BLQ	NC	NC	-	-
Coagulating gland	BLQ	BLQ	NC	NC	-	-
Epididymis	0.147	BLQ	NC	NC	-	-
Epithelial tongue	0.230	BLQ	NC	NC	-	-
Exorbital lachrymal gland	0.234	BLQ	NC	NC	-	-
Eye choroid	BLQ	BLQ	NC	NC	-	-
Eye lens	BLQ	BLQ	NC	NC	-	-
Harderian gland	BLQ	BLQ	NC	NC	-	-
Intra-orbital lachrymal gland	0.293	BLQ	NC	NC	-	-
Kidney cortex-medulla junction	0.180	BLQ	NC	NC	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b		
	Kidney cortex inner	0.881	BLQ	NC	NC	-	-
	Kidney cortex outer	0.264	BLQ	NC	NC	-	-
	Kidney medulla	BLQ	BLQ	NC	NC	-	-
	Large intestine mucosa	0.645	BLQ	NC	NC	-	-
	Liver	1.39	0.277	NC	NC	-	-
	Lung	BLQ	BLQ	NC	NC	-	-
	Mandibular lymph nodes	BLQ	BLQ	NC	NC	-	-
	Meibomium glands	BLQ	BLQ	NC	NC	-	-
	Meninges	BLQ	BLQ	NC	NC	-	-
	Mucus gland	BLQ	BLQ	NC	NC	-	-
	Muscle	BLQ	BLQ	NC	NC	-	-
	Myocardium	BLQ	BLQ	NC	NC	-	-
	Nasal mucosa	0.172	BLQ	NC	NC	-	-
	Oesophageal wall	0.135	BLQ	NC	NC	-	-
	Pancreas	BLQ	BLQ	NC	NC	-	-
	Penis	0.125	BLQ	NC	NC	-	-
	Periodontal membrane	BLQ	BLQ	NC	NC	-	-
	Pineal body	BLQ	BLQ	NC	NC	-	-
	Pituitary	BLQ	BLQ	NC	NC	-	-
	Preputial gland	4.49	BLQ	NC	NC	-	-
	Prostate	BLQ	BLQ	NC	NC	-	-
	Rectum mucosa	0.473	BLQ	NC	NC	-	-
	Salivary glands	BLQ	BLQ	NC	NC	-	-
	Seminal vesicles	BLQ	BLQ	NC	NC	-	-
	Skin (non-pigmented)	BLQ	BLQ	NC	NC	-	-
	Skin (subcutis)	BLQ	BLQ	NC	NC	-	-
	Small intestine mucosa	0.159	BLQ	NC	NC	-	-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b	
	Spinal cord	BLQ	BLQ	NC	NC	-	-
	Spleen	BLQ	BLQ	NC	NC	-	-
	Stomach mucosa (fundic)	0.216	BLQ	NC	NC	-	-
	Stomach (non-fundic)	0.767	BLQ	NC	NC	-	-
	Testis	BLQ	BLQ	NC	NC	-	-
	Thymus	BLQ	BLQ	NC	NC	-	-
	Thyroid	BLQ	BLQ	NC	NC	-	-
	Tongue	BLQ	BLQ	NC	NC	-	-
	Tooth pulp	BLQ	BLQ	NC	NC	-	-
	Trachea	BLQ	BLQ	NC	NC	-	-
	Urinary bladder wall	0.150	BLQ	NC	NC	-	-
	Urine	0.280	BLQ	NC	NC	-	-
	Uveal tract/retina	0.135	BLQ	NC	NC	-	-
	Vitreous humour	BLQ	BLQ	NC	NC	-	-
	White fat	BLQ	BLQ	NC	NC	-	-
	Total dose (nmol/rat)	-	-	-	-	5740	5340
	Animal weight (g)	-	-	-	-	229	207
	Carcass (nmol/g)	-	-	-	-	1.04	BLQ
	Carcass exclusive GIT (nmol/g)	-	-	-	-	0.154	BLQ
	Total in carcass (nmol)	-	-	-	-	238	NA
	Total in carcass exclusive GIT (nmol)	-	-	-	-	35.2	NA
	% dose in carcass	-	-	-	-	4.10	NA
	% dose in carcass exclusive GIT	-	-	-	-	0.614	NA

p.o., 10 mg/kg (pigmented rat)

Tissues / organs	Concentrations (nmol/g)					
	0.125 h	1 h	4 h	24 h	72 h	168 h

Study title: Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1

[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280

Study No. DMPK R1100027-01

DMPK R1100027b

	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6
Blood LSC	6.34	7.66	1.41	ND	ND	ND
Blood QWBA	6.08	7.92	1.74	BLQ	BLQ	BLQ
Adrenal cortex	15.8	12.9	6.37	0.126	BLQ	BLQ
Adrenal medulla	12.1	14.5	4.55	0.416	0.259	0.400
Aortic wall	9.97	13.8	4.37	BLQ	BLQ	BLQ
Bile ducts	107	114	30.7	BLQ	BLQ	BLQ
Bone marrow	6.22	8.26	1.46	BLQ	BLQ	BLQ
Bone surface	3.40	0.916	1.00	BLQ	BLQ	BLQ
Brain	0.599	0.922	0.143	BLQ	BLQ	BLQ
Brown fat	5.15	6.67	1.49	BLQ	BLQ	BLQ
Bulbo-urethral gland	7.36	11.4	3.45	BLQ	BLQ	BLQ
Caecum mucosa	9.00	10.5	4.66	1.62	1.06	BLQ
Carcass (excluding gastrointestinal tract)	7.94	10.3	3.04	0.448	0.346	0.224
Carcass	12.3	13.7	28.5	1.19	0.489	0.217
Cartilage	BLQ	7.07	2.97	1.65	0.264	0.415
Choroid plexus	1.39	3.31	1.06	BLQ	BLQ	BLQ
Coagulating gland	5.33	9.10	2.42	BLQ	BLQ	BLQ
Epididymis	0.981	2.79	2.05	0.227	BLQ	BLQ
Epithelial tongue	3.13	23.3	3.37	0.426	BLQ	BLQ
Exorbital lachrymal gland	9.19	17.3	6.14	0.254	BLQ	BLQ
Eye choroid	20.5	62.5	139	64.4	25.6	31.8
Eye lens	BLQ	0.237	0.581	0.241	BLQ	BLQ
Fur (pigmented)	0.282	0.912	0.352	BLQ	0.545	1.02
Harderian gland	8.07	11.1	3.05	BLQ	BLQ	BLQ
Intra-orbital lachrymal gland	10.3	18.2	6.82	0.233	BLQ	BLQ
Kidney cortex-medulla junction	14.0	17.0	7.76	0.360	0.142	BLQ

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b		
	Kidney cortex inner	23.3	28.3	12.8	0.782	0.572	BLQ
	Kidney cortex outer	27.2	25.3	9.31	0.531	0.511	BLQ
	Kidney medulla	8.42	12.0	3.47	BLQ	BLQ	BLQ
	Large intestine mucosa	3.55	6.86	31.4	3.34	0.196	BLQ
	Liver	59.2	52.3	20.7	2.48	1.67	0.590
	Lung	7.62	9.18	1.88	BLQ	BLQ	BLQ
	Mandibular lymph nodes	4.99	7.64	1.68	BLQ	BLQ	BLQ
	Meibomium glands	20.5	122	NS	20.0	11.4	13.2
	Meninges	2.48	2.00	0.598	BLQ	BLQ	BLQ
	Mucus gland	6.40	9.95	1.93	BLQ	BLQ	BLQ
	Muscle	4.16	4.49	1.01	BLQ	BLQ	BLQ
	Myocardium	8.26	8.73	2.02	BLQ	BLQ	BLQ
	Nasal mucosa	8.00	5.07	3.31	0.272	BLQ	BLQ
	Oesophageal wall	42.7	6.32	4.28	0.348	BLQ	BLQ
	Pancreas	12.0	11.7	3.18	BLQ	BLQ	BLQ
	Penis	3.37	8.46	NS	0.410	BLQ	BLQ
	Periodontal membrane	1.56	5.03	2.01	0.290	BLQ	BLQ
	Pineal body	6.37	6.08	1.75	BLQ	BLQ	BLQ
	Pituitary	4.77	10.0	3.00	BLQ	BLQ	BLQ
	Preputial gland	9.45	22.6	21.9	2.79	3.83	BLQ
	Prostate	5.86	7.58	1.73	BLQ	BLQ	BLQ
	Rectum mucosa	3.55	6.02	1.93	2.22	BLQ	0.158
	Salivary glands	10.7	11.4	2.88	BLQ	BLQ	BLQ
	Seminal vesicles	2.50	3.21	3.81	BLQ	BLQ	BLQ
	Skin (non-pigmented)	3.21	9.89	2.81	0.189	BLQ	BLQ
	Skin (pigmented)	4.45	10.5	2.92	0.602	0.177	BLQ
	Skin (subcutis)	3.79	5.10	1.08	BLQ	BLQ	BLQ

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280			Study No. DMPK R1100027-01 DMPK R1100027b		
	Small intestine mucosa	8.17	55.1	9.57	1.04	0.376	BLQ
	Spinal cord	0.777	0.801	0.194	BLQ	BLQ	BLQ
	Spleen	8.10	8.89	2.27	BLQ	BLQ	BLQ
	Stomach mucosa (fundic)	5.19	46.8	14.6	0.153	BLQ	BLQ
	Stomach (non-fundic)	186	57.1	12.2	2.41	0.134	BLQ
	Testis	1.03	2.95	0.999	BLQ	BLQ	BLQ
	Thymus	5.49	7.16	1.72	BLQ	BLQ	BLQ
	Thyroid	11.6	13.2	3.74	0.157	BLQ	BLQ
	Tongue	3.94	7.60	1.65	BLQ	BLQ	BLQ
	Tooth pulp	2.15	6.90	1.56	BLQ	BLQ	BLQ
	Trachea	6.28	7.69	2.22	BLQ	BLQ	BLQ
	Urinary bladder wall	6.61	30.5	100	0.161	0.313	BLQ
	Urine	3.51	17.9	109	0.166	0.646	BLQ
	Uveal tract/retina	11.5	39.4	100	33.9	21.4	31.1
	Vitreous humour	0.297	0.746	3.16	0.718	0.150	0.374
	White fat	0.365	0.849	0.226	BLQ	BLQ	BLQ

Tissues / organs	Tissue:Blood concentration ratio					
	0.125 h	1 h	4 h	24 h	72 h	168 h
	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6
Blood LSC	1.00	1.00	1.00	NC	NC	NC
Blood QWBA	0.959	1.03	1.24	NC	NC	NC
Adrenal cortex	2.49	1.68	4.53	NC	NC	NC
Adrenal medulla	1.91	1.89	3.23	NC	NC	NC
Aortic wall	1.57	1.80	3.11	NC	NC	NC
Bile ducts	16.9	14.9	21.8	NC	NC	NC
Bone marrow	0.981	1.08	1.04	NC	NC	NC

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b		
	Bone surface	0.536	0.120	0.711	NC	NC	NC
	Brain	0.0945	0.120	0.102	NC	NC	NC
	Brown fat	0.812	0.871	1.06	NC	NC	NC
	Bulbo-urethral gland	1.16	1.49	2.45	NC	NC	NC
	Caecum mucosa	1.42	1.37	3.31	NC	NC	NC
	Carcass (excluding gastrointestinal tract)	1.25	1.35	2.16	NC	NC	NC
	Carcass	1.94	1.79	20.3	NC	NC	NC
	Cartilage	NC	0.923	2.11	NC	NC	NC
	Choroid plexus	0.219	0.432	0.753	NC	NC	NC
	Coagulating gland	0.841	1.19	1.72	NC	NC	NC
	Epididymis	0.155	0.364	1.46	NC	NC	NC
	Epithelial tongue	0.494	3.04	2.40	NC	NC	NC
	Exorbital lachrymal gland	1.45	2.26	4.36	NC	NC	NC
	Eye choroid	3.23	8.16	98.8	NC	NC	NC
	Eye lens	NC	0.0309	0.413	NC	NC	NC
	Fur (pigmented)	0.0445	0.119	0.250	NC	NC	NC
	Harderian gland	1.27	1.45	2.17	NC	NC	NC
	Intra-orbital lachrymal gland	1.62	2.38	4.85	NC	NC	NC
	Kidney cortex-medulla junction	2.21	2.22	5.52	NC	NC	NC
	Kidney cortex inner	3.67	3.70	9.10	NC	NC	NC
	Kidney cortex outer	4.29	3.30	6.62	NC	NC	NC
	Kidney medulla	1.33	1.57	2.47	NC	NC	NC
	Large intestine mucosa	0.560	0.896	22.3	NC	NC	NC
	Liver	9.34	6.83	14.7	NC	NC	NC
	Lung	1.20	1.20	1.34	NC	NC	NC
	Mandibular lymph nodes	0.787	1.00	1.19	NC	NC	NC
	Meibomium glands	3.23	15.9	NC	NC	NC	NC

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280				Study No. DMPK R1100027-01 DMPK R1100027b		
	Meninges	0.391	0.261	0.425	NC	NC	NC
	Mucus gland	1.01	1.30	1.37	NC	NC	NC
	Muscle	0.656	0.586	0.718	NC	NC	NC
	Myocardium	1.30	1.14	1.44	NC	NC	NC
	Nasal mucosa	1.26	0.662	2.35	NC	NC	NC
	Oesophageal wall	6.73	0.826	3.04	NC	NC	NC
	Pancreas	1.89	1.53	2.26	NC	NC	NC
	Penis	0.531	1.11	NS	NC	NC	NC
	Periodontal membrane	0.246	0.657	1.43	NC	NC	NC
	Pineal body	1.00	0.794	1.24	NC	NC	NC
	Pituitary	0.752	1.31	2.13	NC	NC	NC
	Preputial gland	1.49	2.95	15.6	NC	NC	NC
	Prostate	0.924	0.990	1.23	NC	NC	NC
	Rectum mucosa	0.560	0.786	1.37	NC	NC	NC
	Salivary glands	1.69	1.49	2.05	NC	NC	NC
	Seminal vesicles	0.394	0.419	2.71	NC	NC	NC
	Skin (non-pigmented)	0.506	1.29	2.00	NC	NC	NC
	Skin (pigmented)	0.702	1.37	2.08	NC	NC	NC
	Skin (subcutis)	0.598	0.666	0.768	NC	NC	NC
	Small intestine mucosa	1.29	7.20	6.80	NC	NC	NC
	Spinal cord	0.123	0.105	0.138	NC	NC	NC
	Spleen	1.28	1.16	1.61	NC	NC	NC
	Stomach mucosa (fundic)	0.818	6.11	10.4	NC	NC	NC
	Stomach (non-fundic)	29.3	7.46	8.67	NC	NC	NC
	Testis	0.162	0.385	0.710	NC	NC	NC
	Thymus	0.866	0.935	1.22	NC	NC	NC
	Thyroid	1.83	1.72	2.66	NC	NC	NC

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280	Study No. DMPK R1100027-01 DMPK R1100027b

Tongue	0.621	0.993	1.17	NC	NC	NC
Tooth pulp	0.339	0.901	1.11	NC	NC	NC
Trachea	0.990	1.00	1.58	NC	NC	NC
Urinary bladder wall	1.04	3.98	71.1	NC	NC	NC
Urine	0.554	2.34	77.5	NC	NC	NC
Uveal tract/retina	1.81	5.15	71.1	NC	NC	NC
Vitreous humour	0.0468	0.0974	2.25	NC	NC	NC
White fat	0.0576	0.111	0.161	NC	NC	NC

Tissues / organs	Percentage of the dose in carcass (inclusive and exclusive of the gastrointestinal tract)					
	0.125 h	1 h	4 h	24 h	72 h	168 h
	Rat #1	Rat #2	Rat #3	Rat #4	Rat #5	Rat #6
Total dose (nmol/rat)	8470	8120	7130	7070	7000	9300
Animal weight (g)	343	339	288	287	281	373
Carcass (nmol/g)	12.3	13.7	28.5	1.19	0.489	0.217
Carcass exclusive GIT (nmol/g)	7.94	10.3	3.04	0.448	0.346	0.224
Total in carcass (nmol)	4220	4640	8210	342	137	80.9
Total in carcass exclusive GIT (nmol)	2730	3490	876	129	97.1	83.5
% dose in carcass	49.8	57.2	115	4.84	1.96	0.870
% dose in carcass exclusive GIT	32.2	43.0	12.3	1.82	1.39	0.898

Tissues / organs	Pharmacokinetic parameters							
	Tmax (h)	Cmax (nmol/g)	Cmax*	AUClast (nmol/g·h)	AUClast*	Tlast (h)	T1/2 (h)	Range for T1/2 (h)
Blood LSC	1	7.66	1.00	19.6	1.00	4	NC	NA
Blood QWBA	1	7.92	1.03	20.5	1.04	4	NC	NA
Adrenal cortex	0.25	15.8	2.06	107	5.43	24	3.48	1-24

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1						Study No. DMPK R1100027-01	
	[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280						DMPK R1100027b	
	Adrenal medulla	1	14.5	1.89	138	7.00	168	NC	NA
	Aortic wall	1	13.8	1.80	37.4	1.90	4	NC	NA
	Bile ducts	1	114	14.9	313	15.9	4	NC	NA
	Bone marrow	1	8.26	1.08	20.8	1.06	4	NC	NA
	Bone surface	0.25	3.40	0.444	4.92	0.250	4	NC	NA
	Brain	1	0.922	0.120	2.24	0.114	4	NC	NA
	Brown fat	1	6.67	0.871	17.3	0.881	4	NC	NA
	Bulbo-urethral gland	1	11.4	1.49	30.2	1.54	4	NC	NA
	Caecum mucosa	1	10.5	1.37	158	8.06	72	35.7	4-72
	Cartilage	1	7.07	0.923	143	7.29	168	NC	NA
	Choroid plexus	1	3.31	0.432	8.49	0.432	4	NC	NA
	Coagulating gland	1	9.10	1.19	23.4	1.19	4	NC	NA
	Epididymis	1	2.79	0.364	31.6	1.61	24	6.33	1-24
	Epithelial tongue	1	23.3	3.04	88.3	4.49	24	NC	NA
	Exorbital lachrymal gland	1	17.3	2.26	110	5.61	24	3.97	1-24
	Eye choroid	4	139	18.1	7285	371	168	179	24-168
	Eye lens	4	0.581	0.0758	9.6	0.487	24	15.8	4-24
	Fur (pigmented)	168	1.02	0.133	108	5.50	168	NC	NA
	Harderian gland	1	11.1	1.45	29.4	1.50	4	NC	NA
	Intra-orbital lachrymal gland	1	18.2	2.38	120	6.11	24	3.81	1-24
	Kidney cortex-med.	1	17.0	2.22	144	7.32	72	NC	NA
	Kidney cortex inner	1	28.3	3.69	252	12.8	72	NC	NA
	Kidney cortex outer	0.25	27.2	3.55	198	10.1	72	NC	NA
	Kidney medulla	1	12.0	1.57	31.9	1.62	4	NC	NA
	Large intestine	4	31.4	4.10	494	25.1	72	9.65	4-72
	Liver	0.25	59.2	7.73	599	30.5	168	68.7	24-168
	Lung	1	9.18	1.20	23.8	1.21	4	NC	NA

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1						Study No. DMPK R1100027-01	
	[^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280						DMPK R1100027b	
	Mandibular lymph nodes	1	7.64	1.00	19.3	0.984	4	NC	NA
	Meibomium glands	1	122	15.9	3623	184	168	307	24-168
	Meninges	0.25	2.48	0.324	5.89	0.300	4	NC	NA
	Mucus gland	1	9.95	1.30	24.8	1.26	4	NC	NA
	Muscle	1	4.49	0.586	12.0	0.611	4	NC	NA
	Myocardium	1	8.73	1.14	23.5	1.20	4	NC	NA
	Nasal mucosa	0.25	8.0	1.04	54.3	2.76	24	5.48	1-24
	Oesophageal wall	0.25	42.7	5.57	85.9	4.37	24	5.51	1-24
	Pancreas	0.25	12.0	1.57	32.7	1.66	4	NC	NA
	Penis	1	8.46	1.10	107	5.44	24	5.27	1-24
	Periodontal membrane	1	5.03	0.657	36.2	1.84	24	6.07	1-24
	Pineal body	0.25	6.37	0.832	17.2	0.876	4	NC	NA
	Pituitary	1	10.0	1.31	25.6	1.30	4	NC	NA
	Preputial gland	1	22.6	2.95	486	24.7	72	NC	NA
	Prostate	1	7.58	0.990	19.7	1.00	4	NC	NA
	Rectum mucosa	1	6.02	0.786	229	11.6	168	42.2	4-168
	Salivary glands	1	11.4	1.49	31.0	1.58	4	NC	NA
	Seminal vesicles	4	3.81	0.497	13.0	0.661	4	NC	NA
	Skin (non-pigmented)	1	9.89	1.29	54.4	2.77	24	4.37	1-24
	Skin (pigmented)	1	10.5	1.37	80.2	4.08	72	18.1	4-72
	Skin (subcutis)	1	5.10	0.666	13.1	0.666	4	NC	NA
	Small intestine	1	55.1	7.19	262	13.3	72	NC	NA
	Spinal cord	1	0.801	0.105	2.18	0.111	4	NC	NA
	Spleen	1	8.89	1.16	24.1	1.23	4	NC	NA
	Stomach (fundic)	1	46.8	6.11	260	13.2	24	2.87	1-24
	Stomach (non-fundic)	0.25	186	24.3	426	21.7	72	10.6	4-72
	Testis	1	2.95	0.385	7.54	0.384	4	NC	NA

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1 [^{14}C]INC280: Tissue distribution in male rats after a single intravenous (3 mg/kg) or oral (10 mg/kg) administration of [^{14}C]INC280					Study No. DMPK R1100027-01 DMPK R1100027b			
	Thymus	1	7.16	0.935	18.8	0.954	4	NC	NA
	Thyroid	1	13.2	1.72	75.1	3.82	24	3.84	1-24
	Tongue	1	7.6	0.992	18.7	0.952	4	NC	NA
	Tooth pulp	1	6.9	0.901	16.4	0.832	4	NC	NA
	Trachea	1	7.69	1.00	20.9	1.06	4	NC	NA
	Urinary bladder wall	4	100	13.1	1223	62.3	72	NC	NA
	Urine	4	109	14.2	1310	66.7	72	NC	NA
	Uveal tract/retina	4	100	13.1	5416	276	168	NC	NA
	Vitreous humour	4	3.16	0.413	91.1	4.63	168	NC	NA
	White fat	1	0.849	0.111	2.11	0.108	4	NC	NA
Conclusion:	Following oral administration of pigmented rats, the tissue distribution of total radiolabeled components appeared to be moderate to fast (Tmax between 0.25-4 h in most tissues) with ratios of AUClast values mostly above 2. The highest tissue exposure was observed in the melanin-containing eye choroid. Penetration of total radiolabeled components into the brain was observed. Specific uptake and retention of total radiolabeled components to melanin-containing structures was observed, which seems to be at least partly reversible.								

ND: not detected; BLQ: below lower limit of quantification (0.0347 nmol/g); NC: not calculated; GIT: gastrointestinal tract; NA: not applicable; NS: not sectioned

*: normalized to blood value

2.6.5.5C 薬物動態試験：組織分布（ラット）

Study title:	Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1	Study No. DMPK R1300834-01

Location in CTD:	4.2.2.3-3
GLP compliance:	Not required
Test articles:	[^{14}C]INC280 (dihydrochloride monohydrate)
Species / Strain:	Rat / Long Evans, partially pigmented
Gender / No. of animals:	Male / 9
Feeding condition:	Water and food available *ad libitum*
Vehicle / Formulation:	Aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80
Route of dosing:	p.o. (gavage) / single dose
Dose:	10 mg/kg (referring to the free base)
Sampling time:	1 rat per timepoint: 0.25, 1, 4, 24, 72 and 168 h and then 2, 3, and 5 weeks after the last dosing
Analyte	[^{14}C]INC280
Analytical methods:	Radioactivity in blood and plasma: LSC, Concentrations of total radiolabeled components in the tissues, organs, and matrices: QWBA Blood; Limit of detection (LOD): 0.0651 - 0.0445 nmol/g, LOQ: 0.195 - 0.136 nmol/g Plasma; LOD: 0.0295 - 0.0337 nmol/g, LOQ: 0.0886 - 0.101 nmol/g Radioactivity in tissues, organs, and matrices: by means of QWBA; LOD: 0.0478 - 0.107 nmol/g, LOQ: 0.0953 - 0.213 nmol/g

Results: p.o., 10 mg/kg (Long Evans, partially pigmented rats)

Tissues / organs	Concentrations (nmol/g)								
	0.25 h	1 h	4 h	24 h	72 h	168 h	336 h	504 h	840 h
Blood (QWBA)	3.81	5.12	2.37	0	0	0	0	0	0
Blood (LSC)	3.78	5.10	2.20	0	0	0	0	0	0
Plasma (LSC)	3.46	4.98	2.03	0	0	0	0	0	0
Adrenal gland (cortex)	14.4	17.6	8.80	0	0	0	0	0	0
Adrenal gland (medulla)	9.10	10.2	5.23	0.503	0.442	0.414	0.389	0	0
Blood vessel wall	10.8	15.4	10.1	T	0	0	0	0	0
Bone marrow	4.09	5.61	2.45	T	0	0	0	0	0

Study title:	Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1					Study No. DMPK R1300834-01			
	Bone mineral	0.492	0.446	0.405	T	0	0	0	0
	Bone surface	2.67	3.29	1.34	0	0	0	0	0
	Brain	0.660	0.812	0.314	0	0	0	0	0
	Caecum wall	3.24	6.00	8.10	T	0	0	0	0
	Cartilage	0.190	0.569	1.61	0	0	0	0	0
	Choroid plexus	3.55	4.80	2.38	0	0	0	0	0
	Epididymis	1.66	4.89	3.84	0.188	0	0	0	0
	Esophagus	43.9	12.5	7.18	0	0	0	0	0
	Eye (choroid)	32.9	179	288	130	94.0	71.4	63.3	42.5	26.9
	Eye (ciliary body)	38.9	185	282	204	65.4	56.2	44.3	28.1	24.4
	Eye (lens)	T	0.285	0.682	T	0.104	T	T	T	0
	Eye (vitreous body)	0.243	1.26	2.82	0.534	0.372	0.350	0.371	0.355	0
	Fat (brown)	4.38	6.03	2.73	0	0	0	0	0	0
	Fat (white)	1.09	1.82	0.625	0	0	0	0	0	0
	Hair (follicle)	2.05	20.6	53.8	32.6	22.2	17.1	0	0	0
	Hair (tactile)	10.1	47.1	70.0	35.7	9.29	3.65	0	0	0
	Harderian gland	6.45	10.3	5.00	0	0	0	0	0	0
	Heart	4.39	6.22	2.48	0	0	0	0	0	0
	Intestinal wall (colon)	4.22	5.14	2.88	0	0	0	0	0	0
	Intestinal wall (small intestine)	47.8	56.9	19.3	0	0	0	0	0	0
	Kidney (CM junction)	13.3	18.7	10.8	0.474	0.194	0.282	0	0	0
	Kidney (cortex)	12.6	17.5	9.92	0.350	0.166	0.201	0	0	0
	Kidney (medulla)	4.68	6.62	3.09	T	0	T	0	0	0
	Lacrimal gland	8.84	17.7	9.71	T	0	0	0	0	0
	Liver	38.0	38.6	21.0	3.65	1.99	0.796	0.280	T	0
	Lung	4.40	6.02	2.50	0	0	0	0	0	0
	Lymph nodes (submandibular)	3.50	5.32	2.34	0	0	0	0	0	0
	Meibomian gland	NM	NM	NM	NM	NM	NM	NM	NM	NM
	Meninges	3.26	4.87	25.9	14.0	3.67	3.26	2.29	1.49	0.450

Study title:	Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1					Study No. DMPK R1300834-01			
	Muscle	2.13	3.85	1.45	0	0	0	0	0	0
	Nasal mucosa	2.46	3.09	3.72	0.238	0	0	0	0	0
	Pancreas	6.88	8.45	3.73	0	0	0	0	0	0
	Penis	2.72	5.14	2.91	0	0	0	0	0	0
	Pineal body	3.27	4.67	2.18	0	0	0	0	0	0
	Pituitary gland	5.16	7.58	4.30	T	0	0	0	0	0
	Preputial gland	8.73	42.0	57.0	7.97	0.736	0.233	0	0	0
	Prostate	2.57	4.04	2.22	0	0	0	0	0	0
	Salivary gland (submaxiliary)	6.06	8.97	4.03	0	0	0	0	0	0
	Seminal vesicle wall	3.60	5.03	2.75	0	0	0	0	0	0
	Seminal vesicular fluid	1.08	4.39	2.78	0	0	0	0	0	0
	Skin (non-pigmented)	2.23	5.29	3.25	0	0	0	0	0	0
	Skin (pigmented)	2.43	7.05	9.92	3.15	2.66	1.63	0	0	0
	Skin (subcutis)	2.00	5.10	2.76	0	0.100	T	0	0	0
	Spinal cord	0.679	0.845	0.351	0	0	0	0	0	0
	Spleen	5.10	6.21	2.74	0	0	0	0	0	0
	Stomach (glandular)	27.5	29.9	12.9	1.19	0	0	0	0	0
	Stomach (non-glandular)	10.1	8.76	5.28	T	0	0	0	0	0
	Testis	0.833	2.40	1.64	0	0	0	0	0	0
	Thymus	2.95	4.75	2.34	0	0	0	0	0	0
	Thyroid gland	6.79	8.72	4.24	0.215	0	0	0	0	0
	Tongue	3.55	4.83	2.40	0	0	0	0	0	0
	Tongue (mucous gland)	4.21	5.69	2.47	0	0	0	0	0	0
	Tooth (pulp)	3.33	4.68	2.11	0	0	0	0	0	0
	LOD (LSC)	0.0890	0.107	0.0811	0.0803	0.0478	0.0821	0.0977	0.0684	0.104
	LOQ (LSC)	0.178	0.213	0.162	0.161	0.0953	0.164	0.195	0.137	0.209

Tissues / organs	Pharmacokinetic parameters							
	Tmax	Cmax	Cmax*	Tlast	AUClast	AUClast*	T1/2	Range for

Study title: Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1 Study No. DMPK R1300834-01

	(h)	(nmol/g)		(h)	(nmol/g·h)		(h)	T1/2 (h)
Blood (QWBA)	1.0	5.12	1.00	4.0	15.1	1.00	NC	NC
Blood (LSC)	1.0	5.10	0.996	4.0	14.8	0.983	NC	NC
Adrenal gland (cortex)	1.0	17.6	3.44	4.0	53.4	3.55	NC	NC
Adrenal gland (medulla)	1.0	10.2	1.99	336	258 [a)]	17.1 [b)]	NC	NC
Blood vessel wall	1.0	15.4	3.01	4.0	49.4	3.28	NC	NC
Bone marrow	1.0	5.61	1.10	4.0	16.2	1.08	NC	NC
Bone mineral	0.25	0.492	0.0961	4.0	1.69	0.112	NC	NC
Bone surface	1.0	3.29	0.643	4.0	9.51	0.631	NC	NC
Brain	1.0	0.812	0.159	4.0	2.32	0.154	NC	NC
Caecum wall	4.0	8.10	1.58	4.0	25.0	1.66	NC	NC
Cartilage	4.0	1.61	0.314	4.0	3.58	0.238	NC	NC
Choroid plexus	1.0	4.80	0.938	4.0	14.3	0.950	NC	NC
Epididymis	1.0	4.89	0.955	24.0	56.0	3.72	4.78	1-24
Esophagus	0.25	43.9	8.57	4.0	56.2	3.73	NC	NC
Eye (choroid)	4.0	288	56.3	840	50100	3330 [b)]	420	336-840
Eye (ciliary body)	4.0	282	55.1	840	41300	2740 [b)]	544	168-840
Eye (lens)	4.0	0.682	0.133	72.0	28.3	1.88 [b)]	NC	NC
Eye (vitreous body)	4.0	2.82	0.551	504	295 [c)]	19.6 [b)]	258	336-840 [c)]
Fat (brown)	1.0	6.03	1.18	4.0	17.6	1.17	NC	NC
Fat (white)	1.0	1.82	0.355	4.0	4.89	0.325	NC	NC
Hair (follicle)	4.0	53.8	10.5	168	4190	278 [b)]	NC [d)]	NC
Hair (tactile)	4.0	70.0	13.7	168	2960	197 [b)]	NC [d)]	NC
Harderian gland	1.0	10.3	2.01	4.0	30.0	1.99	NC	NC
Heart	1.0	6.22	1.21	4.0	17.6	1.17	NC	NC
Intestinal wall (colon)	1.0	5.14	1.00	4.0	16.1	1.07	NC	NC
Intestinal wall (small intestine)	1.0	56.9	11.1	4.0	160	10.6	NC	NC
Kidney (CM junction)	1.0	18.7	3.65	168	210	13.9 [b)]	NC	NC
Kidney (cortex)	1.0	17.5	3.42	168	187	12.4 [b)]	NC	NC

Study title:	Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1						Study No. DMPK R1300834-01		
	Kidney (medulla)	1.0	6.62	1.29	4.0	19.4	1.29	NC	NC
	Lacrimal gland	1.0	17.7	3.46	4.0	52.2	3.47	NC	NC
	Liver	1.0	38.6	7.54	336	729	48.4 [b)]	95.1	72-336
	Lung	1.0	6.02	1.18	4.0	17.2	1.14	NC	NC
	Lymph nodes (submandibular)	1.0	5.32	1.04	4.0	15.2	1.01	NC	NC
	Meninges	4.0	25.9	5.06	840	2310	153 [b)]	212	336-840
	Muscle	1.0	3.85	0.752	4.0	10.5	0.697	NC	NC
	Nasal mucosa	4.0	3.72	0.727	24.0	52.2	3.47 [b)]	NC	NC
	Pancreas	1.0	8.45	1.65	4.0	24.9	1.65	NC	NC
	Penis	1.0	5.14	1.00	4.0	15.4	1.02	NC	NC
	Pineal body	1.0	4.67	0.912	4.0	13.7	0.910	NC	NC
	Pituitary gland	1.0	7.58	1.48	4.0	23.2	1.54	NC	NC
	Preputial gland	4.0	57.0	11.1	168	1070	71.0 [b)]	30.5 [e)]	24-168
	Prostate	1.0	4.04	0.789	4.0	12.2	0.810	NC	NC
	Salivary gland (submaxiliary)	1.0	8.97	1.75	4.0	25.9	1.72	NC	NC
	Seminal vesicle wall	1.0	5.03	0.982	4.0	15.4	1.02	NC	NC
	Seminal vesicular fluid	1.0	4.39	0.857	4.0	12.9	0.857	NC	NC
	Skin (non-pigmented)	1.0	5.29	1.03	4.0	15.9	1.06	NC	NC
	Skin (pigmented)	4.0	9.92	1.94	168	505	33.5 [b)]	NC [d)]	NC
	Skin (subcutis)	1.0	5.10	0.996	72.0	112	7.44 [b)]	NC	NC
	Spinal cord	1.0	0.845	0.165	4.0	2.45	0.163	NC	NC
	Spleen	1.0	6.21	1.21	4.0	18.3	1.22	NC	NC
	Stomach (glandular)	1.0	29.9	5.84	24.0	230	15.3 [b)]	5.23	1.0-24
	Stomach (non-glandular)	0.25	10.1	1.97	4.0	29.4	1.95	NC	NC
	Testis	1.0	2.40	0.469	4.0	7.38	0.490	NC	NC
	Thymus	1.0	4.75	0.928	4.0	13.9	0.923	NC	NC
	Thyroid gland	1.0	8.72	1.70	24.0	70.7	4.69 [b)]	4.42	1.0-24
	Tongue	1.0	4.83	0.943	4.0	14.4	0.956	NC	NC
	Tongue (mucous gland)	1.0	5.69	1.11	4.0	16.5	1.10	NC	NC

Study title:	Quantitative whole body autoradiography in male partially pigmented rats after a single 10 mg/kg oral administration of [^{14}C]INC280 Amendment No. 1						Study No. DMPK R1300834-01		
	Tooth (pulp)	1.0	4.68	0.914	4.0	13.6	0.903	NC	NC
Conclusion:	After oral administration of 10 mg/kg (referring to free base) [^{14}C]INC280 dihydrochloride monohydrate to male partially pigmented rats, the following was observed: Extravascular tissue distribution of total radiolabeled components was observed (in most tissues, higher concentrations of total radiolabeled components were measured compared to blood). For most tissues, a Cmax at 1 h post-dose was observed. The highest exposure of total radiolabeled components based on Cmax was observed in eye (choroid), eye (ciliary body), hair (tactile), preputial gland, intestinal wall, hair (follicle) and liver. The highest exposure to total radiolabeled components based on AUClast was observed in eye (choroid), eye (ciliary body), hair (follicle), hair (tactile) and meninges. Minor specific uptake into brain was observed. Specific distribution and retention of total radiolabeled components in melanin- containing structures such as eye (choroid), eye (ciliary body) and meninges was observed. For these tissues total radiolabeled components were still measurable at 840 h post-dose (the last time point analyzed) resulting in estimated T1/2 of 420 h for eye (choroid), 544 h for eye (ciliary body) and 212 h for meninges. The presence of total radiolabeled components in those tissues was at least partly reversible.								
Additional information	Concentrations below LOD are reported as 0.								

NM: not measurable as not visible on the tissue sections; T (traces): Concentrations between LOD and LOQ; NC: not calculated, due to limited data set available;

*: Tissue to blood (QWBA) ratio of Cmax and AUClast

a) For AUClast and T1/2 calculation the LOD value was used at 50 4h post-dose. Considering the time range 336-504 h, T1/2 was < 67 h.

b) AUClast* of the respective tissue has to be considered with caution as AUClast in blood (QWBA) is dependent on short Tlast with a large difference in AUCinf and AUClast.

c) For AUClast and T1/2 calculation the LOD value was used at 840 h post-dose.

d) For hair (follicle), hair (tactile) and skin (pigmented), no T1/2 has been calculated as the decrease in tissue concentrations at the late time points is a combination of elimination and excretion via hair and hair is shaved off during animal preparation for embedding.

e) RSQ adjusted was < 0.75 (0.713).

2.6.5.5D 薬物動態試験：組織分布（ラット）

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No.1	Study No. DMPK R1600074-01
Location in CTD:	4.2.2.2-14	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 (dihydrochloride monohydrate)	
Species / Strain:	Rat / Sprague-Dawley (Crl:CD® [SD], albino)	
Gender / No. of animals:	Male / 10 (4 in Group 1, 6 in Group 2)	
Feeding condition:	Water and food *ad libitum*	
Vehicle / Formulation:	Aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	p.o. (gavage) / single and repeated dosing (10 days)	
Dose:	40 mg/kg/day (doses referring to the free base)	
Sampling times:	1 rat per time point	
	Group 1: 1, 4, 8 and 24 h post-dose	
	Group 2: 1, 4, 8, 24, 72 and 168 h post-dose	
Analyte:	[^{14}C]INC280	
Analytical methods:	Radioactivity in blood and plasma: LSC	
	Group 1: Blood; LOD: 0.179 nmol/g, plasma; LOD: 0.168 nmol/g	
	Group 2: Blood; LOD: 0.197 nmol/g, plasma; LOD: 0.185 nmol/g	
	Concentration of total radiolabeled components in tissues, organs and slices: QWBA:	
	Group 1: LOQ: 0.351 - 0.435 nmol/g	
	Group 2: LOQ: 0.394 - 0.857 nmol/g	

Results: p.o., 40 mg/kg/day (SD rats, albino)

Tissues / organs	Group 1: Single dose				Group 2: Repeated dose (10 days)					
	1 h	4 h	8 h	24 h	1 h	4 h	8 h	24 h	72 h	168 h
Blood (QWBA)	16.2	15.2	5.05	0	13.8	6.86	11.3	0	0	0
Blood (LSC)	17.6	16.2	5.50	0.224	13.2	7.03	11.3	0.751	0.378	0
Plasma (LSC)	24.7	22.3	6.39	0	18.6	8.44	13.1	0.326	0	0
Adrenal gland (cortex)	34.8	36.8	16.7	0	48.9	23.4	40.7	1.66	0	0

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No.1						Study No. DMPK R1600074-01			
	Adrenal gland (medulla)	26.2	28.6	11.3	0	40.5	28.7	55.5	19.2	9.47	0
	Blood vessel wall	36.7	32.3	15.2	1.02	34.2	21.7	27.7	1.53	0	0
	Bone marrow	13.5	13.8	5.66	0	10.5	6.39	11.2	0	0	0
	Bone mineral	2.08	2.02	0.659	0	0.773	0.900	1.10	0	0	0
	Brain	1.73	1.55	0.809	0	1.36	0.741	1.48	0	0	0
	Brain (cerebellum)	1.87	1.65	0.893	0	1.34	0.778	1.56	0	0	0
	Brain (choroid plexus)	10.8	4.25	1.96	0	10.3	4.51	3.92	0	0	0
	Brain (cortex)	1.56	1.52	0.678	0	1.76	0.768	1.03	0	0	0
	Brain (medulla oblongata)	2.27	1.85	0.941	0	1.22	0.796	1.52	0	0	0
	Brain (olfactory bulb)	1.47	1.75	0.722	0	1.54	0.876	1.92	0	0	0
	Brain (thalamus)	1.82	1.20	0.682	0	1.37	0.682	1.35	0	0	0
	Cartilage	1.14	2.94	2.43	0	1.68	1.90	3.39	0	0	0
	Epididymis	12.2	20.1	11.1	1.21	11.1	9.58	13.4	1.31	0	0
	Esophagus	20.7	18.4	6.44	1.50	30.6	9.29	16.2	2.15	0	0
	Eye (choroid)	14.3	14.0	6.35	0	13.2	8.87	15.8	1.20	0	0
	Eye (ciliary body)	6.18	5.21	3.03	0.608	7.73	5.29	3.04	2.37	0	0
	Eye (lens)	0.503	1.67	1.47	0	2.95	3.05	4.47	3.09	2.22	1.82
	Eye (vitreous body)	0	0	0	0	0.446	0	0	0	0	0
	Fat (brown)	16.7	19.1	7.61	0	17.5	9.41	17.3	1.67	0	0
	Fat (white)	4.98	4.13	1.58	0	3.76	1.86	3.40	0	0	0
	Hair (follicle)	13.9	25.0	31.3	1.31	12.1	16.6	14.4	7.13	1.47	0
	Hair (tactile)	9.53	12.4	2.05	0	5.12	3.49	8.09	0	0	0
	Harderian gland	22.5	21.9	10.5	0	20.1	12.5	25.4	0	0	0
	Heart	14.9	14.1	5.32	0	12.5	7.10	13.1	0.912	0	0
	Intestinal wall (colon)	11.6	12.1	8.40	0.503	11.4	8.76	18.3	3.07	0	0
	Intestinal wall (small intestine)	65.4	44.3	41.9	0	38.7	41.8	36.5	0	0	0
	Kidney (CM junction)	41.3	39.3	20.3	1.15	43.2	29.3	50.2	5.38	1.80	0.805
	Kidney (cortex)	33.1	35.0	17.7	0.644	37.4	24.3	48.8	4.02	1.06	0.529
	Kidney (medulla)	21.1	18.3	5.90	0	20.7	10.3	16.2	1.10	0.791	0.551

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No.1						Study No. DMPK R1600074-01			
	Lacrimal gland	21.6	29.7	15.6	0	20.5	24.2	40.0	1.58	0.784	0
	Liver	58.3	68.3	43.7	4.21	79.7	73.1	87.4	18.9	10.7	3.67
	Lung	16.6	16.0	5.83	0	14.0	8.03	12.7	1.01	0	0
	Lymph node (submandibular)	13.9	17.5	5.83	0	13.7	6.69	11.7	0	0	0
	Meninges	7.38	8.07	4.85	0	3.56	6.45	5.69	0	0	0
	Muscle	7.95	7.32	3.30	0	6.27	3.70	6.18	0	0	0
	Pancreas	17.4	16.8	6.89	0	14.3	9.15	16.2	0.826	0	0
	Penis	15.7	16.8	7.39	0	14.0	9.83	13.2	0	0	0
	Pineal body	13.5	15.3	6.78	0	11.9	6.97	13.1	0	0	0
	Pituitary gland	16.9	16.0	7.70	0	16.3	8.80	16.7	0	0	0
	Preputial gland	143	235	158	30.8	204	272	297	99.7	0.914	0
	Salivary gland (submaxillary)	16.6	18.1	7.60	0	16.5	11.3	20.4	1.54	0.700	0
	Seminal vesicle fluid	11.5	14.4	7.72	0	10.9	8.98	12.9	0	0	0
	Seminal vesicle wall	10.5	8.16	3.13	0	11.2	4.82	5.46	1.05	0.821	0
	Skin	12.5	14.0	12.2	0.679	11.7	10.3	11.5	1.23	0	0
	Skin (subcutis)	12.3	9.58	5.08	0	8.69	7.96	8.20	0	0	0
	Spinal cord	1.80	1.64	0.791	0	1.72	0.861	1.37	0	0	0
	Spinal cord (grey matter)	1.78	1.45	0.731	0	1.68	0.859	1.40	0	0	0
	Spinal cord (white matter)	0.909	1.29	0	0	1.50	0.873	0.864	0	0	0
	Spleen	12.9	12.9	5.75	0	12.1	7.17	13.3	1.67	0	0
	Stomach (glandular)	99.0	54.0	24.9	0	87.0	46.6	50.5	0.831	0	0
	Stomach (non-glandular)	53.2	32.3	29.2	2.46	56.9	70.8	67.5	1.28	0	0
	Testis	5.44	6.85	3.59	0	3.90	3.82	4.25	0	0	0
	Thymus	10.7	11.5	5.10	0	10.0	6.20	11.0	0	0	0
	Thyroid gland	17.5	22.6	9.28	0.492	22.0	14.7	22.6	3.83	1.22	0
	Tongue	13.1	12.7	5.36	0	11.8	6.07	11.8	0.913	0	0
	Tongue (mucous gland)	20.2	19.7	7.59	0.465	14.4	9.32	18.8	0.974	0	0
	Tooth (pulp)	13.1	11.8	5.03	0	11.5	5.17	8.40	1.50	1.56	0
	LOQ	0.369	0.435	0.419	0.351	0.434	0.514	0.857	0.745	0.633	0.394

Study title: Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 Amendment No.1 Study No. DMPK R1600074-01

Tissues / organs	Group 1: Pharmacokinetic parameters					
	Tmax (h)	Cmax (nmol/g)	Cmax*	AUClast (nmol/g·h)	AUClast*	Tlast (h)
Blood (QWBA)	1	16.2	1.00	95.7	1.00	8
Blood (LSC)	1	17.6	1.09	149	1.55	24
Plasma (LSC)	1	24.7	1.52	140	1.47	8
Adrenal (cortex)	4	36.8	2.27	232	2.42	8
Adrenal (medulla)	4	28.6	1.77	175	1.83	8
Blood vessel wall	1	36.7	2.27	347	3.62	24
Bone marrow	4	13.8	0.852	86.6	0.905	8
Bone mineral	1	2.08	0.128	12.5	0.131	8
Brain	1	1.73	0.107	10.5	0.110	8
Brain (cerebellum)	1	1.87	0.115	11.3	0.118	8
Brain (choroid plexus)	1	10.8	0.667	40.4	0.422	8
Brain (cortex)	1	1.56	0.0963	9.80	0.102	8
Brain (medulla oblongata)	1	2.27	0.140	12.9	0.135	8
Brain (olfactory bulb)	4	1.75	0.108	10.5	0.110	8
Brain (thalamus)	1	1.82	0.112	9.20	0.0962	8
Cartilage	4	2.94	0.181	17.4	0.182	8
Epididymis	4	20.1	1.24	215	2.25	24
Esophagus	1	20.7	1.28	182	1.90	24
Eye (choroid)	1	14.3	0.883	90.3	0.944	8
Eye (ciliary body)	1	6.18	0.381	65.8	0.687	24
Eye (lens)	4	1.67	0.103	9.79	0.102	8
Eye (vitreous body)	NC	NC	NC	NC	NC	NC
Fat (brown)	4	19.1	1.18	115	1.21	8
Fat (white)	1	4.98	0.307	27.6	0.288	8
Hair (follicle)	8	31.3	1.93	439	4.58	24

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	Hair (tactile)	4	12.4	0.765	66.6	0.696	8
	Harderian gland	1	22.5	1.39	143	1.49	8
	Heart	1	14.9	0.920	89.8	0.938	8
	Intestinal wall (colon)	4	12.1	0.747	154	1.60	24
	Intestinal wall (small intestine)	1	65.4	4.04	370	3.86	8
	Kidney (CM junction)	1	41.3	2.55	432	4.52	24
	Kidney (cortex)	4	35.0	2.16	371	3.88	24
	Kidney (medulla)	1	21.1	1.30	118	1.23	8
	Lacrimal gland	4	29.7	1.83	178	1.86	8
	Liver	4	68.3	4.22	826	8.63	24
	Lung	1	16.6	1.02	101	1.05	8
	Lymph node (submandibular)	4	17.5	1.08	101	1.05	8
	Meninges	4	8.07	0.498	52.7	0.551	8
	Muscle	1	7.95	0.491	48.1	0.503	8
	Pancreas	1	17.4	1.07	107	1.12	8
	Penis	4	16.8	1.04	105	1.10	8
	Pineal body	4	15.3	0.944	94.1	0.983	8
	Pituitary gland	1	16.9	1.04	105	1.10	8
	Preputial gland	4	235	14.5	2935	30.7	24
	Salivary gland (submaxillary)	4	18.1	1.12	112	1.17	8
	Seminal vesicle fluid	4	14.4	0.889	88.8	0.928	8
	Seminal vesicle wall	1	10.5	0.648	55.8	0.583	8
	Skin	4	14.0	0.864	201	2.10	24
	Skin (subcutis)	1	12.3	0.759	68.3	0.714	8
	Spinal cord	1	1.80	0.111	10.9	0.114	8
	Spinal cord (grey matter)	1	1.78	0.110	10.1	0.106	8
	Spinal cord (white matter)	4	1.29	0.0796	3.75	0.0392	4
	Spleen	1	12.9	0.796	82.5	0.862	8
	Stomach (glandular)	1	99.0	6.11	437	4.56	8

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Stomach (non-glandular)	1	53.2	3.28	531	5.55	24
Testis	4	6.85	0.423	42.0	0.439	8
Thymus	4	11.5	0.710	71.9	0.751	8
Thyroid gland	4	22.6	1.40	211	2.20	24
Tongue	1	13.1	0.809	81.4	0.850	8
Tongue (mucous gland)	1	20.2	1.25	189	1.97	24
Tooth (pulp)	1	13.1	0.809	77.6	0.810	8

Tissues / organs	Group 2: Pharmacokinetic parameters							
	Tmax (h)	Cmax (nmol/g)	Cmax*	Tlast (h)	AUClast (nmol/g·h)	AUClast*	T1/2 (h)	Range for T1/2 (h)
Blood (QWBA)	1	13.8	1.00	74.2	1.00	8	NC[a)]	NC[a)]
Blood (LSC)	1	13.2	0.957	197	2.66	72	NC[a)]	NC[a)]
Plasma (LSC)	1	18.6	1.35	200	2.70	24	3.81	4-24
Adrenal (cortex)	1	48.9	3.54	600	8.08	24	NC	NC
Adrenal (medulla)	8	55.5	4.02	1578	21.3	72	28.1	8-72
Blood vessel wall	1	34.2	2.48	434	5.84	24	NC	NC
Bone marrow	8	11.2	0.812	65.8	0.886	8	NC	NC
Bone mineral	8	1.10	0.0797	6.90	0.0929	8	NC	NC
Brain	8	1.48	0.107	8.27	0.111	8	NC	NC
Brain (cerebellum)	8	1.56	0.113	8.52	0.115	8	NC	NC
Brain (choroid plexus)	1	10.3	0.746	44.2	0.596	8	NC [a)]	NC [a)]
Brain (cortex)	1	1.76	0.128	8.27	0.111	8	NC [a)]	NC [a)]
Brain (medulla oblongata)	8	1.52	0.110	8.27	0.111	8	NC	NC
Brain (olfactory bulb)	8	1.92	0.139	10.0	0.135	8	NC	NC
Brain (thalamus)	1	1.37	0.0993	7.83	0.105	8	NC	NC
Cartilage	8	3.39	0.246	16.8	0.226	8	NC	NC
Epididymis	8	13.4	0.971	200	2.70	24	NC	NC
Esophagus	1	30.6	2.22	273	3.68	24	NC [a)]	NC [a)]

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	Eye (choroid)	8	15.8	1.14	225	3.03	24	NC [a)]	NC [a)]
	Eye (ciliary body)	1	7.73	0.560	83.3	1.12	24	NC [a)]	NC [a)]
	Eye (lens)	8	4.47	0.324	407	5.49	168	201	24-168
	Eye (vitreous body)	1	0.446	0.0323	NC	NC	1	NC	NC
	Fat (brown)	1	17.5	1.27	254	3.43	24	NC [a)]	NC [a)]
	Fat (white)	1	3.76	0.272	20.8	0.281	8	NC	NC
	Hair (follicle)	4	16.6	1.20	490	6.60	72	19.8	8-72
	Hair (tactile)	8	8.09	0.586	38.6	0.521	8	NC	NC
	Harderian gland	8	25.4	1.84	135	1.82	8	NC	NC
	Heart	8	13.1	0.949	188	2.54	24	NC[a)]	NC [a)]
	Intestinal wall (colon)	8	18.3	1.33	261	3.52	24	NC [a)]	NC [a)]
	Intestinal wall (small intestine)	4	41.8	3.03	297	4.00	8	NC [a)]	NC [a)]
	Kidney (CM junction)	8	50.2	3.64	1031	13.9	168	55.4	24-168
	Kidney (cortex)	8	48.8	3.54	878	11.8	168	52.9 [b)]	24-168
	Kidney (medulla)	1	20.7	1.50	358	4.82	168	149	24-168
	Lacrimal gland	8	40.0	2.90	595	8.02	72	NC [a)]	NC [a)]
	Liver	8	87.4	6.33	2841	38.3	168	61.1	24-168
	Lung	1	14.0	1.01	191	2.58	24	NC	NC
	Lymph node(submandibular)	1	13.7	0.993	74.2	1.00	8	NC	NC
	Meninges	4	6.45	0.467	41.1	0.553	8	NC	NC
	Muscle	1	6.27	0.454	37.9	0.510	8	NC	NC
	Pancreas	8	16.2	1.17	229	3.09	24	NC [a)]	NC [a)]
	Penis	1	14.0	1.01	88.8	1.20	8	NC [a)]	NC [a)]
	Pineal body	8	13.1	0.949	74.4	1.00	8	NC	NC
	Pituitary gland	8	16.7	1.21	96.8	1.30	8	NC	NC
	Preputial gland	8	297	21.5	7542	102	72	7.53	8-72
	Salivary gland (submaxillary)	8	20.4	1.48	343	4.62	72	NC [a)]	NC [a)]
	Seminal vesicle fluid	8	12.9	0.935	79.0	1.06	8	NC	NC
	Seminal vesicle wall	1	11.2	0.812	147	1.98	72	NC [a)]	NC [a)]

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Skin	1	11.7	0.848	184	2.48	24	NC	NC
Skin (subcutis)	1	8.69	0.630	61.6	0.831	8	NC [a)]	NC [a)]
Spinal cord	1	1.72	0.125	9.19	0.124	8	NC [a)]	NC [a)]
Spinal cord (grey matter)	1	1.68	0.122	9.17	0.124	8	NC [a)]	NC [a)]
Spinal cord (white matter)	1	1.50	0.109	7.78	0.105	8	NC [a)]	NC [a)]
Spleen	8	13.3	0.964	196	2.64	24	NC [a)]	NC [a)]
Stomach (glandular)	1	87.0	6.30	849	11.4	24	NC	NC
Stomach (non-glandular)	4	70.8	5.13	1047	14.1	24	NC	NC
Testis	8	4.25	0.308	29.7	0.400	8	NC	NC
Thymus	8	11.0	0.797	63.7	0.858	8	NC	NC
Thyroid gland	8	22.6	1.64	473	6.38	72	NC [a)]	NC [a)]
Tongue	1	11.8	0.855	170	2.29	24	NC [a)]	NC [a)]
Tongue (mucous gland)	8	18.8	1.36	257	3.47	24	NC [a)]	NC [a)]
Tooth (pulp)	1	11.5	0.833	211	2.84	72	NC [a)]	NC [a)]

Tissues / organs	AUClast ratio total radiolabeled components in tissues of albino rats after single and repeated oral doses				
	Group 1: Single dose		Group 2: Repeated dose (10 days)		AUClast ratios
	Tlast (h)	AUClast (nmol/g·h)	Tlast (h)	AUClast (nmol/g·h)	Repeated dose / single dose
Blood (QWBA)	8	95.7	8	74.2	0.775
Blood (LSC)	24	149	72	197	1.33
Plasma (LSC)	8	140	24	200	1.43
Adrenal (cortex)	8	232	24	600	2.59
Adrenal (medulla)	8	175	72	1578	9.01
Blood vessel wall	24	347	24	434	1.25
Bone marrow	8	86.6	8	65.8	0.759
Bone mineral	8	12.5	8	6.90	0.550
Brain	8	10.5	8	8.27	0.788
Brain (cerebellum)	8	11.3	8	8.52	0.754

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	Brain (choroid plexus)	8	40.4	8	44.2	1.09
	Brain (cortex)	8	9.80	8	8.27	0.844
	Brain (medulla oblongata)	8	12.9	8	8.27	0.641
	Brain (olfactory bulb)	8	10.5	8	10.0	0.950
	Brain (thalamus)	8	9.20	8	7.83	0.850
	Cartilage	8	17.4	8	16.8	0.963
	Epididymis	24	215	24	200	0.929
	Esophagus	24	182	24	273	1.50
	Eye (choroid)	8	90.3	24	225	2.49
	Eye (ciliary body)	24	65.8	24	83.3	1.27
	Eye (lens)	8	9.79	168	407	41.6
	Eye (vitreous body)	NC	NC	1	NC	NC
	Fat (brown)	8	115	24	254	2.20
	Fat (white)	8	27.6	8	20.8	0.755
	Hair (follicle)	24	439	72	490	1.12
	Hair (tactile)	8	66.6	8	38.6	0.580
	Harderian gland	8	143	8	135	0.945
	Heart	8	89.8	24	188	2.10
	Intestinal wall (colon)	24	154	24	261	1.70
	Intestinal wall (small intestine)	8	370	8	297	0.803
	Kidney (CM junction)	24	432	168	1031	2.39
	Kidney (cortex)	24	371	168	878	2.37
	Kidney (medulla)	8	118	168	358	3.03
	Lacrimal gland	8	178	72	595	3.34
	Liver	24	826	168	2841	3.44
	Lung	8	101	24	191	1.90
	Lymph node (submandibular)	8	101	8	74.2	0.737
	Meninges	8	52.7	8	41.1	0.779
	Muscle	8	48.1	8	37.9	0.787

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	Pancreas	8	107	24	229	2.13
	Penis	8	105	8	88.8	0.846
	Pineal body	8	94.1	8	74.4	0.791
	Pituitary gland	8	105	8	96.8	0.920
	Preputial gland	24	2935	72	7542	2.57
	Salivary gland (submaxillary)	8	112	72	343	3.07
	Seminal vesicle fluid	8	88.8	8	79.0	0.890
	Seminal vesicle wall	8	55.8	72	147	2.64
	Skin non-pigmented	24	201	24	184	0.915
	Skin non-pigmented (subcutis)	8	68.3	8	61.6	0.903
	Spinal cord	8	10.9	8	9.19	0.842
	Spinal cord (grey matter)	8	10.1	8	9.17	0.908
	Spinal cord (white matter)	4	3.75	8	7.78	2.07
	Spleen	8	82.5	24	196	2.37
	Stomach (glandular)	8	437	24	849	1.94
	Stomach (non-glandular)	24	531	24	1047	1.97
	Testis	8	42.0	8	29.7	0.706
	Thymus	8	71.9	8	63.7	0.887
	Thyroid gland	24	211	72	473	2.24
	Tongue	8	81.4	24	170	2.09
	Tongue (mucous gland)	24	189	24	257	1.36
	Tooth (pulp)	8	77.6	72	211	2.71
Conclusion:	After single and multiple oral administrations of 40 mg/kg/day [^{14}C]INC280 dihydrochloride monohydrate (dose referring to free compound) to male Sprague-Dawley rats, the following was observed: The tissue distribution pattern was qualitatively similar after single and multiple dosing. Tissue Cmax values were generally comparable. The highest exposure of total radiolabeled components, based on Cmax and AUClast were observed in preputial gland, liver, stomach (glandular and non-glandular), intestinal wall, (small intestine), kidney (CM junction and cortex), and blood vessel wall. The highest accumulation potential was observed in eye (lens) and adrenal (medulla) with AUClast ratios single versus multiple dosing of 41.6 and 9.01. AUClast ratios between 2.57 and 3.44 were observed in adrenal (cortex and medulla), kidney (medulla), lacrimal gland, liver, preputial gland, salivary gland (submaxillary), seminal vesicle wall, and tooth (pulp). For the other tissues investigated, the accumulation potential was estimated to be low (AUClast ratio					

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	≤ 2.5 fold). In brain, radiolabeled material reflecting compound and/or its metabolites passed the blood-brain barrier to a minor extent with no major differences in most of the brain regions. Compared to single dose, no accumulation was observed.	
Additional information	Concentrations below LOQ are reported as 0.	

NC: not calculated, due to limited data set available.

*: Tissue to blood ratio of Cmax and AUClast

a) RSQ adjusted was < 0.75

b) RSQ adjusted for kidney (cortex) was 0.739

2.6.5.6A 薬物動態試験：血漿タンパク結合

Study title:	The *in vitro* protein binding of INCB028060 in human, cynomolgus monkey, dog, rat and mouse serum and plasma and *ex vivo* protein binding in cynomolgus monkey and rat plasma	Study No. INCYTE-DMB-08.122.1
Location in CTD:	4.2.2.3-4	
GLP compliance:	Not required	
Test article:	INC280 (synonym: INCB028060) (Lots 1 and 2, trifluoroacetic acid salts; Lot 15, dihydrochloride salt; Lot 16, dihydrochloride salt)	
Species / Strain:	Human / 10 donors (male and female); Cynomolgus monkey, Beagle dog, Sprague-Dawley rat, CD-1 mouse (for all species no information about sex)	
Samples:	Serum and plasma	
Method:	*In vitro* plasma and serum protein binding and *ex vivo* protein binding: fraction unbound (fu) investigation by equilibrium dialysis.	
Analyte:	INC280	
Analytical method:	LC-MS/MS (details in 4.2.2.2-2-INCYTE-DMB-08.118.1)	

Results:

Species	Nominal free concentration (µM)	Serum		Plasma		Ex vivo	
		fu (%)	fu (%) mean ± SD	fu (%)	fu (%) mean ± SD	fu (%)	fu (%) mean ± SD
Human	1	4.3	4.9 ± 1.3	7.3 [a)]	6.7 ± 0.5 [b)]	-	-
		4.1		6.4 [a)]		-	-
		4.2		6.2 [a)]		-	-
		6.8		6.8 [a)]		-	-
	3	3.8	3.8 [b)]	-	-	-	-
	10	4.8	4.7 ± 0.6	6.5 [a)]	6.8 ± 0.3 [b)]	-	-
		5.4		7.2 [a)]		-	-
		5.1		6.5 [a)]		-	-
		4.4		6.8 [a)]		-	-
Cynomolgus monkey	1	2.3	2.4 ± 0.1	2.9	2.8 ± 0.2	-	-
		2.4		2.9		-	-
		2.5		2.9		-	-
		-		2.6		-	-
	10	2.6	2.7 ± 0.2	3.4	3.2 ± 0.4	-	-

Study title:	The *in vitro* protein binding of INCB028060 in human, cynomolgus monkey, dog, rat and mouse serum and plasma and *ex vivo* protein binding in cynomolgus monkey and rat plasma					Study No. INCYTE-DMB-08.122.1	
			2.9		3.4	-	-
			2.7		3.4	-	-
					2.6	-	-
		5.8	-	-	-	2.8	2.8 ± 0.1
			-	-	-	2.7	
			-	-	-	2.8	
		58	-	-	-	4.2	4.1 ± 0.4
			-	-	-	4.4	
			-	-	-	3.6	
	Dog	1	16.9	17.1 ± 0.3	17.8	17.2 ± 0.7	-	-
			16.9		16.8	-	-
			17.5		17.6	-	-
			-		16.4	-	-
		10	19.9	20.2 ± 0.6	20.4	18.4 ± 3.0	-	-
			19.9		19.7	-	-
			20.9		19.5	-	-
			-		14.0	-	-
	Rat	1	6.4	6.1 ± 0.3	4.4	4.1 ± 0.3	-	-
			5.9		3.8	-	-
			6.0		3.9	-	-
			-		4.2	-	-
		10	6.4	6.7 ± 0.4	4.9	5.0 ± 0.3	-	-
			7.1		5.1	-	-
			6.7		4.6	-	-
			-		5.2	-	-
		6.8	-	-	-	-	5.9	5.2 ± 0.6
			-	-	-	-	4.8	
			-	-	-	-	4.9	

Study title:	The *in vitro* protein binding of INCB028060 in human, cynomolgus monkey, dog, rat and mouse serum and plasma and *ex vivo* protein binding in cynomolgus monkey and rat plasma					Study No. INCYTE-DMB-08.122.1		
		22.8	-	-	-	-	6.6	6.0 ± 0.7
			-	-	-	-	6.2	
			-	-	-	-	5.2	
	Mouse	1	6.4	5.5 ± 0.2	3.9	4.1 ± 0.8	-	-
			5.4		3.9		-	-
			5.3		3.3		-	-
			-		5.1		-	-
		10	8.1	6.7 ± 1.5	4.8	5.0 ± 0.2	-	-
			7.5		4.9		-	-
			6.4		5.0		-	-
			4.6		5.3		-	-
Conclusion:	The fu for INC280 was similar for humans, rats and mice, while it was lower in cynomolgus monkeys and much higher in Beagle dogs. Minimal differences were observed between serum and plasma in each species. In general, the fraction unbound of INC280 was independent of the concentration of INC280, with the potential exception of cynomolgus monkey *ex vivo* plasma.							

a) Preliminary human data using a Multi-equilibrium dialyzer system over a concentration range of 1-10 µM (412-4120 ng/mL), the *in vitro* report 5.3.2.1-1-DMPK R1400051 provides final human data obtained over a broader concentration range of 10 -10000 ng/mL using an ultrafiltration method (selected based on control experiments showing acceptable recovery and free permeation via membrane)

b) n = 1

2.6.5.6B 薬物動態試験：血漿タンパク結合

Study title:	The *in vitro* blood-to-plasma ratio of INCB028060 in human, rat, beagle dog, & cynomolgus monkey			Study No. INCYTE-DMB-08.123.1
Location in CTD:	4.2.2.3-5			
GLP compliance:	Not required			
Test articles:	INC280 (synonym: INCB028060) (Lot 4, hydrochloric acid salt)			
Species / Strain:	Human, Rat, Beagle dog, Cynomolgus monkey (for all species no information about sex)			
Samples:	Blood			
Method:	Blood to plasma ratio: Blood and plasma samples were incubated for 60 min at 37°C in a shaking water bath. Blood samples were centrifuged to collect plasma. INC280 was analyzed in both, blood and plasma.			
Analyte:	INC280			
Analytical method:	LC-MS/MS using ESI			
Results:	Blood to plasma ratio (nominal concentration: 3 µM; incubation time: 1 h) [a]			
	Human	Rat	Beagle dog	Cynomolgus monkey
	1.7 ± 0.3 [b]	1.1 ± 0.1	7.9 ± 0.6	1.4 ± 0.1
Conclusion:	The blood-to-plasma ratios of INC280 in human, cynomolgus monkey, and rat whole blood were similar and close to unity (1.7, 1.4, and 1.1, respectively). Beagle dog was the clear outlier with a blood-to-plasma ratio of 7.9.			

a) Values are given as mean ± SD (no information in the report about the replicates per species)

b) Preliminary data at 3 µM (1240 ng/mL), the *in vitro* report 5.3.2.1-1-DMPK R1400051 provides final human data obtained over a concentration range of 10 -10000 ng/mL indicating concentration dependency.

2.6.5.6C 薬物動態試験：血漿タンパク結合

Study title:	CMN288: Determination of *in vitro* protein binding in rat, monkey and human plasma			Study No. DMPK R1600760
Location in CTD:	4.2.2.3-6			
GLP compliance:	Not required			
Test articles:	CMN288			
Species / Strain:	Rat / Sprague-Dawley (male), Cynomolgus monkey (male), Human (male)			
Samples:	Defrosted plasma; pools of n ≥ 3. K3-EDTA was used as an anticoagulant.			
Method:	*In vitro* plasma protein binding: fu investigated by ultrafiltration			
Analyte:	CMN288			
Analytical method:	LC-MS/MS using ESI in positive mode			
Results:	*In vitro* plasma protein binding			

Species	Concentration tested	fu in plasma of CMN288 (%, mean ± SD, n = 3)	Fraction bound (fb) in plasma of CMN288 (%, mean ± SD, n = 3)
Rat	300	0.340 ± 0.0330	99.7
	3000	0.373 ± 0.00521	99.6
	Mean	0.356	99.6
Monkey	300	1.46 ± 0.0421	98.5
	3000	1.68 ± 0.0495	98.3
	Mean	1.57	98.4
Human	300	0.423 ± 0.0335	99.6
	3000	0.509 ± 0.0128	99.5
	Mean	0.466	99.5

Conclusion: CMN288 was highly bound to rat, monkey and human plasma proteins (a mean of 98.4%-99.6%).

In each species, the extent of plasma protein binding was similar at both CMN288 concentrations tested. The extent of plasma protein binding appeared to display some degree of inter-species variation.

2.6.5.7 薬物動態試験：妊娠動物における試験

該当なし

2.6.5.8 薬物動態試験：その他の分布試験

該当なし

2.6.5.9A 薬物動態試験：*in vivo* 代謝（無処置／胆管カニューレ挿入ラット）

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01
Location in CTD:	4.2.2.2-4	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 dihydrochloride	
Species / Strain:	Rat / Hanover Wistar (albino)	
Gender / No. of animals:	Male / 10 (3 for i.v. [Group 3],4 for p.o. [Group 4], 3 for i.v. [Group 5])	
Feeding condition:	Water and food *ad libitum*	
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 300 / 80% aqueous glucose solution (5%)	
	p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	i.v. bolus (into vena femoralis) / single dose	
	p.o. (gavage) / single dose	
Dose:	i.v.: 3 mg/kg (doses referring to the free base)	
	p.o.: 10 mg/kg (doses referring to the free base)	
Samples:	Plasma, urine and feces	
Sample times:	i.v. (Group 3): Analyzed plasma; 0.083, 0.5, 1, 4 and 8 h post-dose (pools of n = 3), Analyzed urine and feces; 0-48 h (pools of n = 3)	
	p.o. (Group 4): Analyzed plasma; 0.25, 0.5, 1, 4, 8 and 24 h post-dose (pools of n = 4), Analyzed urine and feces; 0-48 h (pools of n = 4)	
	i.v. (Group 5): Analyzed urine and feces; 0-24 h, Analyzed bile; 0-8 h	
Analyte:	INC280 and metabolites	
Analytical methods:	Radioactivity: LSC	
	Liquid chromatography-mass spectrometry (LC-MS) with on- or off-line radioactivity detection	

Results:

[^{14}C]INC280 and metabolites in rat plasma [a)]

Metabolite	i.v., 3 mg/kg (pools of n = 3 per time point)				p.o., 10 mg/kg (pools of n = 4 per time point)			
	Tmax (h)	Cmax (μM)	AUC0-8h (μM·h)	(%)	Tmax (h)	Cmax (μM)	AUC0-24h (μM·h)	(%)
INC280 (parent)	0.083	6.78	6.40	50.60	0.25	2.27	14.6	33.40
M3 - CNN019	0.083	0.00273	0.000682	0.01	0.5	0.00445	0.00167	0.004
M4	0.5	0.0269	0.0697	0.55	1	0.0213	0.228	0.520

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1					Study No. DMPK R1100027-01		
	M8 - CMN290 [a)]	0.083	0.505	1.08	8.54	1	0.370	3.53	8.09
	M13 - CMC583	0.083	0.104	0.176	1.39	0.25	0.0693	0.508	1.16
	M16 - CMN288	0.5	1.44	2.94	23.2	0.5	1.70	14.4	33.1
	M17 - CNJ292	0.083	0.0282	0.0309	0.24	0.25	0.0171	0.00799	0.020
	M18 - CNJ294	0.083	0.100	0.214	1.67	0.5	0.0663	0.508	1.16
	M19 - CJK530	0.5	0.0252	0.0560	0.44	1	0.0282	0.246	0.560
	M21 - CJH800	0.5	0.0965	0.261	2.06	0.25	0.166	1.10	2.53
	M24	0.083	0.0309	0.0574	0.45	0.5	0.0302	0.246	0.560
	M26	0.5	0.0335	0.0864	0.68	1	0.0547	0.377	0.860
	M28 [a)]	1	0.131	0.403	3.18	1	0.221	1.94	4.44
	M29	0.5	0.0592	0.144	1.14	0.5	0.0614	0.511	1.17
	P8.1	8	0.000762	0.00152	0.012	24	0.00129	0.0103	0.0200
	P10.0	0.083	0.0282	0.0291	0.23	1	0.0217	0.186	0.430
	P19.8	ND	ND	ND	ND	24	0.00143	0.0114	0.0300
	P21.7	0.5	0.0274	0.0731	0.58	1	0.0200	0.180	0.410
	P39.3	0.5	0.0126	0.0207	0.16	1	0.0334	0.299	0.690
	Sum of additional components	1	0.0369	0.0900	0.71	0.5	0.0653	0.102	0.230
	Total components detected	0.083	9.09	12.1	95.80	0.5	4.95	39.0	89.40
	Lost during sample processing	1	0.230	0.527	4.16	0.25	0.672	4.63	10.60
	Lost during HPLC	0.00	0.00	0.00	0.00	0.00	0.0	0.0	0.00
	Total radiolabeled components in original sample	0.083	9.09	12.7	100.00	0.5	5.16	43.6	100.00

[^{14}C]INC280 and metabolites in rat excreta (amount expresses as % of dose)

Metabolite	i.v., 3 mg/kg (pool of n = 3)		p.o., 10 mg/kg (pool of n = 4)	
	Urine (0-48 h)	Feces (0-48 h)	Urine (0-48 h)	Feces (0-48 h)

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1				Study No. DMPK R1100027-01
	INC280 (Parent)	ND	8.52	ND	11.69
	M2	0.05	0.93	0.05	0.59
	M3 - CNN019	0.04	1.35	0.06	1.64
	M4	0.32	0.99	0.25	0.91
	M17 - CNJ292	ND	0.35	ND	1.15
	M8 - CMN290 [a)]	0.78	11.44	0.93	11.29
	M13 - CMC583	0.29	16.81	0.36	15.52
	M16 - CMN288	0.82	20.69	1.77	17.53
	M18 - CNJ294	ND	0.71	ND	0.32
	M19 - CJK530	0.04	ND	0.09	1.22
	M21 - CJH800	0.53	1.91	0.89	ND
	M24	0.40	ND	0.54	ND
	M27	0.20	0.84	0.24	0.72
	M28 [a)]	0.17	1.02	0.21	0.90
	M29	0.61	1.86	0.67	0.42
	M30	ND	2.77	ND	2.43
	P16.7	0.06	ND	0.08	ND
	P22.1	ND	1.54	ND	2.16
	P39.3	0.15	2.34	0.40	1.53
	Sum of additional components	0.58	4.73	0.83	7.47
	Total components detected	5.04	78.82	7.35	77.49
	Lost during sample processing	0.35	9.06	0.12	7.87
	Lost during HPLC	0.20	-	0.29	-
	Total radiolabeled components in original sample (0-48 h)	5.58	87.88	7.76	85.36
	Total excretion of radiolabeled components	5.71	88.62	7.82	86.41

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01
	(0-168 h)	

[^{14}C]INC280 and metabolites in excreta of bile duct-cannulated rats (amount expressed as % of dose)

Metabolite	i.v., 3 mg/kg (pool of n = 3)		
	Urine (0-48 h)	Feces (0-48 h)	Bile (0-8 h)
INC280 (Parent)	ND	2.3	ND
M2	0.08	ND	0.92
M3 - CNN019	0.09	ND	1.38
M4	0.25	0.25	1.08
M5	0.14 [b)]	ND	ND
M6	ND	ND	0.81
M8 - CMN290 [c)]	0.69	2.66	1.15
M13 - CMC583	0.63	0.37	15.80
M14	ND	ND	1.03
M16 - CMN288	2.11	0.67	6.58
M17 - CNJ292	ND	0.10	ND
M18 - CNJ294	ND	0.11	ND
M19 - CJK530	0.06	0.19	0.25
M20	0.09	ND	0.47
M21 - CJH800	0.98	0.24	0.75
M22	ND	ND	4.07
M24	1.45	ND	3.71
M25	ND	ND	6.33
M27	0.49	ND	1.73
M28[c)]	0.26	ND	0.77
M29	0.98	0.18	0.26

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1		Study No. DMPK R1100027-01
	M30	ND	ND	2.05
	P16.7	0.14	ND	ND
	P22.1	0.17	0.22	ND
	P35.1	0.28	ND	0.76
	P39.3 [d)]	0.85	0.45	1.91
	Sum of additional components	1.96	0.52	11.87
	Total components detected	11.69	8.27	63.68
	Lost during sample processing	0.00	0.97	0.00
	Lost during HPLC	0.46	-	-
	Total radiolabeled components in original sample (0-24 h) [e)]	12.15	9.24	63.68
	Total excretion of radiolabeled components (0-24 h)	12.15	9.24	66.28

Conclusion:

[^{14}C]INC280 and metabolites in rat plasma / [^{14}C]INC280 and metabolites in rat excreta

The biotransformation of INC280 occurred essentially by phase I metabolic reactions including *C*-hydroxylation, lactam formation, *N*-oxidation, *N*-dealkylation, hydrogenation, carboxylic acid formation and combinations thereof. Phase II reactions involved glucuronidation of oxygenated metabolites.

In plasma, the patterns of metabolites were qualitatively and quantitatively comparable after intravenous and oral administration of [^{14}C]INC280 dihydrochloride. Unchanged [^{14}C]INC280 accounted for the main proportion of radioactive compound in plasma extracts. The exposure of the rats to parent compound amounted to 50.6% (i.v.) of the total plasma [^{14}C]-AUC0-8h and 33.4% (p.o.) of the total plasma [^{14}C]-AUC0-24h. The exposure to the main metabolites M8 and M16 accounted for 8.54% and 23.2% of total radioactivity after i.v. administration and 8.09% and 33.1% of total radioactivity after oral administration, respectively. Numerous minor metabolite peaks were detected.

In feces and urine, the metabolites profiles after i.v. and p.o. administration were comparable. Feces contained three major metabolites after both routes of administration; the metabolites M13, M8 and M16 represented in sum 48.9% (i.v.) and 44.3% (p.o.) of the radioactive dose. In addition numerous minor metabolites were detected in feces. In urine various ^{14}C-labeled metabolites were detected with metabolites M8 and M16 as major components amounting up to 1.8% of the total radioactive dose. No unchanged [^{14}C]INC280 was excreted with urine.

[^{14}C]INC280 and metabolites in excreta of bile duct-cannulated rats

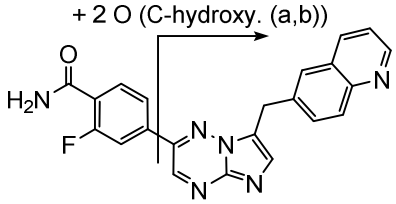
The biotransformation of INC280 occurred essentially by phase I metabolic reactions including *C*-hydroxylation, lactam formation, *N*-oxidation, *N*-

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01

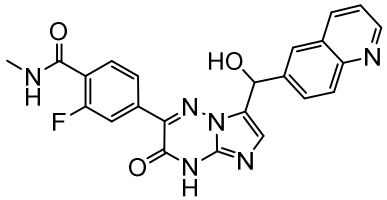
dealkylation, hydrogenation, carboxylic acid formation and combinations thereof. Phase II reactions involved glucuronidation of oxygenated metabolites.

The metabolite pattern of bile showed five major metabolites; the metabolites M13, M16 and M24, M22 and M25 accounted in sum 36.5% of the total radioactive dose. In addition sixteen minor metabolites were detected in bile and ranged between 0.2% and 2.1% of the dose each. No unchanged [^{14}C]INC280 was excreted in bile.

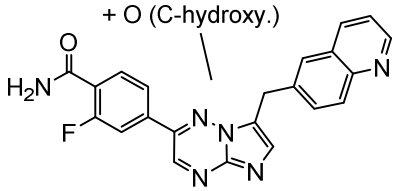
Metabolite structures:



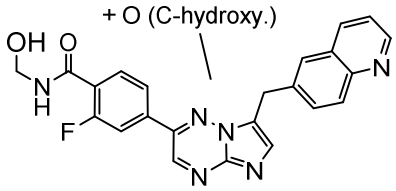
M2



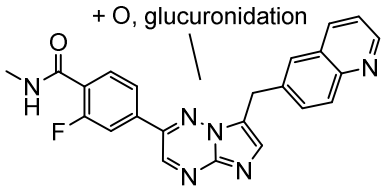
M3 (CNN019)



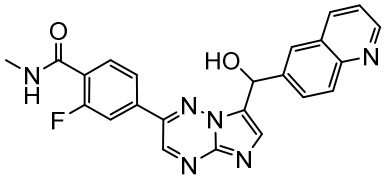
M4



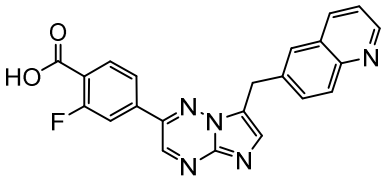
M5



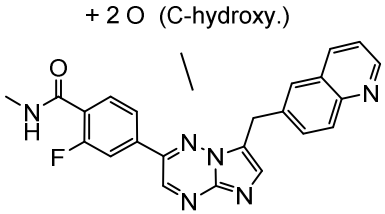
M6



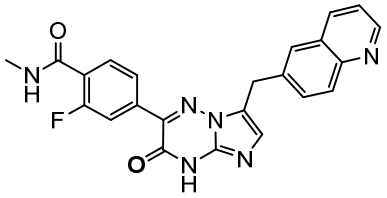
M8 (CMN290)



M13 (CMC583)

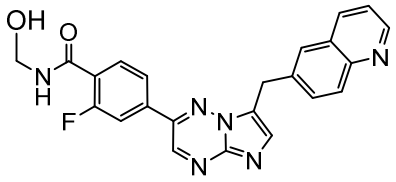


M14

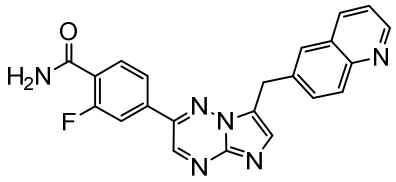


M16 (CMN288)

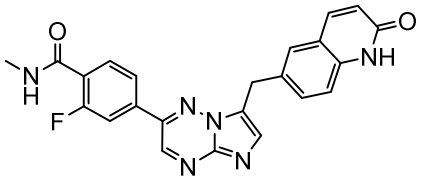
Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01



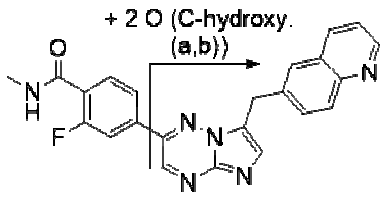
M17 (CNJ292)



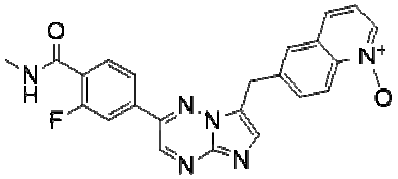
M18 (CNJ294)



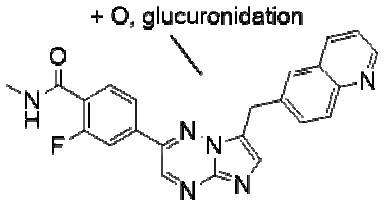
M19 (CJK530)



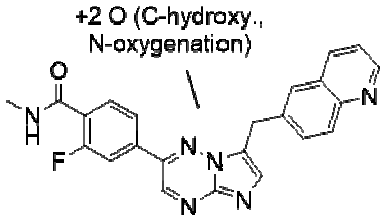
M20



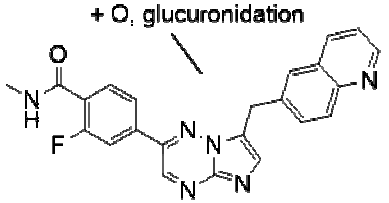
M21 (CJH800)



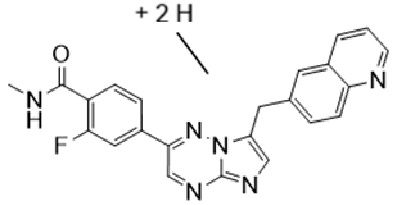
M22



M24

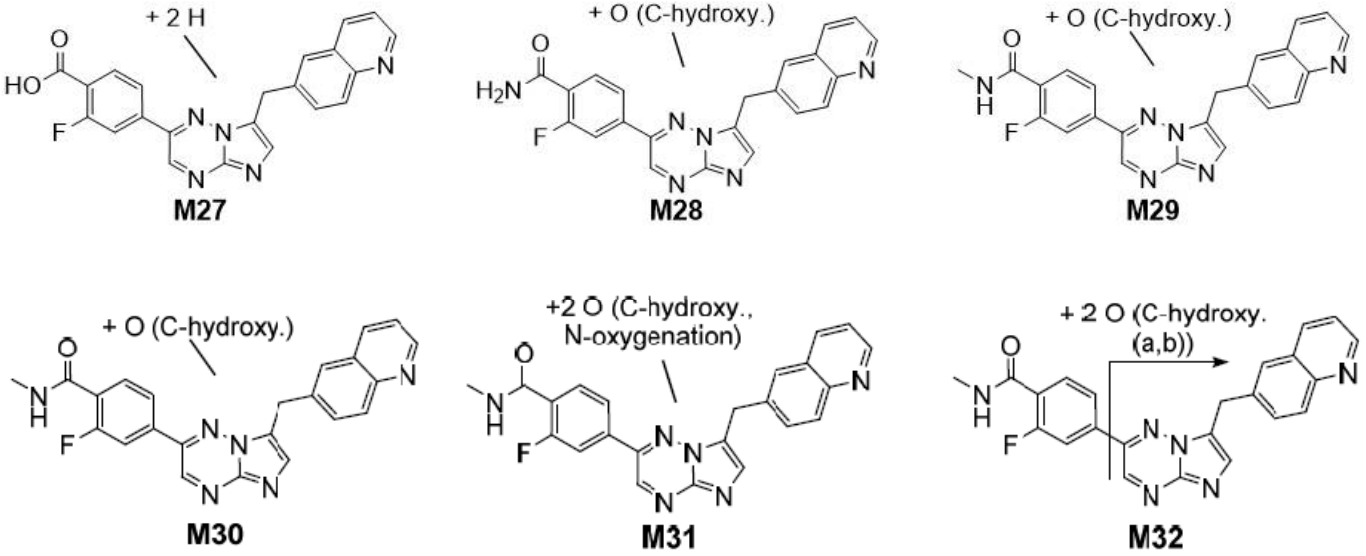


M25



M26

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride Amendment No.1	Study No. DMPK R1100027-01



a Metabolic reaction in imidazo-triazine moiety
b Metabolic reaction in quinoline moiety

C-hydroxy. hydroxylation on a carbon atom or further isomerization to lactam moiety

ND: not detected, -: data not obtained

a) Co-eluting metabolites were separated with a different chromatographic method.

b) Metabolite M5 co-eluted with metabolite M4. Peaks co-eluting in the radio chromatogram were quantified based on MS-responses assuming similar ionization yield.

c) The metabolite M28 co-eluted with metabolite M8. Peaks co-eluting in the radio chromatogram were quantified based on MS-responses assuming similar ionization yield.

d) P39.3 represents the co-eluting isobaric metabolites M31 and M32 which were separated in bile and urine. In urine the metabolite M32 represented approx. one-third of P39.3 in the radio chromatogram. In bile both metabolites M31 and M32 appeared in similar ratios.

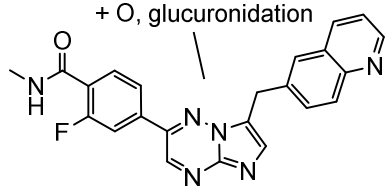
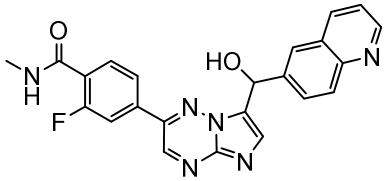
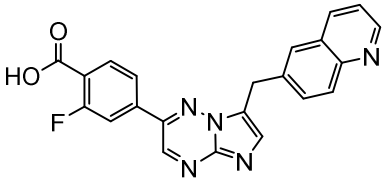
e) For bile 0-8 h.

2.6.5.9B 薬物動態試験：*in vivo* 代謝（無処置ラット）

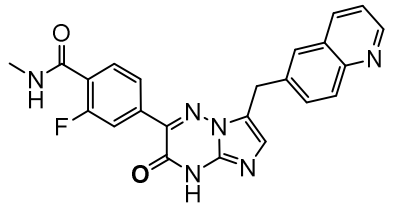
Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administration of 40 mg/kg/day [^{14}C]INC280 Amendment No.1	Study No. DMPK R1600074-01
Location in CTD:	4.2.2.2-14	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 dihydrochloride monohydrate	
Species / Strain:	Rat / Sprague-Dawley (Crl:CD® [SD], albino)	
Gender / No. of animals:	Male / 8 (3 in single dose group, 5 in multiple dose group)	
Feeding condition:	Water and food *ad libitum*	
Vehicle / Formulation:	aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	p.o. (gavage) / single and repeated dosing (10 days)	
Dose:	40 mg/kg/day (referring to free base)	
Samples:	Plasma	
Sample time:	Analyzed plasma: 0.25, 1, 4, 8 and 24 h post-dose (pools of n = 3 [single dose]; pools of n = 5 [multiple doses])	
Analyte:	INC280 and metabolites	
Analytical methods:	Radioactivity: LSC LC-MS with on- or off-line radioactivity detection	

Results: [^{14}C]INC280 and metabolites in rat plasma

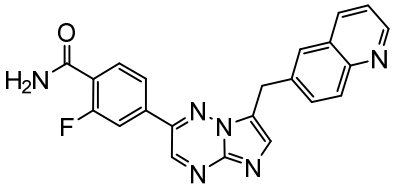
Metabolite	Single dose: p.o. 40 mg/kg/day (pools of n = 3 per time point)				Multiple dose: p.o. 40 mg/kg/day (pools of n = 5 per time point)			
	Tmax (h)	Cmax (µM)	AUC0-24h (µM·h)	(%)	Tmax (h)	Cmax (µM)	AUC0-24h (µM·h)	(%)
INC280	0.25	7.730	68.031	42.04	0.25	9.134	78.955	40.13
M6	1	0.070	0.323	0.20	1	0.075	0.583	0.30
M8 (CMN290)	1	0.928	9.944	6.15	1	1.154	13.017	6.62
M13	1	0.203	1.572	0.97	0.25	0.343	3.121	1.59
M16 (CMN288)	1	5.043	60.454	37.36	1	5.621	65.666	33.38
M18 (CNJ294)	0.25	0.182	1.815	1.12	0.25	0.198	1.850	0.94
M19 (CJK530)	1	0.115	0.677	0.42	1	0.078	1.006	0.51
M21 (CJH800)	1	0.249	1.971	1.22	0.25	0.285	2.544	1.29

Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administration of 40 mg/kg/day [^{14}C]INC280 Amendment No.1						Study No. DMPK R1600074-01		
	M24	1	0.053	0.203	0.13	1	0.053	0.534	0.27
	M28	1	0.394	4.541	2.81	4	0.428	5.189	2.64
	Sum of additional metabolites.	1	0.551	3.487	2.16	1	0.565	7.286	3.70
	Total components detected	1	14.227	153.019	94.57	0.25	15.584	179.758	91.37
	Lost during sample processing	1	0.809	8.792	5.43	8	1.165	16.971	8.63
	Lost during HPLC	ND	ND	ND	ND	ND	ND	ND	ND
	Total radiolabeled components in original sample	1	15.036	161.811	100.00	0.25	16.156	196.730	100.00
Conclusion:	In plasma, the pattern of metabolites were qualitatively and quantitatively comparable after single and multiple oral dosing of [^{14}C]INC280. Unchanged [^{14}C]INC280 accounted for the main proportion of radioactive compound in plasma extracts. The exposure of the rats to parent compound amounted to 42.0% (single dose) and 40.1% (multiple dose) of the total plasma [^{14}C]AUC0-24h. The exposure to the main metabolites M8 and M16 accounted for 6.15% and 37.4% of total radioactivity after single dose and 6.62% and 33.4% of total radioactivity after multiple oral doses, respectively. Numerous minor metabolite peaks were detected. All other identified metabolites in plasma (M6, M13, M18, M19, M21, M24, M28) accounted for less than 3% of the total plasma [^{14}C]AUC0-24h each.								
Metabolite structures:	 **M6**			 **M8** (CMN290)			 **M13** (CMC583)		

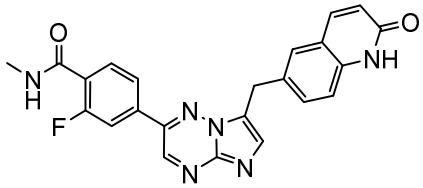
Study title:	Metabolism and quantitative whole body autoradiography in male Sprague-Dawley rats after single and multiple oral administration of 40 mg/kg/day [^{14}C]INC280 Amendment No.1	Study No. DMPK R1600074-01



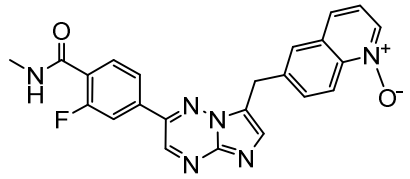
M16 (CMN288)



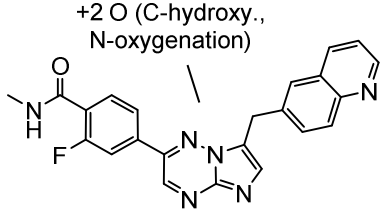
M18 (CNJ294)



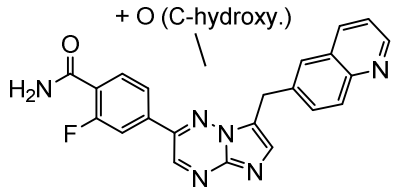
M19 (CJK530)



M21 (CJH800)



M24



M28

C-hydroxy.: hydroxylation on a carbon atom or further isomerization to lactam moiety

ND: not detected

2.6.5.9C 薬物動態試験：*in vivo* 代謝（サル）

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280 Study No. DMPK R1300820
Location in CTD:	4.2.2.2-10
GLP compliance:	Not required
Test articles:	[^{14}C]INC280 hydrochloride monohydrate
Species / Strain:	Monkey / Cynomolgus
Gender / No. of animals:	Male / 5 (2 for i.v., 3 for p.o.)
Feeding condition:	Water *ad libitum*, food once daily (normal diet)
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 200 / 80% aqueous glucose solution (5%) p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80
Route of dosing:	i.v. bolus (into saphenous vein) / single dose p.o. (gavage) / single dose
Dose:	i.v.: 3 mg/kg (doses referring to the free base) p.o.: 30 mg/kg (doses referring to the free base)
Samples:	Plasma, urine and feces
Sample time(s):	i.v.: Analyzed plasma; Pre-dose, 0.083, 0.25, 1, 2, 4 and 7 h post-dose (pools of n = 2), Analyzed urine and feces; 0-72 h (pools of n = 2) p.o.: Analyzed plasma; Pre-dose, 0.25, 0.5, 1, 2, 4, 7 and 10 h post-dose (pools of n = 2), Analyzed urine and feces; 0-72 h (pools of n = 2)
Analyte:	INC280 and metabolites
Analytical methods:	Radioactivity: LSC LC-MS with on- or off-line radioactivity detection

Results:

[^{14}C]INC280 and metabolites in monkey plasma

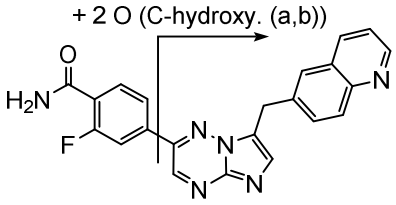
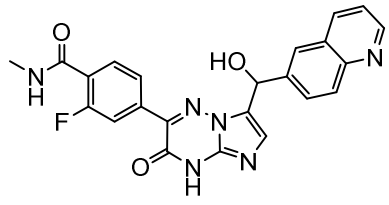
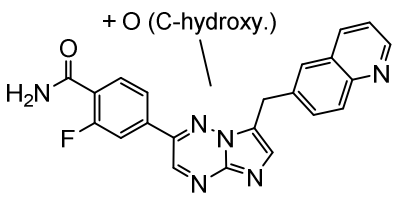
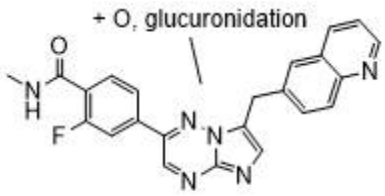
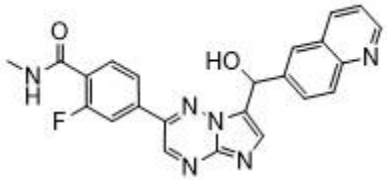
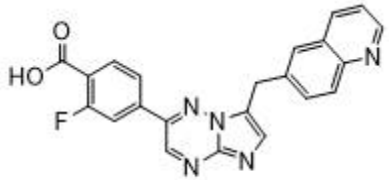
Metabolite	i.v., 3 mg/kg (pools of n = 2 per time point)				p.o., 30 mg/kg (pools of n = 2 per time point)			
	Tmax (h)	Cmax (µM)	AUC0-7h (µM·h)	(%)	Tmax (h)	Cmax (µM)	AUC0-10h (µM·h)	(%)
INC280	0.083	15.20 [a)]	15.25	54.30	2	47.67 [a)]	161.08	42.53
M3 (CMN019)	0.5	0.07	0.14	0.51	1	0.81	3.51	0.93
M4	0.5	0.07	0.24	0.85	2	0.60	4.07	1.08
M6	0.5	0.16	0.38	1.34	1	2.42	11.70	3.09

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280						Study No. DMPK R1300820	
	M8 (CMN290)	0.5	1.10[b)]	3.83	13.65 [b)]	2	17.69 [b)]	86.32	22.79 [b)]
	M13 (CMC583)	0.5	0.24[a)]	0.58	2.07	1	0.71 [a)]	3.05	0.80
	M14	1	0.05	0.16	0.56	2	0.57	2.51	0.66
	M16 (CMN288)	0.5	2.16	3.76	13.39	2	14.21	51.25	13.53
	M17 (CNJ292)	0.083	0.23	0.14	0.49	2	0.24	0.41	0.11
	M18 (CNJ294)	0.5	0.33	0.58	2.07	2	1.61	6.46	1.71
	M19 (CJK530)	0.5	0.24	0.65	2.31	2	1.90	7.61	2.01
	M21 (CJH800)	0.5	0.12	0.43	1.52	2	2.59	10.97	2.90
	M24	1	0.03	0.10	0.37	2	0.45	2.16	0.57
	M28	0.25	0.27 [b)]	0.59	2.08 [b)]	2	1.31 [b)]	6.06	1.60 [b)]
	Sum of additional components or metabolites	0.5	0.30	0.56	1.98	1	2.59	8.20	2.17
	Total components detected	0.083	17.31	27.39	97.51	2	93.71	365.36	96.46
	Lost during sample processing	0.25	1.12	0.70	2.49	2	4.72	13.42	3.54
	Total radiolabeled components in original sample	0.083	17.43	28.09	100.00	2	98.42	378.78	100.00

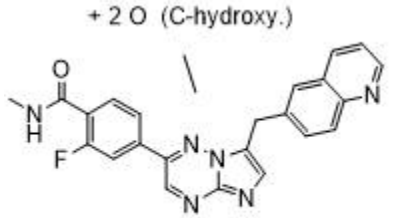
[^{14}C]INC280 and metabolites in monkey excreta (amount expressed as % of dose)

Metabolite	i.v., 3 mg/kg (pools of n = 2 per time point)		p.o., 30 mg/kg (pools of n = 2 per time point)	
	Urine (0-72 h)	Feces (0-72 h)	Urine (0-72 h)	Feces (0-72 h)
INC280	0.03	5.28	0.04	6.59
M2	0.22	0.52	0.26	0.59
M3 (CNN019)	0.39	1.99	0.66	2.67
M4	0.30	1.00	0.33	1.77
M6	0.34	ND	0.66	ND
M8 (CMN290)	0.50	6.21	0.37	12.57 [c)]

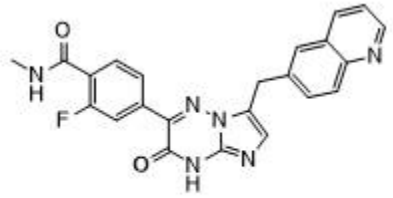
Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280				Study No. DMPK R1300820
	M13 (CMC583)	0.34	5.32	0.37	3.58
	M14	0.23 [d)]	ND	0.21 [e)]	ND
	M16 (CMN288)	1.17 [d)]	24.77	1.85 [e)]	18.83
	M17 (CNJ292)	ND	ND	ND	0.81
	M18 (CNJ294)	ND	ND	ND	0.78
	M19 (CJK530)	0.11	1.83	0.07	2.12
	M20	0.09	2.55	0.09	1.98
	M21 (CJH800)	0.76	ND	0.56	ND
	M22	0.19	ND	0.23	ND
	M24	0.70	ND	0.59	ND
	M28	0.40	6.06	0.64	3.08 [c)]
	M38	0.18	ND	0.19	ND
	M40	0.08	ND	0.12	ND
	M41	ND	2.65	ND	1.80
	P33.2	0.05	ND	0.06	ND
	Sum of other components	1.20	11.77	1.21	10.23
	Total components detected	7.28	69.96	8.51	67.41
	Lost during sample processing	0.00	3.74	0.00	0.68
	Lost during HPLC	0.20	0.75	0.51	1.54
	Total radiolabeled components in original sample (0-72 h)	7.48	74.40	9.02	69.60
	Total excretion of radiolabeled components (0-168 h)	7.92	77.40	9.67	72.00
Conclusion:	The biotransformation of INC280 occurred essentially by phase I metabolic reactions including C-hydroxylation, lactam formation, N-oxidation, N-dealkylation, carboxylic acid formation and combinations thereof. Phase II reactions involved glucuronidation of oxygenated metabolites. In plasma, the patterns of metabolites were qualitatively and quantitatively comparable after intravenous and oral administration of [^{14}C]INC280.				

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280 Study No. DMPK R1300820
	Unchanged [^{14}C]INC280 accounted for the main proportion of radioactive compound in plasma. The exposure of the unchanged drug accounted for 54.1% (i.v.) of the total plasma [^{14}C]-AUC0-7h and 42.5% (p.o.) of the total plasma [^{14}C]-AUC0-10h. The exposure to the main metabolites M8 and M16 accounted for 13.7% and 13.4% of total radioactivity after i.v. administration and 22.8% and 13.5% of total radioactivity after oral administration, respectively. Numerous minor metabolite peaks were detected: The sum of the phase II metabolites M6 and M28 accounted for 3.4% (i.v.) and 4.7% (p.o.) of the respective plasma [^{14}C]-AUClast. All other detected metabolites contributed each to ≤ 2.3% (i.v.) and ≤ 2.9% (p.o.). In urine and feces from monkeys, the metabolite profiles after i.v. and p.o. administration were comparable. In excreta the metabolites M8 and M16 were the important drug related compounds. Metabolite M8 ranged between 6.7% (i.v.) and 13.0% (p.o.) of the radioactive dose. The major metabolite M16 amounted to 25.9% (i.v.) and 20.7% (p.o.) of the radioactive dose in urine and feces. In addition various minor metabolites were detected in excreta after both routes of administration ranging between 0.1% and 6.5%. [^{14}C]INC280 was mainly metabolized as unchanged [^{14}C]INC280 accounted for 0.03% (i.v.) and 0.04% (p.o.) in urine and 5.30% (i.v.) and 6.64% (p.o.) in feces, respectively.
Metabolite structures:	 **M2**  **M3** (CNN019)  **M4**  **M6**  **M8** (CMN290)  **M13** (CMC583)

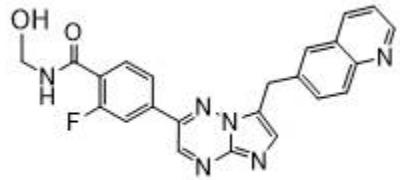
Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280	Study No. DMPK R1300820



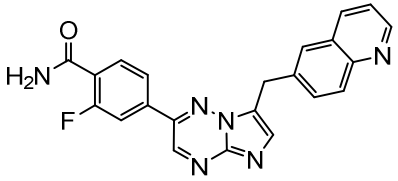
M14



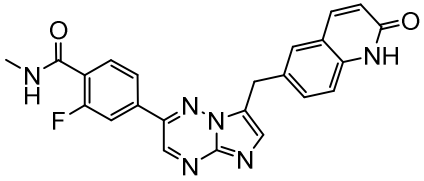
M16 (CMN288)



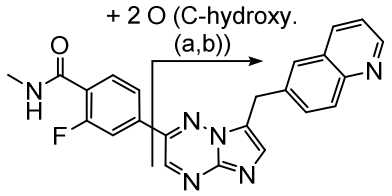
M17 (CNJ292)



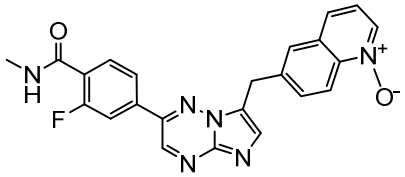
M18 (CNJ294)



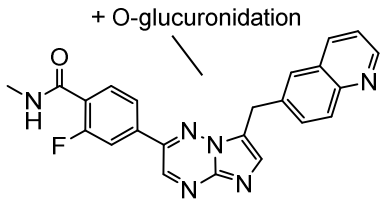
M19 (CJK530)



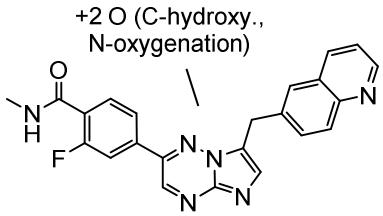
M20



M21 (CJH800)

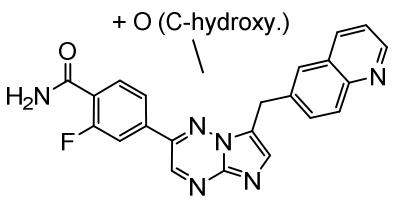


M22

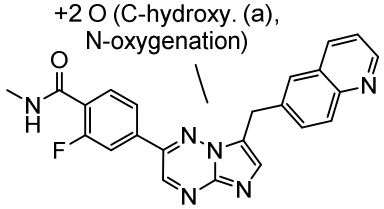


M24

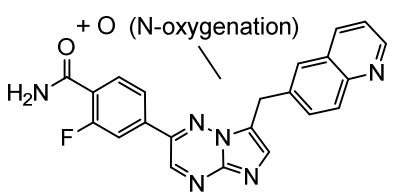
Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280	Study No. DMPK R1300820



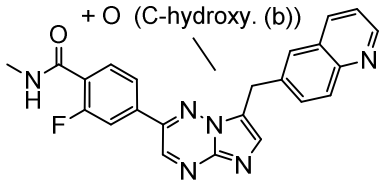
M28



M38



M40



M41

a Metabolic reaction in imidazo-triazine moiety
b Metabolic reaction in quinoline moiety

C-hydroxy. hydroxylation on a carbon atom or further isomerization to lactam moiety

ND: not detected

a) Co-elution. The abundance of the components was derived from the MS data assuming an ionization strength ratio INC280:M13 = 1.3:1. This was proved in three LC/MS runs, where the components were separated (Runs INC280e_42, INC280e_43 and INC280e_44).

b) Co-elution. The abundance of the components was derived from the MS data assuming an identical ionization strength. This was proved in two LC/MS runs, where the components were separated (Runs INC280e_27 and INC280e_28). LC/RA analysis of a plasma AUC0-10h pool extract yielded 2.2% (M28) and 20.3% (M8).

c) Co-eluting peaks were separated in run INC280e_28.

d) Co-eluting peaks were separated in run INC280e_22.

e) Co-eluting peaks were separated in run INC280e_21.

2.6.5.10A 薬物動態試験：*in vitro* 代謝

Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes	Study No. DMPK R1000705
Location in CTD:	4.2.2.4-1	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 dihydrochloride	
Study system:	Commercially available cryopreserved human liver microsomes, as well as commercially cryopreserved hepatocytes from mouse, rat, dog, monkey and human were used as biological material. The incubations of [^{14}C]INC280 were performed at 37°C. Enzyme reactions were stopped by the addition of 2 volumes of acetonitrile.	
Initial concentration:	5 µmol/L (microsomes); 10 µmol/L (hepatocytes)	
Analytical methods:	Radioactivity: LSC LC-MS	

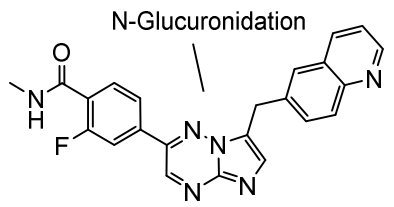
Results: % of Total

Metabolite	Incubation with hepatocytes (24 h)					Incubation with liver microsomes (30 min)
	Mouse	Rat	Dog	Monkey	Human	Human
INC280	23.13	27.55	0.64	2.40	12.87	40.97
M1	ND	ND	ND	ND	0.78	ND
M2	Tr.	ND	ND	1.19	1.56	ND
M3 (CNN019)	1.52	1.04	ND	6.89	0.80	ND
M4	0.70	Tr.	1.78 [a)]	3.54 [a)]	11.34 [a)]	0.74 [a)]
M5	Tr.	Tr.	3.37 [a)]	3.20 [a)]	10.54 [a)]	4.05 [a)]
M6	ND	Tr.	1.60	4.03 [b)]	Tr.	ND
M7	ND	ND	1.76	ND	ND	ND
M8 (CMN290) [c)]	19.23	16.24	8.37	23.97	24.05	32.31
M9	ND	ND	1.94	ND	ND	ND
M10	ND	ND	ND	ND	1.72	ND
M11	ND	ND	1.93	ND	ND	ND
M12	ND	ND	0.1	ND	ND	ND
M13 (CMC583)	7.99	12.19	49.26	1.90	0.65	Tr.

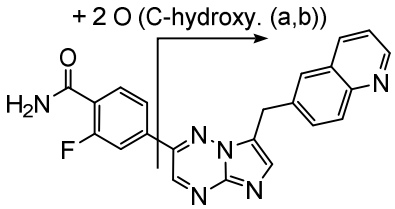
Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes					Study No. DMPK R1000705	
	M14	2.13	Tr.	Tr.	1.79	1.68	ND
	M15	ND	ND	0.62 [d)]	ND	ND	ND
	M16 (CMN288)	21.56	25.96	1.55 [d)]	10.03	4.35	Tr.
	M17 (CNJ292)	ND	ND	ND	ND	1.95	5.39
	M18 (CNJ294)	ND	ND	ND	ND	3.17	0.73
	M19 (CJK530)	3.68	2.32	ND	1.50	1.67	0.70
	M20	3.28	1.47	ND	1.26	0.38	ND
	M21 (CJH800)	3.19	0.81	2.60	5.06	2.31	7.04
	M22	0.83	2.53	ND	4.03 [b)]	1.38	ND
	M23	ND	ND	0.51	ND	ND	ND
	M24	1.11	0.42	4.14	4.49 [b)]	1.73	1.34
	M25	Tr.	0.64	ND	0.70 [b)]	Tr.	ND
	M26	ND	ND	ND	ND	1.31	ND
	P9.32	ND	ND	ND	0.63	1.67	ND
	P20.80	ND	ND	ND	1.05	1.77	0.95
	P25.68	ND	ND	5.75	2.94	Tr.	ND
	Others [d)]	11.65	8.83	14.08	19.4	12.32	5.78
Conclusion:	As main metabolic pathways *C*-oxygenations(s) and/or *N*-oxygenation of INC280 were detected across all species forming the metabolites M3, M5, M8, M14, M16, M17, M20, M21 and M24. The hydroxylated metabolite M8 and the imidazo-triazinone (lactam) M16 were main metabolites in hepatocyte incubations of all species except for dog. The minor cabinolamide M17 was only detected for human. Hydrolysis of the amide bond and formation of the carboxylic acid metabolite M13 was observed with some differences across the species. In dog this metabolic reaction was the most prominent metabolic pathway. In rat and mouse hepatocyte incubations metabolite M13 was less important than for dog. In monkey and human hepatocyte incubations hydrolysis of the amide bond was only observed to a minor extent. The formation of the minor quinolinone metabolite M19 was detected across all species but not for dog. Glucuronidation of oxygenated metabolites yielding the metabolites M6, M22 and M25 was detected across all species. A minor direct *N*-glucuronide of the parent drug (M1) was observed in human hepatocyte incubations. Glucuronidation of the carboxylic acid metabolite M13 yielded the minor metabolites M7, M9, M11, M12, M15 and M23 in dog hepatocyte incubations. These isomers are indicative for an acyl-glucuronide and its isomers formed by acyl-migration. *N*-dealkylation of INC280 in combination with C-hydroxylation (M2, M4) was found in hepatocyte incubations of all species. Metabolite M18 (*N*-dealkylation) was only detected for human. Minor other human specific metabolites were M10 and M26 formed by hydrogenation, or hydrogenation and hydroxylations, respectively.						

Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes	Study No. DMPK R1000705

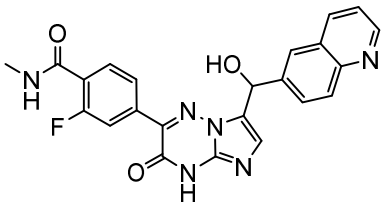
Metabolite structures



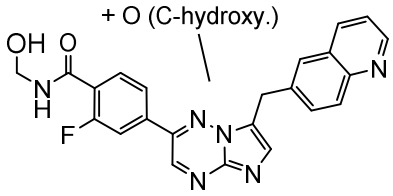
M1



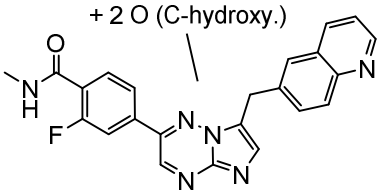
M2



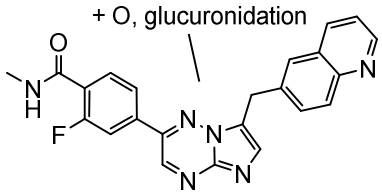
M3 (CNN019)



M4

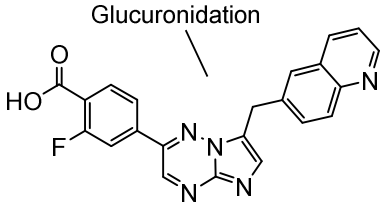


M5

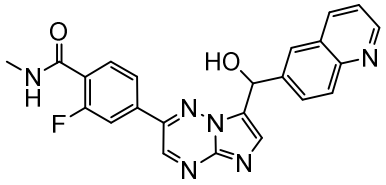


M6

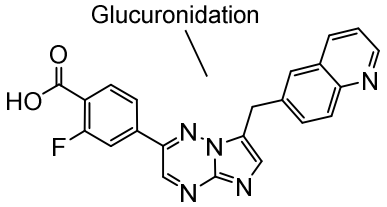
Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes	Study No. DMPK R1000705



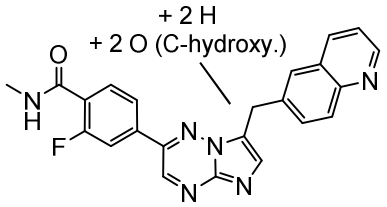
M7



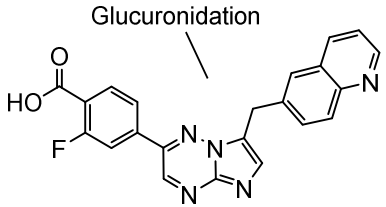
M8 (CMN290)



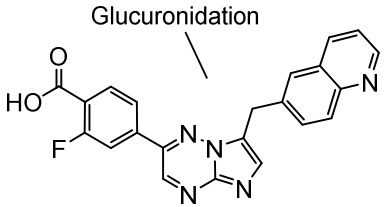
M9



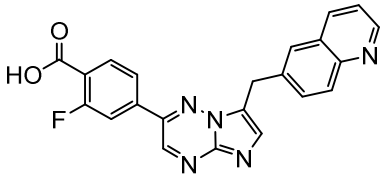
M10



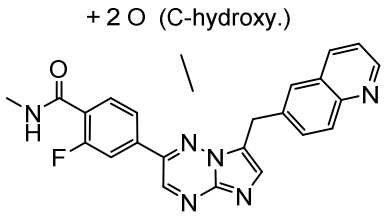
M11



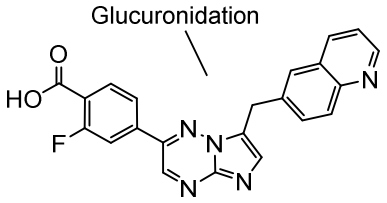
M12



M13 (CMC583)

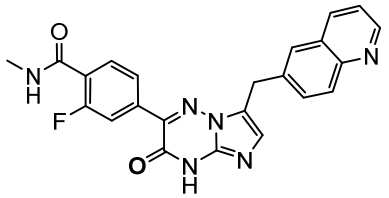


M14

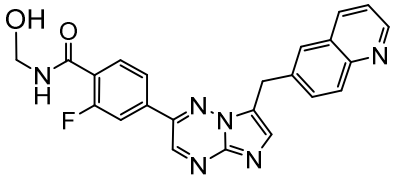


M15

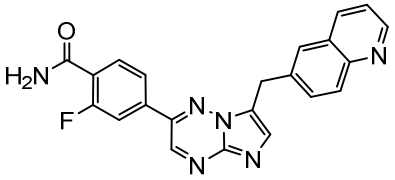
Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes	Study No. DMPK R1000705



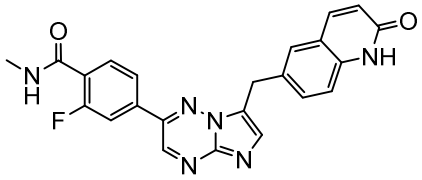
M16 (CMN288)



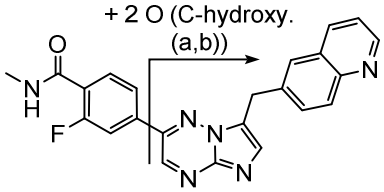
M17 (CNJ292)



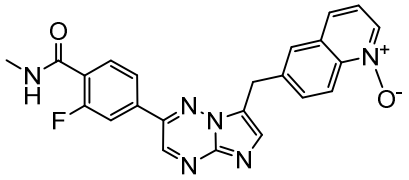
M18 (CNJ294)



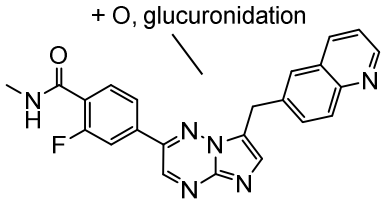
M19 (CJK530)



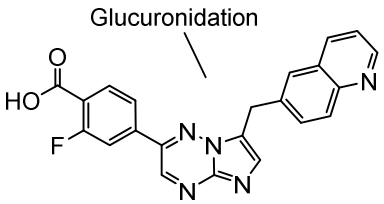
M20



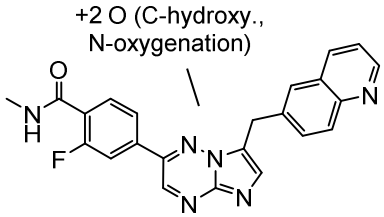
M21 (CJH800)



M22

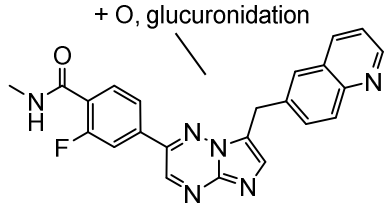


M23

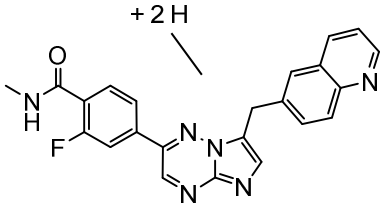


M24

Study title:	*In vitro* metabolism of [^{14}C]INC280 in mouse, rat, dog, monkey and human hepatocytes and in human liver microsomes	Study No. DMPK R1000705



M25



M26

a Metabolic reaction in imidazo-triazine moiety
b Metabolic reaction in quinoline moiety

C-hydroxy. hydroxylation on a carbon atom or further isomerization to lactam moiety

ND: not detected

Tr.: Traces of the metabolite were detected by MS.

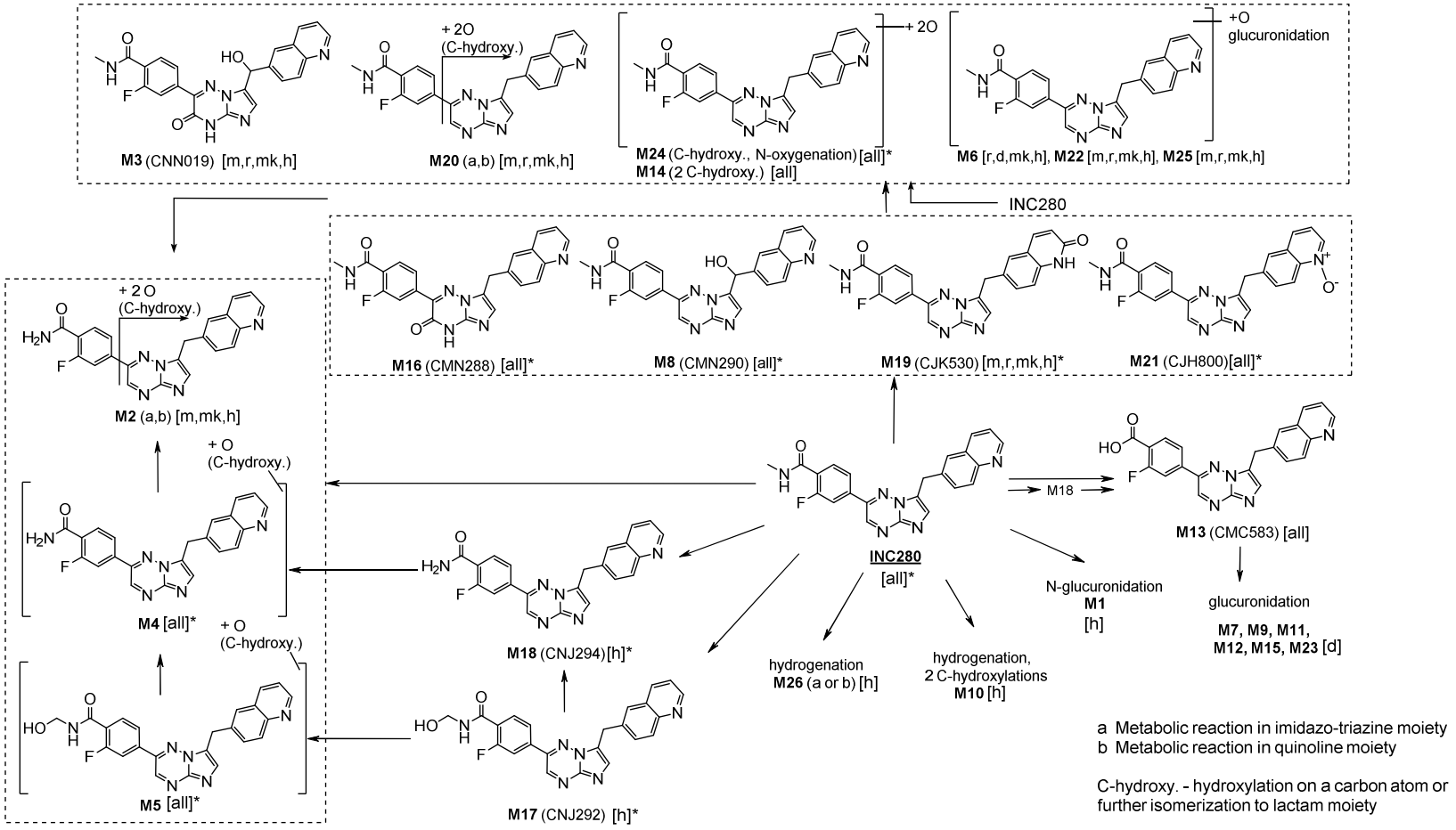
a) In case of human hepatocyte incubation M4 and M5 were separated with different chromatographic conditions. Otherwise the M4 and M5 were estimated from the MS abundance of the respective protonated molecule ions.

b) The abundances of co-eluting metabolites were estimated from the MS abundance of the protonated molecule or fragment ions.

c) In a control incubation with HepatoZYME™, M8 was detected in traces (1.7%, after 6 hours incubation time).

d) Sum of other radiolabeled components. None of them represented more than 1% in human and 3% in other species, of the total radioactivity.

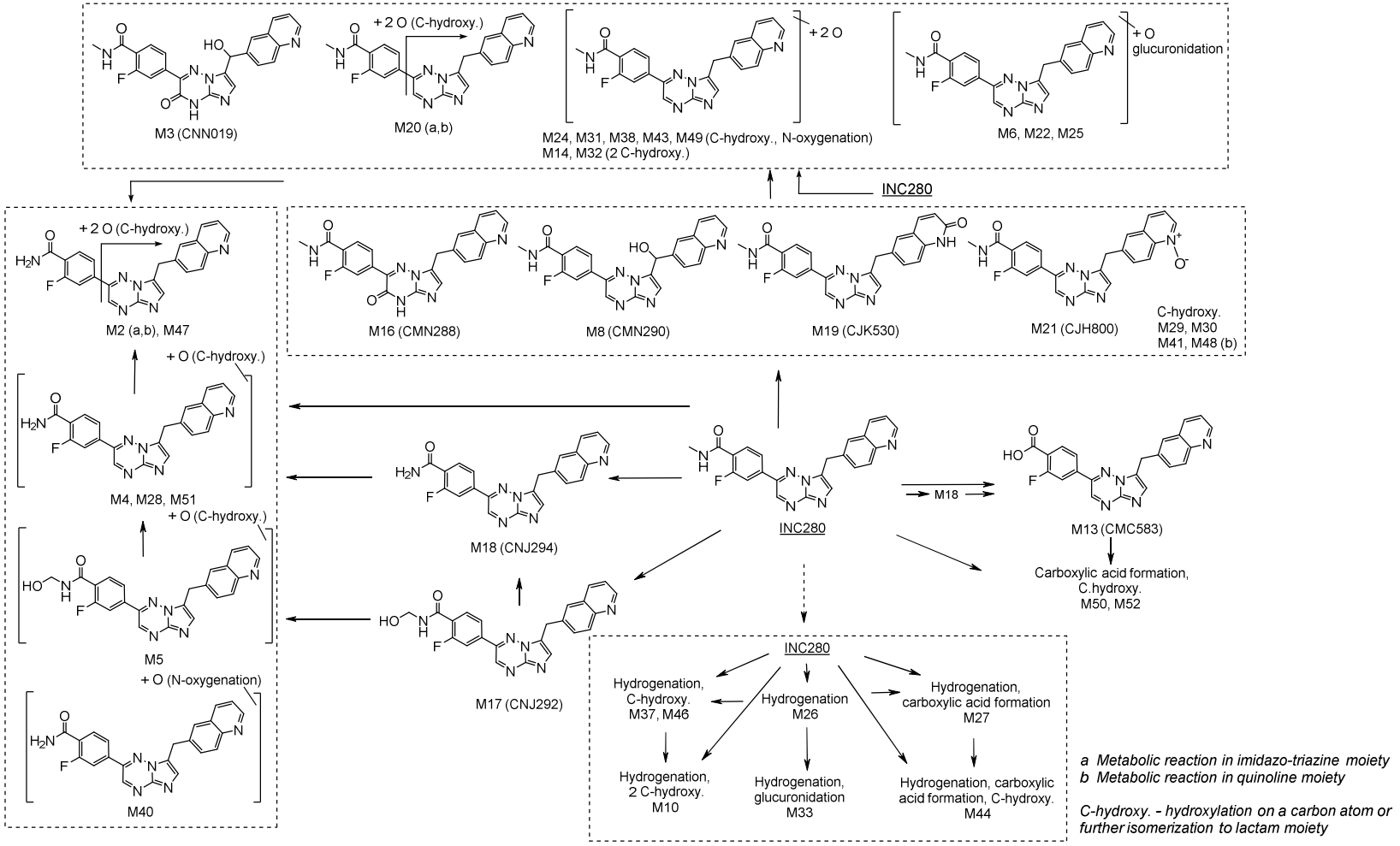
2.6.5.11A 薬物動態試験：推定代謝経路／*in vitro*（マウス，ラット，イヌ，サル及びヒト）



Source: 4.2.2.4-1-DMPK R1000705

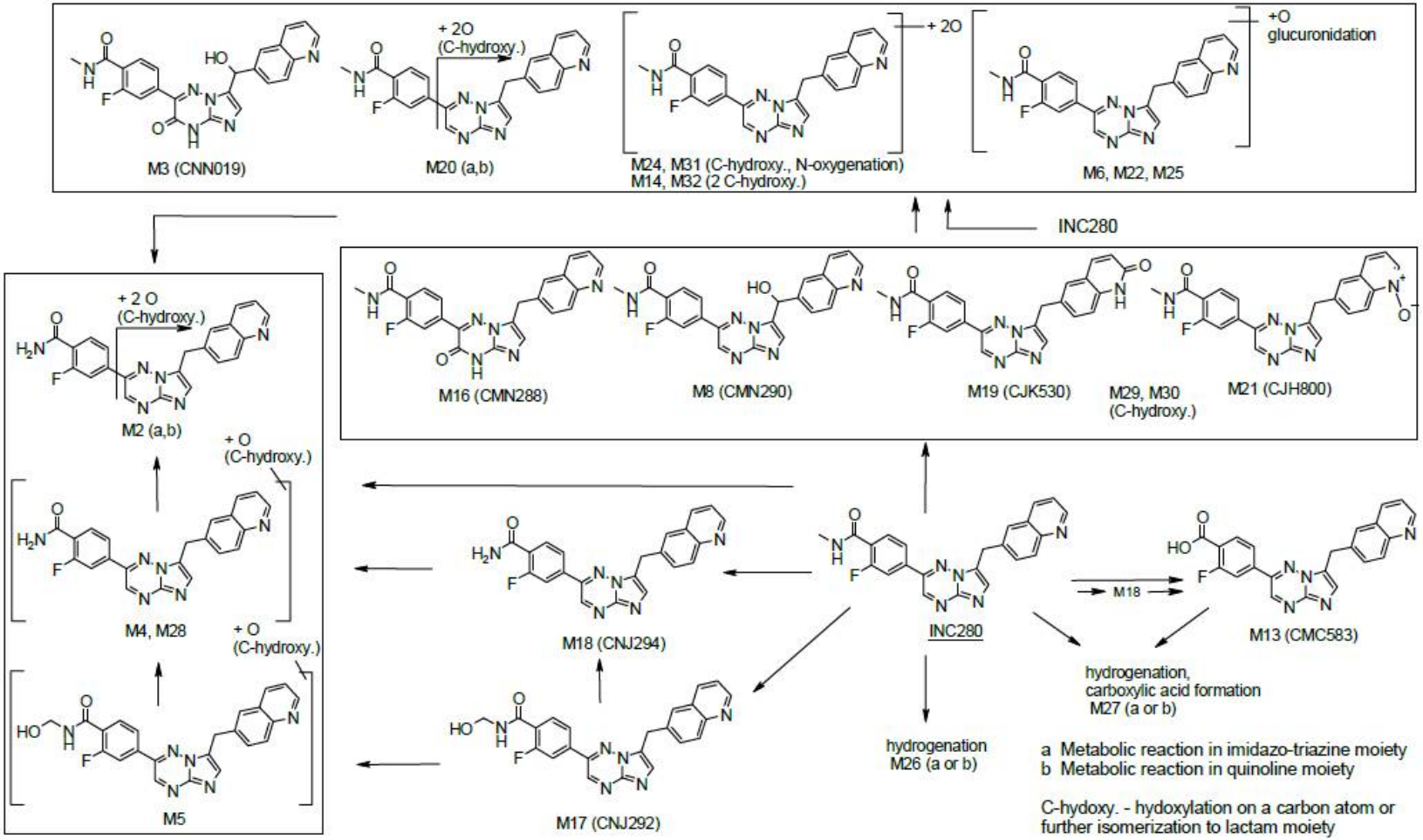
m: mouse, r: rat, d: dog, mk: monkey, h: human, all: mouse, rat, dog, monkey and human, *: human liver microsome

2.6.5.11B 薬物動態試験：推定代謝経路／*in vivo*（ラット，サル及びヒト）



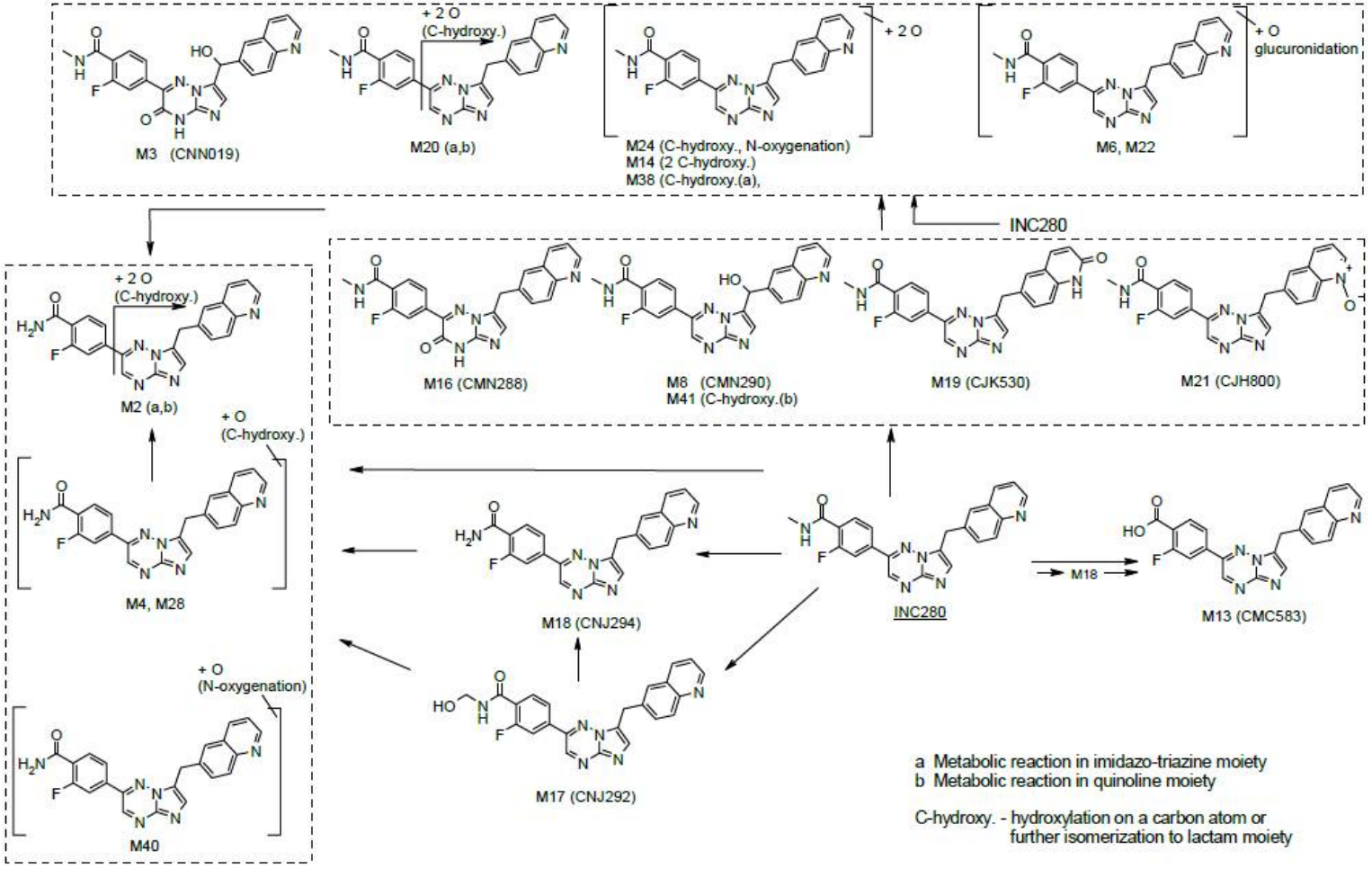
Source: 4.2.2.2-4-DMPK R1100027-01, 4.2.2.2-10-DMPK R1300820, 5.3.1.4-9-DMPK RINC280X2106d

2.6.5.11C　薬物動態試験：推定代謝経路／*in vivo*（ラット）



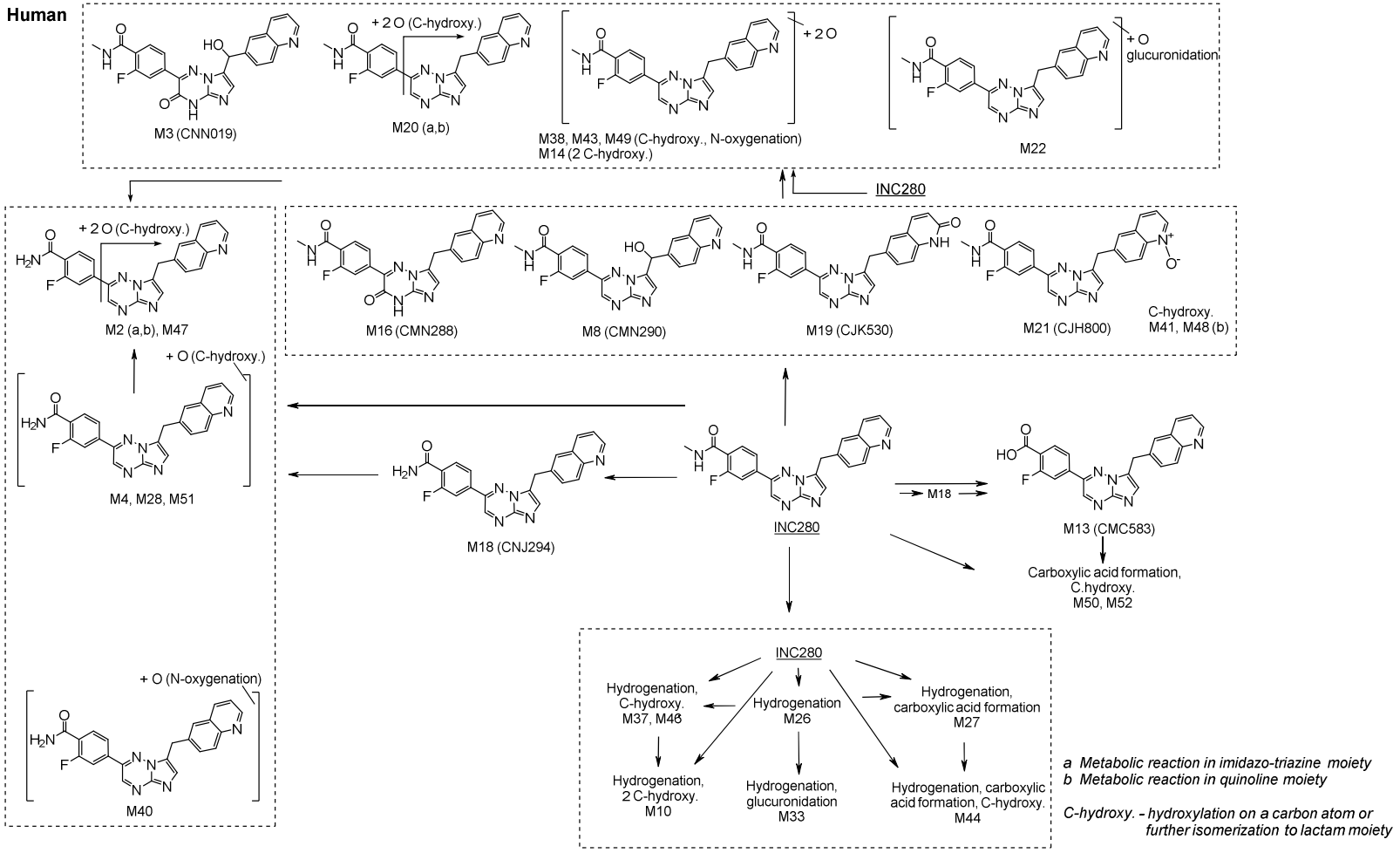
Source: 4.2.2.2-4-DMPK R1100027-01

2.6.5.11D 薬物動態試験：推定代謝経路／*in vivo*（サル）



Source: 4.2.2.2-10-DMPK R1300820

2.6.5.11E 薬物動態試験：推定代謝経路／*in vivo*（ヒト）



Source: 5.3.1.4-9-DMPK RINC280X2106d

2.6.5.12A 薬物動態試験：薬物代謝酵素の誘導／阻害

Study title:	Pregnane X receptor (PXR) activation by INCB028060				Study No. INCYTE-DMB-08.135.1
Location in CTD:	4.2.2.6-1				
GLP compliance:	Not required				
Test articles:	INC280 (synonym: INCB028060), (dihydrochloride, Lot 17)				
Test system:	Transfected HepG2 cells				
Analytical methods:	Measurement of luminiscence				
Results:	Human PXR mediated gene activation (CYP3A4 induction) by INC280 and rifampicin (positive control) versus DMSO vehicle control				
	Species		3 µM	10 µM	30 µM
	Human PXR	INC280	ND	1	ND
		rifampicin	10-18	20-25	23-29
	Rat PXR mediated gene activation (CYP3A4 induction) by INC280 and pregnenolone 16α-carbonitrile (PCN, positive control)versus DMSO vehicle control				
	Species		3 µM	10 µM	30 µM
	Rat PXR	INC280	ND	1	ND
		PCN	19-28	23-44	27-54
Conclusion:	PXR mediated human CYP3A4 induction: The hPXR reporter gene assay was not induced by 10 µM INC280, suggesting that the potential for INC280 to induce CYP3A4 in clinical studies is low. Rifampin (10 µM), a known CYP3A4 inducer, increased the PXR-mediated pathway of gene induction 20 to 25-fold versus vehicle control. PXR mediated rat CYP3A4 induction: The rPXR reporter gene assay was not inducted by 10 µM INC280. PCN (10 µM), a known rat CYP3A inducer, increased the rPXR-mediated pathway of gene induction 23 to 44-fold versus vehicle control.				

ND: not detected.

2.6.5.13A 薬物動態試験：単回投与後の排泄／*in vivo*（無処置ラット）

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride	Study No. DMPK R1100027-01
Location in CTD:	4.2.2.2-4	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 (dihydrochloride)	
Species / Strain:	Rat / Hanover Wistar (albino)	
Gender / No. of animals:	Male / 7 (3 for i.v. [Group 3], 4 for p.o. [Group 4])	
Feeding condition:	Water and food at libitum	
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 300 / 80% aqueous glucose solution (5%)	
	p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80	
Route of dosing:	i.v. bolus (into vena femoralis) / single dose	
	p.o. (gavage) / single dose	
Dose:	i.v.: 3 mg/kg (doses referring to the free base)	
	p.o.: 10 mg/kg (doses referring to the free base)	
Samples:	Urine and feces	
Sample times:	daily up to 168 h	
Analyte:	INC280	
Analytical methods:	Radioactivity: LSC	
	INC280: HPLC analysis including radioactivity detection (on- and off-line) (details in 4.2.2.2-5-DMPK R1100027a)	

Results: Excretion and recovery of total components

Component [a)]	Interval (h)	i.v., 3 mg/kg		p.o., 10 mg/kg	
		Urine (% of dose)	Feces (% of dose)	Urine (% of dose)	Feces (% of dose)
Radioactivity	0-24	5.52 ± 2.01	83.8 ± 3.63	7.56 ± 1.17	72.5 ± 9.54
Radioactivity	0-168	5.71 ± 2.00	88.6 ± 2.71	7.82 ± 1.14	86.4 ± 1.54
INC280	0-48	ND	8.52	ND	11.7
Total recovery (excreta, carcass and cage wash)	0-168	96.9 ± 1.77		95.5 ± 1.42	

Conclusion: After intravenous and oral dosing, total radiolabeled components were predominantly excreted via feces (86-88%) and only to a minor extent via urine (6-8%). Total recovery of radioactivity in the excreta, carcass and cage wash was with (96% [p.o.] and 97% [i.v.]) almost complete.

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride	Study No. DMPK R1100027-01
	Note: Excretion data from bile duct-cannulated rats (Group 5) are listed in 2.6.5.14 Excretion into Bile.	

ND: not detected

a) All data are expressed as mean ± SD

2.6.5.13B 薬物動態試験：単回投与後の排泄／*in vivo*（サル）

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280 Study No. DMPK R1300820
Location in CTD:	4.2.2.2-10
GLP compliance:	Not required
Test articles:	[^{14}C]INC280 (dihydrochloride)
Species / Strain:	Monkey / Cynomolgus
Gender / No. of animals:	Male / 5 (2 for i.v., 3 for p.o.)
Feeding condition:	Water *ad libitum*, food once daily (normal diet)
Vehicle / Formulation:	i.v.: 20% polyethylene glycol 200 / 80% aqueous glucose solution (5%) p.o.: aqueous solution containing 0.5% methylcellulose and 0.5% Tween 80
Route of dosing:	i.v. bolus (into saphenous vein) / single dose p.o. (gavage) / single dose
Dose:	i.v.: 3 mg/kg (doses referring to the free base) p.o.: 30 mg/kg (doses referring to the free base)
Samples:	Urine and feces
Sample times:	0-168 h with 24 h intervals for both routes of administration
Analyte:	INC280
Analytical methods:	Radioactivity: LSC INC280: LC-MS/MS

Results:

Excretion and recovery of total components

Component [a]	Interval (h)	i.v., 3 mg/kg		p.o., 30 mg/kg [b]	
		Urine (% of dose)	Feces (% of dose)	Urine (% of dose)	Feces (% of dose)
Radioactivity	0-24	4.47	31.7	7.28	41.5
Radioactivity	0-168	7.92	77.4	9.67	72.0
INC280	0-72	0.03	5.28	0.04	6.59
Total recovery (excreta and cage wash)	0-168	85.3		84.6	

Conclusion: After both i.v. and p.o. dosing of [^{14}C]INC280, the radioactivity was predominantly excreted through feces (72.0% - 77.4% of the dose).
Renal excretion of radioactivity was minor, which accounted for only 7.92% - 9.67% of the dose in monkeys. Majority of radioactivity (> 70%) was

Study title:	Absorption, metabolism and excretion of INC280 in the monkey following an intravenous (3 mg/kg) or oral dose (30 mg/kg) of [^{14}C]INC280	Study No. DMPK R1300820
	excreted by 72 h post-dose.	

a) All data are expressed as mean of n = 2.

b) Mean value of parameters was calculated using the data from two monkeys since one monkey in the oral group had emesis after the oral dosing.

2.6.5.14A 薬物動態試験：胆汁中排泄（カニューレ処置ラット）

Study title:	Absorption, distribution, metabolism, and excretion in male rats after single intravenous (3 mg/kg) and oral (10 mg/kg) administration of [^{14}C]INC280 dihydrochloride	Study No. DMPK R1100027-01
Location in CTD:	4.2.2.2-4	
GLP compliance:	Not required	
Test articles:	[^{14}C]INC280 (dihydrochloride, dihydrochloride salt tetra-hydrate)	
Species / Strain:	Rat / Hanover Wistar (albino); bile-duct cannulated	
Gender / No. of animals:	Male / 4 (i.v. [Group 5])	
Feeding condition:	Water and food at libitum	
Vehicle / Formulation:	20% polyethylene glycol 300 / 80% aqueous glucose solution (5%)	
Route of dosing:	i.v. bolus (into vena femoralis) / single dose	
Dose:	3 mg/kg (referring to free base)	
Samples:	Bile, urine and feces	
Sample times:	Bile: 0-8 h and 8-24 h	
	Urine and feces: daily up to 24 h	
Analyte:	INC280	
Analytical methods:	Radioactivity: LSC	
	INC280: HPLC analysis including radioactivity detection (on- and off-line) (details in 4.2.2.2-5-DMPK R1100027a)	

Results: Excretion and recovery of total components

Component [a]	Interval (h)	i.v., 3 mg/kg (actual dose: 3.50 ± 0.0403 mg/kg)		
		Urine (% of dose)	Feces (% of dose)	Bile (% of dose)
Radioactivity	0-24	12.1 ± 1.50	9.23 ± 5.24	66.3 ± 2.94
INC280	0-24	ND	2.30	ND
Total recovery (excreta, cage wash and carcass)	0-168		96.4 ± 1.91	

Conclusion: After intravenous administration of [^{14}C]INC280 dihydrochloride (3 mg/kg, referring to the free base) to bile duct-cannulated rats, 12.1 ± 1.50%, 9.23 ± 5.24%, and 66.3 ± 2.94% of the administered radioactivity was recovered within the collection period of 24h post-dose in urine, feces and bile, respectively. Based on these values, the main excretion route of total radiolabeled components was via bile, and only less than 10% of the dose was directly excreted into feces. No unchanged [^{14}C]INC280 was excreted in bile.

ND: not detected

a) All data are expressed as mean ± SD.

2.6.5.15 薬物動態試験：薬物相互作用

該当なし

2.6.5.16A 薬物動態試験：組織脈管容積（ラット）

Study title:	Assessment of tissue vascular volume by investigation of the [^{14}C]inulin distribution in rat after single intravenous (10 mg/kg) dosage	Study No. DMPK R0101302
Location in CTD:	4.2.2.7-1	
GLP compliance:	Not required	
Test articles:	[^{14}C]inulin ([^{14}C]-carboxyinulin)	
Species / Strain:	Rat / Hanover Wistar	
Gender / No. of animals:	Male / 6	
Feeding condition:	Fasted	
Vehicle / Formulation:	20 mg of [^{14}C]inulin (1.6 MBq or 45 µCi) were dissolved in 4 mL of saline solution 0.9%	
Route of dosing:	i.v. (2 mL/kg were injected into the surgically exposed femoral vein)	
Dose:	10 mg/kg	
Samples:	Blood, plasma, brain, spinal cord, liver, kidney, lung, muscle, white fat, skin, bone plus bone marrow, testes, spleen, adrenals, thymus and heart	
Sample times:	0.08 h and 1 h post-dose (n = 3 per sampling time)	
Analyte:	Total radioactivity measurement	
Analytical methods:	Radioactivity: LSC	

Results:

Comparison of residual blood volumes (in mL per g of tissue) obtained in study using [^{14}C]inulin (n = 3) [a)]

Tissue	Mean ± SD (%CV)	Range
Brain	0.061 ± 0.017 (28)	0.045-0.078
Spinal cord	0.107 ± 0.016 (15)	0.091-0.123
Liver	0.292 ± 0.013 (4)	0.281-0.307
Kidney	NA	NA
Lung	0.822 ± 0.117 (14)	0.689-0.910
Muscle	0.311 ± 0.043 (14)	0.264-0.349
White fat	0.188 ± 0.039 (21)	0.163-0.233
Skin	0.880 ± 0.586 (67)	0.382-1.525
Heart	0.535 ± 0.163 (30)	0.432-0.723
Bone [b)]	0.249 ± 0.027 (11)	0.221-0.274
Testes	0.182 ± 0.041 (22)	0.148-0.227

Study title:	Assessment of tissue vascular volume by investigation of the [^{14}C]inulin distribution in rat after single intravenous (10 mg/kg) dosage		Study No. DMPK R0101302
	Spleen	0.300 ± 0.040 (13)	0.276-0.346
	Adrenals	0.627 ± 0.136 (22)	0.474-0.736
	Thymus	0.247 ± 0.043 (17)	0.221-0.297
Conclusion:	The tissue distribution of inulin determined after 5 min circulation period provided a fairly good estimation of the intravascular volume with minimal interstitial diffusion. Therefore this tracer is a suitable model for assessing the minimal distribution volume for small molecules unbound to plasma proteins. The maximum determined vascular volume of brain amounted up to 8%.		

NA: not applicable as inulin is excreted through the kidney

a) The residual blood volumes (mL/g) were calculated by dividing the tissue [^{14}C]inulin concentration (ng-eq/g) by the blood [^{14}C]inulin concentration (ng-eq/mL), both obtained at 0.08 h after intravenous bolus injection of 20 mg/kg [^{14}C]inulin to rats.

b) Bone samples included bone plus bone marrow.

2.6.5.16B 薬物動態試験：脳脊髄液移行（ラット）

Study title:	INCB028060 cerebrospinal fluid (CSF) concentrations in rats from a 28-day oral toxicity and toxicokinetic Study (Safety Assessment Protocol T08-04-11)	Study No. INCYTE-DMB-09.01.1
Location in CTD:	4.2.2.7-2	
GLP compliance:	Not required	
Test articles:	INC280 (synonym: INCB028060) (dihydrochloride)	
Species / Strain:	Rat / Spraque Dawley	
Gender / No. of animals:	Male / 15, Female / 14	
Route of dosing:	p.o.	
Dose:	Male: 20, 60, or 120 mg/kg for 28 days Female: 10, 30, or 60 mg/kg for 28 days	
Samples:	CSF	
Sample times:	4 and 24 h post-dose on Day 27	
Analyte:	INC280	
Analytical methods:	LC-MS/MS (details in 4.2.2.1-4-INCYTE-DMB-08.119.1)	

Results: CSF / unbound plasma concentrations (%) of INC280 in rats on Day 27

Gender	Dose (mg/kg/day)	Time (h)	CSF / unbound plasma [a)]
M	20	4	31
M	20	4	32
M	20	4	38
M	20	24	115
M	20	24	58
M	20	24	40
M	60	4	22
M	60	4	35
M	60	4	23
M	60	24	57
M	60	24	36
M	60	24	19

Study title:	INCB028060 cerebrospinal fluid (CSF) concentrations in rats from a 28-day oral toxicity and toxicokinetic Study (Safety Assessment Protocol T08-04-11)			Study No. INCYTE-DMB-09.01.1
	M	120	4	26
	M	120	4	28
	M	120	24	33
	F	10	4	20
	F	10	4	22
	F	10	4	17
	F	10	24	NC
	F	10	24	NC
	F	30	4	26
	F	30	4	19
	F	30	4	18
	F	30	24	25
	F	30	24	33
	F	30	24	36
	F	60	4	29
	F	60	4	43
	F	60	24	25
				Mean ± SD: 33.5 ± 19
Conclusion:	The cerebrospinal fluid (CSF) concentrations of INC280 in rats at 4 and 24 h post-dose were determined on the final day of a 28-Day oral toxicity and toxicokinetic study (Safety Assessment Protocol T08-04-11, 4.2.3.2-5-INCYTE-DMB-08.102.1). The mean cerebrospinal fluid concentration across all dose groups, genders, and time points of INC280 was 33.5 ± 19% of the corresponding estimated free plasma concentration. These results correlate well with those from the rat steady-state infusion study (36.2 ± 6.0%, Table 2.6.5.5.A-INCYTE DMB-08.129.1) and corroborate the conclusion that INC280 can cross the blood-brain barrier in rats.			

NC: not calculated

a) Plasma concentrations and details of determination thereof are reported in 4.2.3.2-5-INCYTE-DMB-08.102.1. Unbound plasma concentrations were estimated based on *ex vivo* plasma free fraction of 5.6% unbound, as reported in Table 2.6.5.6A-INCYTE-DMB-08.122.1.

2.6.5.16C 薬物動態試験：脳脊髄液移行（サル）

Study title:	INCB028060 cerebrospinal Fluid (CSF) concentrations in Cynomolgus monkeys from a 28-day oral toxicity and toxicokinetic Study (Safety Assessment Protocol T08-01-08)	Study No. INCYTE-DMB-09.02.1
Location in CTD:	4.2.2.7-3	
GLP compliance:	Not required	
Test articles:	INC280 (synonym: INCB028060) (dihydrochloride)	
Species / Strain:	Monkey / Cynomolgus	
Gender / No. of animals:	Male / 16, Female / 16	
Route of dosing:	p.o.	
Dose:	0, 30, 75, or 150 mg/kg for 28 days	
Samples:	CSF	
Sample times:	approximately 23 h following Day 28 administration	
Analyte:	INC280	
Analytical methods:	LC-MS/MS (details in 4.2.2.1-8-INCYTE-DMB-08.120.1)	

Results: CSF/ unbound plasma concentrations (%) of INC280 in Cynomolgus Monkeys on Day 28

Gender	Dose (mg/kg/day)	CSF / unbound plasma [a)]
M	0	NC
M	0	NC
M	0	NC
M	0	NC
M	30	60.1
M	30	85.6
M	30	57.2
M	30	220
M	75	145
M	75	40.6
M	75	157
M	75	50.9
M	150	58.8

Study title:	INCB028060 cerebrospinal Fluid (CSF) concentrations in Cynomolgus monkeys from a 28-day oral toxicity and toxicokinetic Study (Safety Assessment Protocol T08-01-08)		Study No. INCYTE-DMB-09.02.1
	M	150	2560 [b)]
	M	150	63.8
	F	150	135
	F	0	NC
	F	0	NC
	F	0	NC
	F	0	NC
	F	30	101
	F	30	55.8
	F	30	121
	F	30	187
	F	75	47.4
	F	75	16.5
	F	75	57.0
	F	75	92.9
	F	150	136
	F	150	19.7
	F	150	85.4
	F	150	73.2
			Mean ± SD: 89.8 ± 53
Conclusion:	Concentrations of INC280 in CSF in Cynomolgus monkeys at 23 h post-dose were determined on Day 28 of a 28-day oral toxicity and toxicokinetic study (Safety Assessment Protocol T08-01-08); these data and the corresponding (24 h) plasma concentrations (reported in 4.2.3.2-8-INCYTE-DMB-08.103.1) are summarized in the table above. The mean cerebrospinal fluid concentration across all genders and dose groups of INCB028060 was 89.8 ± 53% of the corresponding estimated free plasma concentration. These results indicate that INC280 can cross the blood brain barrier in Cynomolgus monkeys.		

NC: not calculated

a) Plasma concentrations and details of determination thereof previously reported in 4.2.3.2-8-INCYTE-DMB-08.103.1, unbound plasma concentrations were estimated based on *ex vivo* plasma free fraction of 3.4% unbound, as reported in Table 2.6.5.6A-INCYTE-DMB-08.122.1.

b) Value excluded from mean calculation