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用語及び略号一覧

略号	英語	日本語
A/G	albumin/globulin	アルギニン／グロブリン比
ALP	alkaline phosphatase	アルカリホスファターゼ
ALT	alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
AUC	area under the plasma concentration-time curve	血漿中濃度時間曲線下面積
AUC(0-24h)	AUC from time 0 to 24 hours	投与後 0 時間から 24 時間までの AUC
CHO	Chinese hamster ovary	チャイニーズハムスター卵巣
Cmax	maximum plasma concentration	最高血漿中濃度
FDA	United States Food and Drug Administration	米国食品医薬品局
GALT	gut-associated lymphoid tissue	腸管関連リンパ組織
GGT	gamma glutamyl transferase	ガンマグルタミルトランスフェラーゼ
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
HCT	Hematocrit	ヘマトクリット
HGB	hemoglobin	ヘモグロビン
IC50	half maximal inhibitory concentration	50%阻害濃度
ICH	International Council for Harmonisation	医薬品規制調和国際会議
JAK2	Janus Kinase 2	ヤヌスキナーゼ 2
MNU	N-methyl-N-nitrosourea	N−メチル−N−ニトロソ尿素
NA	not applicable	該当せず
NOEL	no effect level	無作用量
NOAEL	no observed adverse effect level	無毒性量
PDE	permissible daily exposure	許容 1 日曝露量
PIF	photo irritation factor	光刺激係数
PO	oral	経口投与
RBC	red blood cells	赤血球
Tmax	time to Cmax	最高濃度到達時間
TK	toxicokinetics	トキシコキネティクス
TTC	threshold of toxicological concern	毒性学的懸念の閾値
UVA	ultraviolet A	紫外線 A
WBC	white blood cells	白血球

1 まとめ

フェドラチニブ（別名 SAR302503 又は TG101348）の毒性について、単回投与毒性試験（ラット及びイヌ）、反復投与毒性試験（マウスで最長 1 ヵ月間、ラットで最長 6 ヵ月間、イヌで最長 9 ヵ月間）、in vitro 及び in vivo 遺伝毒性試験、受胎能試験（ラット）、胚・胎児発生毒性試験（ラット及びウサギ）、出生前及び出生後の発生並びに母体の機能に関する試験（ラット）、がん原性試験（トランスジェニックマウス 6 ヵ月間）、in vitro 光毒性試験のほか、遺伝毒性不純物の安全性評価を実施した （Table 1-1）。

本概要では、すべての試験のフェドラチニブの用量をフリー体として示す。動物を用いた試験の投与経路は、ヒトへの臨床投与経路である経口投与を選択し、媒体には特記のない限り 0.5%メチルセルロース溶液を用いた。すべての重要な毒性試験は、非臨床試験に関する米国食品医薬品局（FDA）の医薬品の安全性に関する非臨床試験の実施の基準（GLP）の規制要件（21 CFR Part 58）を適用して実施した。

Table 1-1: 毒性試験プログラム

Study Type and Duration	Route of Administration	Species / Strain or Breed	Compound Administered
Single-dose toxicity / 10-day repeat dose	PO	Rat / Crl:CD(SD); Dog / Beagle	Fedratinib
Repeat-dose toxicity			
up to 14 days	PO	Mouse / BALB/c; Rat / Sprague Dawley	Fedratinib
1 month	PO	Mouse / Wild type Tg(HRAS)2Jic; Rat / Crl:CD (SD); Dog / Beagle	Fedratinib
6 months	PO	Rat / Crl:CD (SD)	Fedratinib
9 months	PO	Dog / Beagle	Fedratinib
Genotoxicity			
Ames assay	in vitro	*S. typhimurium* / TA98, TA100, TA1535 and TA1537; *E. coli* / WP2 *uvrA*	Fedratinib and *不純物A
Chromosomal aberration assay	in vitro	CHO cells	Fedratinib
Micronucleus test	PO	Rat / Sprague-Dawley	Fedratinib
Carcinogenicity			
6-month	PO	Mouse / Hemizygous Tg(HRAS)2Jic	Fedratinib
Reproductive and Developmental toxicity			
Fertility	PO	Rat / Crl:CD(SD)	Fedratinib
Range-finding embryo-fetal toxicity	PO	Rat / CD[Crl:CD(SD)]; Rabbit / New Zealand White	Fedratinib

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Table 1-1: 毒性試験プログラム

Study Type and Duration	Route of Administration	Species / Strain or Breed	Compound Administered
Definitive embryo-fetal toxicity	PO	Rat / CD[Crl:CD(SD)]; Rabbit / New Zealand White	Fedratinib
Pre- and post-natal development	PO	Rat / Crl:CD(SD)	Fedratinib
Impurity Qualification			
1 month	PO	Rat / Crl:CD(SD)	Fedratinib + *不純物A
Phototoxicity	in vitro	3T3 cells	Fedratinib
Impurity Studies			
Ames assay and chromosomal aberration assay	in vitro	*S. typhimurium* / TA98, TA100, TA1535, TA1537, and TA102; HPBL cells	Indentified impurities

3T3 = BALB/c mouse fibroblasts; HPBL = human peripheral blood lymphocytes; *不純物A = impurity of fedratinib; *不純物A is a [redacted] also known as [redacted].

マウスにおける主な標的器官は、骨髄、リンパ系器官、腎臓、胃、雌性生殖器、横隔膜筋及び膀胱であった。

ラットにおける主な標的器官は骨髄及び肝臓（胆管）であった。その他、リンパ系組織、肺、心臓、前胃及び骨格筋にも影響が認められたほか、肝細胞肥大も認められた。

イヌにおける主な標的器官は骨髄及び肝臓（主に胆管）であった。リンパ系組織、胆嚢及び消化管への影響も認められた。致死量で認められた肺炎・膿瘍は、骨髄及びリンパ系器官の変化に伴う免疫系への影響による二次的なものと考えられた。

反復投与毒性試験で得られた最高血漿中濃度（Cmax）及び血漿中濃度時間曲線下面積（AUC）は特記すべき毒性所見と関連しており、臨床試験において予定臨床推奨用量 400 mg を投与した患者の血漿中曝露量よりも低かったことから、ヒトはフェドラチニブの毒性に対する感受性が非臨床動物種よりも低いことが示唆される。

フェドラチニブの遺伝毒性について、細菌を用いた in vitro 復帰突然変異（Ames）試験、チャイニーズハムスター卵巣（CHO）細胞を用いた in vitro 染色体異常試験及びラットを用いた in vivo 小核試験により評価した結果、いずれも陰性であった。

トランスジェニックマウスを用いた 6 ヵ月間がん原性試験では、フェドラチニブ投与に起因すると考えられる腫瘍発生は認められなかった。

生殖毒性に関しては、受胎能及び雌雄ラットの生殖能に影響は認められなかった。胚・胎児発生に関する試験の結果、ラットでは胚・胎児毒性が認められたが、ウサギでは認められなかった。ラットを用いた出生前及び出生後の発生並びに母体の機能に関する試験では、次世代の発育分化及び行

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動並びに、交配、生殖能、受胎能及び帝王切開所見にフェドラチニブ投与に関連した影響は認められなかった。

3T3 細胞を用いた in vitro 試験において、フェドラチニブは光毒性を示さなかった。

2 単回投与毒性試験

ラット及びイヌを用いた単回投与及び 10 日間反復投与試験を実施した（試験番号 TX-[redacted]-101348-061 及び TX-[redacted]-101348-062）。

2.1 ラットを用いた試験

単回投与では、ラット（1 群雌雄各 3 匹）にフェドラチニブを 200、400、600 及び 1000 mg/kg の用量（投与容量 10 mL/kg）で単回経口投与した。反復投与では、ラット（1 群雌雄各 5 匹）にフェドラチニブを 100 及び 125 mg/kg の用量（投与容量 5 mL/kg）で 10 日間反復投与した（試験番号 TX-[redacted]-101348-061）。本試験ではトキシコキネティクス（TK）を評価しなかった。

単回投与の評価項目は、生死、一般状態、体重及び Day 4 の剖検とした。反復投与の評価項目は、生死、一般状態、体重、体重増加量、摂餌量、剖検、器官重量及び病理組織学的検査とし、Day 11 に剖検した。フェドラチニブに関連する主な影響を Table 2.1-1 に要約する。

Table 2.1-1: ラット単回及び 10 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
Single-Dose	
200	Clinical signs: Gasping (1 female)
400	Mortality: 1 female euthanized moribund on Day 2; gross necropsy (lung discoloration) suggested possible aspiration of fedratinib Clinical signs: Gasping and abnormally colored urine (1 female) Body weight: ↓ Body weight gain
600	Clinical signs: Diarrhea, soft stools, mucoid stools, and few feces Body weight and/or weight gain: ↓ (−9% to −20% in males and females) Gross necropsy: Stomach foci, and discoloration of the stomach and mesenteric lymph node
1000	Clinical signs: Diarrhea, soft stools, mucoid stools, and few feces Body weight and/or weight gain: ↓ (−9% to −14% in males and females) Gross necropsy: Abnormal content of the GI tract, distended stomach, stomach foci, and discoloration of the liver and mesenteric lymph node
Repeat-Dose	
100	Body weight: ↓ (≤ 2%) Gross necropsy: ↓ thymus size in females

Table 2.1-1: ラット単回及び 10 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
125	Clinical signs: Soft stools, diarrhea, and few feces Body weight and food consumption: ↓ Body weight (≤ 8% in males and females; Day 1 to Day 10) and ↓ Food consumption (−7% to −32% compared to values at 100 mg/kg) Gross necropsy: Stomach foci and decreased thymus size

GI = gastrointestinal; ↓ = decreased.
Source: Study TX-[redacted]-101348-061

2.2 イヌを用いた試験

ビーグル犬（雌雄各 1 匹）にフェドラチニブを 200、100、150、300 及び 100 mg/kg の用量（投与容量 5 又は 10 mL/kg）で、72 時間間隔で順次強制経口投与した。反復投与試験では、ビーグル犬（1 群雌雄各 1 匹）にフェドラチニブを 50 及び 75 mg/kg の用量（投与容量 5 mL/kg）で 10 日間反復経口投与した（試験番号 TX-[redacted]-101348-062）。

単回投与の評価項目は、生死、一般状態、体重及び剖検とした。全例が Day 21 の計画剖検時まで生存した。反復投与の評価項目は、生死、一般状態、体重、体重増加量、摂餌量、剖検及び器官重量とした。75 mg/kg 群の 2 例を状態悪化により Day 8（雄）及び Day 9（雌）に早期剖検した。50 mg/kg 群は全例が Day 11 の計画剖検時まで生存した。フェドラチニブに関連する主な影響を Table 2.2-1 に要約する。

反復投与試験の 75 mg/kg では死亡例が発生したため TK を算出できなかったが、早期剖検日（Day 9）の雌の血漿中トラフ濃度は 3900 ng/mL であった。50 mg/kg での 10 日間投与後の投与後 0 時間から 24 時間までの AUC（AUC(0-24h)）及び Cmax は、雄でそれぞれ 27700 ng•h/mL 及び 3800 ng/mL、雌でそれぞれ 55400 ng•h/mL 及び 5400 ng/mL であった。血漿中トラフ濃度は、雄で 1900 ng/mL、雌で 1200 ng/mL であった。

Table 2.2-1: イヌ単回及び 10 日間反復投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
Single-Dose Phase	
≥ 100	Clinical signs: Vomiting, diarrhea, mucoid and soft stools
Repeat-Dose Phase	
50	Clinical signs: Vomiting, diarrhea Body weight and food consumption: ↓ Body weight (−8% to −14% compared to Day 1 values) and ↓ Food consumption Gross necropsy: Gallbladder and ileal discoloration and jejunal abnormal contents

Table 2.2-1: イヌ単回及び 10 日間反復投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
75	Mortality: 2 dogs euthanized moribund on Days 8 (male) or 9 (female) Clinical signs: Vomiting, diarrhea, decreased activity, wobbly gait, abnormal posturing, and breathing abnormalities, head tilt, increased activity, vocalization, and impaired mobility Body weight and food consumption: ↓ Body weight (−5% to −9% compared to Day 1 values) and ↓ Food consumption Gross necropsy: Distension, foci, and abnormal content of the gallbladder; discoloration of the mediastinal and mesenteric lymph nodes; stomach foci and abnormal stomach content; and abnormal content in the small and large intestine

↓ = decreased.
Source: Study TX-[redacted]-101348-062

3 反復投与毒性試験

マウス 29 日間投与試験、ラット及びイヌ 28 日間投与試験、ラット 6 ヵ月間投与試験、イヌ 9 ヵ月間投与試験の 5 試験を GLP 適合で実施した。また、マウス及びラットの最長 14 日間の試験を GLP 非適合（非 GLP）で実施した。

3.1 重要な試験以外の試験

フェドラチニブの初期の毒性評価として、げっ歯類を用いた経口投与試験（試験番号 PH-[redacted]-101348-023）及び TK 試験（試験番号 PDM-[redacted]-101348-021）を非 GLP で実施した。

3.1.1 マウス 10 日間投与毒性試験

雄性 BALB/c マウス（各群 5 匹）にフェドラチニブを 100、200 及び 400 mg/kg の用量（投与容量 0.2 mL）で 1 日 2 回（200、400 及び 800 mg/kg/day）、10 日間反復経口投与した。対照群には媒体（50%プロピレングリコール及び 10% Tween 80）のみを投与した。評価項目は、生死、一般状態、体重、血液学的検査（ヘマトクリット及び骨髄塗沫標本検査）、剖検及び病理組織学的検査とした。TK は測定しなかった。

200 mg/kg の忍容性は良好であった。400 及び 800 mg/kg で死亡例が認められ、その死因は特定できなかった。

3.1.2 ラット 14 日間投与毒性試験

雄性 Sprague Dawley ラット（各群 6 匹）にフェドラチニブを 35、70 及び 140 mg/kg の用量（投与容量 1.0 mL）で 1 日 1 回 14 日間経口投与した。対照群には媒体（0.5%メチルセルロース及び 0.05% Tween 80）のみを投与した。評価項目はマウス試験と同様としたが、ヘマトクリットは測定せず、TK 解析用の血液試料を Day 1 及び Day 14 に採取した。

35 及び 70 mg/kg の忍容性は良好であった。140 mg/kg では大部分が死亡した。本用量群の病理組織学的検査では、骨髄の細胞数減少、脾臓白脾髄の細胞減少が認められた。

単回投与後（Day 1）の AUC は用量に比例して増加したが、Cmax は用量比を下回った。13 日間投与後の定常状態での血漿中トラフ濃度は用量線形性を示した。35、70 及び 140 mg/kg での血漿中トラフ濃度は、それぞれ 206、708 及び 1397 ng/mL であった。最終投与後（Day 14）の AUC は、35 及び 70 mg/kg で用量に比例して増加した。Day 14 の曝露量は、Day 1 と比較して Cmax で 3 倍、AUC で 3～5 倍増加した。TK 測定値を Table 3.1.2-1 に要約する。

Table 3.1.2-1: ラット 14 日間投与試験におけるトキシコキネティクス値

Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
	Day 1	Day 14	Day 1	Day 14
35	394	1280	3716	10600
70	515	1460	5122	27600
140	586	NA[a]	9848	NA[a]

[a] Due to animal mortality complete plasma toxicokinetic parameters were not determined on Day 14 at 140 mg/kg.
Source: Study PDM-[redacted]-101348-021

3.2 ラットを用いた試験

3.2.1 ラット 28 日間投与毒性試験

Sprague-Dawley ラット（1 群雌雄各 10 匹）にフェドラチニブを 0（媒体対照）、5、30 及び 80 mg/kg の用量（投与容量 5 mL/kg）で 1 日 1 回 28 日間強制経口投与した。対照群及び 80 mg/kg 群には回復群（雌雄各 5 匹）を追加し、投与期間終了後に 14 日間休薬した（試験番号 TX-[redacted]-101348-074F）。また、TK 測定用サテライト群（対照群雌雄各 6 匹、フェドラチニブ投与群 1 群雌雄各 9 匹）を設け、同様に 28 日間投与して Day 1 及び 28 に採血した。

評価項目は、生死、一般状態、体重、摂餌量、眼科学的検査、臨床検査（血液学的検査、凝固検査、血液生化学的検査、尿検査）、TK 測定、剖検、器官重量及び病理組織学的検査とした。

眼科学的検査、血液学的検査及び尿検査ではフェドラチニブに関連した有害所見は認められなかった。

フェドラチニブに関連する特記すべき所見を Table 3.2.1-1 に示し、Day 1 及び 28 の TK 測定値を Table 3.2.1-2 に要約する。

Table 3.2.1-1: ラット 28 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
5	Body weight: ↓ Body weight (males) Clinical pathology: ↑ Phosphorus
30	Body weight: ↓ Body weight (−1 to −7%) Clinical pathology: ↑ ALT , ↑ Bilirubin (females), ↑ Phosphorus Organ weights: ↓ Salivary gland, spleen, and thymus (females) Histopathology: Changes in the bone marrow, thymus, lymph nodes, spleen, and lungs similar to those observed at 80 mg/kg; but less severe and lower incidence
80	Clinical signs: Signs of hypothermia, salivation, and salivation prior to dosing in a small number of rats Body weight: ↓ Body weight (−1 to −13%) Clinical pathology: ↑ AST, ALT; ↑ ALP, GGT, and bilirubin (females), ↑ Phosphorus Gross pathology: Small thymus Organ weight: ↓ Salivary gland, spleen, thymus, prostate, and seminal vesicles, and, in females, ↑ lung Histopathology: Bone marrow – hypoplasia, Liver – bile duct epithelial hypertrophy; and, in females, bile duct epithelial necrosis with fibrosis and mononuclear cell inflammation, Lymphoid tissues – thymus (lymphoid atrophy), spleen (lymphoid atrophy), mesenteric lymph nodes (lymphoid atrophy and histiocytic infiltrates), Lungs – histiocytic infiltration, Heart – minimal-mild cardiomyopathy (females) Recovery: Most changes in the high-dose group resolved during recovery. The following changes were present at the end of the recovery period: ↑ Body weight gain; extramedullary hematopoiesis in the spleen (females) considered a regenerative response associated with recovery of the bone marrow; histiocytic infiltrates in the lung (females)

↑ = increased; ↓ = decreased.
Source: Study TX-[redacted]-101348-074F

Table 3.2.1-2: ラット 28 日間投与試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
		Day 1	Day 28	Day 1	Day 28
Male	5	15.6	19.3	127	145
	30	153	182	1450	1870
	80	257	509	2830	7250
Female	5	23.4	20.7	177	155
	30	376	342	3670	3840
	80	618	691	7550	10400

Source: Study TX-[redacted]-101348-074F

Day 1 の Cmax 及び AUC は用量に依存して増加し、5 及び 30 mg/kg では概して用量比を上回り、30 及び 80 mg/kg では用量比を下回った。雌雄で蓄積が認められ、5、30 及び 80 mg/kg の各用量における Day 28 と Day 1 の AUC 比は雄でそれぞれ 1.14、1.29 及び 2.56、雌でそれぞれ 0.88、1.05 及び 1.38 であった。曝露量はいずれも雌の方が雄より一貫して高かった。

以上より、フェドラチニブを 28 日間反復投与したラットにおける標的器官は骨髄、肝臓（胆管）、胸腺、脾臓、腸間膜リンパ節、肺及び心臓と考えられ、無毒性量（NOAEL）は決定できなかった。

3.2.2 ラット 6 ヵ月間投与毒性試験

Sprague-Dawley ラット（1 群雌雄各 30 匹）にフェドラチニブを 0（媒体対照）、3、10 及び 30 mg/kg の用量（投与容量 3 mL/kg）で 1 日 1 回、90 日間（3 ヵ月間投与後に中間剖検）又は 182 日間（6 ヵ月間）強制経口投与した。3 ヵ月間投与後の中間剖検時に 1 群雌雄各 10 匹を剖検し、残りの 1 群雌雄各 20 匹を 6 ヵ月間の投与期間終了後に剖検した（試験番号 TX-[redacted]-101348-044）。回復期間は設定しなかった。

評価項目は、生死、一般状態、体重、摂餌量、眼科学的検査、臨床検査（血液学的検査、凝固検査、血液生化学的検査、尿検査）、TK、剖検、器官重量及び病理組織学的検査とした。

フェドラチニブに関連した死亡例はみられず、一般状態並びに眼科学的検査、血液凝固検査、尿検査及び剖検所見にフェドラチニブに関連した有害所見は認められなかった。試験期間中に 5 例が状態悪化により死亡発見又は早期剖検された。これらのうち、対照群の雌 1 例は 111 日目に死亡発見されたが、死因は特定されなかった。10 mg/kg 群の雄 1 例は誤投与による状態悪化のため Day 106 に早期剖検した。他の 3 例の早期死亡は 30 mg/kg 群にみられ、雌 1 例は誤投与による状態悪化により Day 40 に早期剖検した。雄 1 例は Day 66 に死亡発見され、死因は不明であったがフェドラチニブとの関連性はないと判断された。さらに雌 1 例は Day 137 に死亡発見され、誤投与によるものと判定された。フェドラチニブに関連した特記すべき所見を Table 3.2.2-1 に要約する。

Table 3.2.2-1: ラット 6 ヵ月間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
3	Organ weights (Day 91): ↓ Thymus (males) and salivary gland
10	Clinical pathology: Hematology 3-month (Day 91): ↓ Lymphocytes (females) Organ weights (Day 91): ↓ Thymus (males) and salivary gland
30	Body weight: ↓ Body weight (≤ 12%, males; ≤ 8%, females) and/or body weight gain throughout study Food consumption: ↓ (males) Hematology 3 months (Day 91): ↑ Platelets (males), ↓ Leukocytes and lymphocytes Hematology 6 months (Day 183): ↓ RBC, HGB and HCT, ↑ Platelets, ↓ Leukocytes (males) and lymphocytes Clinical chemistry 3 months (Day 91): ↑ ALT, AST, ALP and GGT (females)

Table 3.2.2-1: ラット 6 ヵ月間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
	Clinical chemistry 6 months (Day 183): ↑ ALP and GGT (females)
	Organ weights: ↓ Absolute and relative salivary gland and spleen weights (Days 91 and 183); ↓ thymus weight (Day 91)
	Histopathology (3-month termination): Liver – minimal bile duct epithelial cell hypertrophy (females), Bone marrow – minimal hypoplasia (females)
	Histopathology (6-month termination): Liver – minimal bile duct epithelial cell hypertrophy, Bone marrow – minimal hypoplasia (females)

↑ = increased; ↓ = decreased.
Source: Study TX-[redacted]-101348-044

TK 測定値を Table 3.2.2-2 に要約する。

Table 3.2.2-2: ラット 6 ヵ月間投与試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)			AUC(0-24h) (ng•h/mL)		
		Day 1	Day 90	Day 180	Day 1	Day 90	Day 180
Male	3	7.03	10.4	6.25	42.5	92.4	76.9
	10	62.1	58.2	87.8	363	560	716
	30	150	188	200	1430	2910	3080
Female	3	9.65	9.72	10.6	66.3	83.1	76.6
	10	86.5	60.7	67.8	680	711	725
	30	302	349	357	3210	4300	4440

Source: Study TX-[redacted]-101348-044

フェドラチニブは速やかに吸収され、最高濃度到達時間（Tmax）はおおむね投与 4 時間後であった。Day 1、90 及び 180 のいずれの時点でも雌雄で Cmax 及び AUC の用量比を上回る増加が認められた。Day 1 の曝露量は、雄よりも雌の方がわずかに高かった。Day 90 及び 180 では、曝露量の性差は 30 mg/kg のみで認められた。Day 90 及び 180 の曝露量は Day 1 よりわずかに高かった。

以上より、フェドラチニブを 6 ヵ月間投与したラットにおける忍容性は、3 及び 10 mg/kg の用量で良好であった。標的器官は肝臓（胆管）及び骨髄と考えられた。本試験の NOAEL は、30 mg/kg で認められた体重の変化、血液生化学的検査所見並びに骨髄及び肝臓の病理組織学的変化に基づき、10 mg/kg と考えられた。

3.3 イヌを用いた試験

3.3.1 イヌ 28 日間投与毒性試験

ビーグル犬（1 群雌雄各 3 匹）にフェドラチニブを 0（媒体対照）、2、5、10 及び 40/30 mg/kg の用量（投与容量 2 mL/kg）で 1 日 1 回、28 日間強制経口投与した。対照群及び最高用量群には回復群（雌雄各 2 匹）を追加し、投与期間終了後に 14 日間休薬した（試験番号 TX-[redacted]-101348-075F）。最高用量の 40 mg/kg は重篤な毒性症状が認められたため、Day 12～15 の投与を中断し、Day 16 に 30 mg/kg に減量した。

評価項目は、生死、一般状態、体重、体重増加量、摂餌量、眼科学的検査、心電図、臨床検査（血液学的検査、凝固検査、血液生化学的検査、尿検査）、TK、剖検、器官重量及び病理組織学的検査とした。

最高用量群（40/30 mg/kg）の雄 4 例及び雌 2 例を有害作用により早期剖検した。雄 2 例は有害な臨床症状が継続してみられたため Day 24 に投与を終了し、回復期間に移行した。これらのうち雄 1 例を Day 26 に早期剖検し、他の 1 例の回復期間後の剖検を Day 38 に実施した。最高用量群の雌の生存例は試験を継続して Day 29 に計画剖検を実施し、2 例を回復期間に移行した。他の投与群では全例が計画剖検時まで生存した。眼科学的検査、心電図、血圧及び尿検査所見にフェドラチニブに関連した影響は認められなかった。フェドラチニブに関連する特記すべき所見を Table 3.3.1-1 に要約する。

Table 3.3.1-1: イヌ 28 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
2	Clinical signs: Gastrointestinal disturbances (vomiting, diarrhea, soft stools, and mucoid stools) Clinical Chemistry: ↑ AST (females) Histopathology: Thymic atrophy and/or bone marrow hypoplasia
5	Clinical signs: Gastrointestinal disturbances (vomiting, diarrhea, soft stools, and mucoid stools) Clinical Chemistry: ↑ AST (females) Organ weights: ↓ Thymus (females) Histopathology: Thymic atrophy and/or bone marrow hypoplasia
10	Clinical signs: Gastrointestinal disturbances (vomiting, diarrhea, soft stools, and mucoid stools) Body weight: ↓ Body weight (< 5%, females) Hematology: ↓ Platelets (females), ↓ Leukocytes (females) Clinical Chemistry: ↑ AST (females) and ALT Organ weights: ↓ Spleen and thymus Histopathology: Bone marrow – hypoplasia, Liver – bile duct epithelium hypertrophy (males), Thymus – atrophy (males)

Table 3.3.1-1: イヌ 28 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
40/30	Mortality: 4 males and 2 females (Days 11 to 26)
	Clinical signs: Gastrointestinal disturbances (vomiting, diarrhea, soft stools, and mucoid stools); intermittent tremors; decreased activity; impaired mobility; wobbly gait; abnormal posture; thin appearance; abnormal breathing [shallow, rapid, and labored]; apparent hypothermia [i.e., cool to the touch]; dehydration; partially closed eyelid[s]; ocular discharge; increased incidence of salivation; ↑ body temperatures (moribund sacrifices only)
	Body weight and food consumption: ↓ Body weight (−24%, males and −5% females, Day 28), ↓ Body weight gain and food consumption (males)
	Hematology: ↓ RBC, HGB, HCT; ↓ reticulocytes; ↓ Platelets; ↓ Leukocytes, neutrophils, lymphocytes, eosinophils, and basophils (most prominent in moribund sacrifices); ↑ monocytes
	Clinical Chemistry: ↑ AST, ALT, GGT, ALP and total bilirubin (most prominent in moribund sacrifices); ↓ Total protein, albumin, and A/G ratio (most prominent in moribund sacrifices)
	Organ weights: ↓ Spleen and thymus (females)
	Histopathology:
	Animals sacrificed moribund Bone marrow – hypoplasia, Male reproductive – epididymal and testicular aspermia and oligospermia; seminiferous tubule degeneration, Gastrointestinal – glandular atrophy of the intestines, Liver – bile duct epithelium hypertrophy, necrosis, and proliferation; basophilic particulate material in bile duct epithelial cells (males); hepatocellular necrosis (males); Kupffer cell hyperplasia; fibrosis and mononuclear cell inflammation (males); cholestasis (one male) Lymphoid tissue – atrophy of lymph nodes, spleen and thymus, Bacterial bronchopneumonia and pleuritis (possibly secondary to effects on bone marrow and lymphoid tissues and resulting immunosuppression)
	Animals surviving to the terminal sacrifice Bone marrow – hypoplasia (females), Liver – bile duct epithelium hypertrophy; bile duct proliferation (one female); particulate material in bile duct epithelial cells (one female), Lymphoid tissue – atrophy of the thymus, lymph node and/or Peyer's patch
	Recovery: During recovery period, clinical signs resolved, animals gained more weight than controls and most clinical pathology changes resolved. The following changes were noted/persisted at end of recovery: ↓ spleen and thymus weights; Minimal to mild histopathologic changes in bone marrow, testes and epididymides, liver, spleen and lymphoid tissues

↑ = increased; ↓ = decreased.
Source: Study TX-[redacted]-101348-075F

本試験の病理組織学的検査で骨髄低形成と診断されたすべての投与群の骨髄切片について、外部専門家によるレビューを実施した（試験番号 EXP0092）。その結果、40/30 mg/kg 群の骨髄の造血が対照群の正常骨髄と比較して減少し、骨髄低形成であることが確認された。造血の減少は、有糸分裂後の造血細胞（成熟分化した骨髄系及び赤血球系細胞）集団の減少による細胞密度の全体的な減少と定義された。造血の減少がみられた 40/30 mg/kg の数例では、骨髄の初期段階の造血前駆細胞の明

らかな増加も認められたが、本試験でみられた初期段階の造血骨髄細胞の増加は、9 ヵ月間投与試験（3.3.2 項）の高用量群の大部分でみられた骨髄所見と比較しておおむね軽度であった。2、5 及び 10 mg/kg 群の数例で報告された軽微～軽度な骨髄低形成については、外部専門家のレビューの結果、これらの例の骨髄像は正常範囲内と判断された。

Day 1 及び Day 28 の TK 測定値を Table 3.3.1-2 に要約する。

Table 3.3.1-2: イヌ 28 日間投与試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
		Day 1	Day 28	Day 1	Day 28
Male	2	8.8	19.8	86.0	226
	5	69.7	104	550	1200
	10	178	271	1230	3230
	40/30	756	2800[a,b]	4970	30100[a,b,]
Female	2	10.6	21.6	77.4	183
	5	62.1	106	439	882
	10	166	216	1000	2290
	40/30	529	777	3730	7170

[a] Day 24
[b] N = 2
Source: Study TX-[redacted]-101348-075F

5～40/30 mg/kg の用量範囲では、平均 Cmax 及び AUC は用量に依存して増加した。2、5 及び 10 mg/kg での Day 28 の AUC は、Day 1 の 2.01～2.63 倍であった。最高用量 40/30 mg/kg は試験期間中に用量を減量したため比較できなかった。雌雄の Cmax 及び AUC は 2～10 mg/kg では同程度であったが、40/30 mg/kg では雄の方が顕著な高値を示した。

以上より、フェドラチニブを 28 日間反復投与したイヌにおける標的器官は、骨髄、精巣、腸、肝臓及び胆管、リンパ節、脾臓及び胸腺であった。状態悪化の数例では、骨髄及びリンパ系器官の変化に伴う免疫系への影響の二次的変化と考えられる肺炎も認められた。2～10 mg/kg の用量では軽度～中等度の毒性が発現し、40/30 mg/kg は重篤な毒性及び死亡例が発生する不耐用量であった。

3.3.2 イヌ 9 ヵ月間投与毒性試験

ビーグル犬（1 群雌雄各 10 匹）にフェドラチニブを 0（媒体対照）、2、6 及び 20/15 mg/kg の用量（投与容量 2 mL/kg）で 1 日 1 回、最長 9 ヵ月間強制経口投与した（試験番号 TX-[redacted]-101348-046A）。最高用量は、死亡例の発生により Day 26 以降 15 mg/kg に減量した。3 ヵ月間及び 6 ヵ月間投与後に 1 群雌雄各 3 匹を中間剖検し、残りの 1 群雌雄各 4 匹を 9 ヵ月間投与後に最終剖検した。さらに、高用量群で状態悪化・死亡例が発生したため、雄 1 匹及び雌 2 匹を Day 26（雌）及び Day 27（雄）に追加した。回復期間は設定しなかった。

評価項目は、生死、一般状態、体重、体重増加量、摂餌量、眼科学的検査、心電図、臨床検査（血液学的検査、凝固検査、血液生化学的検査、尿検査）、血液及び骨髄塗抹標本検査（高用量群の選択例のみ）、剖検、器官重量及び病理組織学的検査とした。

20/15 mg/kg でフェドラチニブに関連する死亡例がみられ、雄 1 例及び雌 3 例を状態悪化により Day 18～26 に早期剖検した。投与量を 15 mg/kg に減量した後、さらに雄 4 例を状態悪化により Day 61、89、109 及び 232 に早期剖検し、雄 1 例が Day 188 に死亡発見された。残りの全例は計画剖検時まで生存した。眼科学的検査、尿検査及び心電図所見にフェドラチニブに関連した影響は認められなかった。フェドラチニブに関連した特記すべき所見を Table 3.3.2-1 に要約する。

Table 3.3.2-1: イヌ 9 ヵ月間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effectsa
2	Clinical signs: Vomiting, soft stools, mucoid material, and diarrhea Clinical pathology: ↑ Reticulocytes (males)
6	Clinical signs: Vomiting, soft stools, mucoid material, and diarrhea. Hematology: ↓ RBC, HGB, and HCT; ↑ reticulocytes; ↓ Leukocytes, neutrophils, and eosinophils Clinical chemistry (throughout study): ↑ AST and ALT Organ weights: Day 91 – ↓ Spleen, and salivary gland (female) Day 182 – ↓ Spleen Day 272 – ↓ Spleen (male) Histopathology: Liver – Minimal proliferation of small bile ducts, small caliber vessels, and fibroblasts in the portal triads (3 months)
20/15	Mortality: 9 dogs were euthanized moribund or found dead: 4 dogs (1 male and 3 females) given 20 mg/kg euthanized (Days 18 to 26); 4 males euthanized moribund (Days 61, 89, 109, and 232) after dose reduction to 15 mg/kg; 1 male was found dead on Day 188 Clinical signs: Clinical signs throughout group included: Vomiting, soft stools, mucoid material, and diarrhea. In dogs euthanized moribund: Decreased activity, impaired mobility of the forelimb, facial edema, ocular discharge, rapid and labored breathing, partially closed eyelids, wobbly gait, shivering, thin appearance, tremors, dehydration, and ↑ body temperature. Body weight and food consumption: ↓ During the first 3 months of the study (males). Hematology: ↓ RBC, HGB, and HCT; ↑ Reticulocytes; ↓ Leukocytes, segmented neutrophils, and eosinophils Clinical chemistry: ↑ AST, ALT, ALP, and GGT; ↓ Cholesterol; ↓ Albumin and A/G ratio; ↑ Globulin (males) Organ weights: Day 91 – ↓ Spleen, and salivary gland (female) Day 182 – ↓ Spleen Day 272 – ↓ Spleen (male) Histopathology: Findings in early death animals were similar, but generally of greater severity, to those listed below. In addition to these findings, early euthanasia animals exhibited microscopic findings consistent with pneumonia; internal bleeding related to ulcers and chronic-active

Table 3.3.2-1: イヌ 9 ヵ月間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effectsa
	inflammation of the esophagus and stomach; abscesses; bile duct and gall bladder epithelial degeneration/regeneration and/or necrosis; and findings associated with stress and inappetence, including lymphoid depletion in lymphoid tissues.
	3-Month termination Bone marrow – hematopoietic cell hypoplasia and increase in hematopoietic (myeloid) progenitor cells[a], Liver – Minimal proliferation of small bile ducts, small caliber vessels, and fibroblasts in the portal triads; increased myeloid progenitor cells[a]/hematopoiesis, Spleen – Increased myeloid progenitor cells[a]/hematopoiesis
	6-Month termination Bone marrow – mild increase in hematopoietic (myeloid) progenitor cells[a], minimal hematopoietic cell hyperplasia and minimal megakaryocyte hyperplasia (one male), Liver – Increased myeloid progenitor cells[a]/hematopoiesis, Spleen – Increased myeloid progenitor cells[a]/hematopoiesis
	9-Month termination Bone marrow – Hematopoietic cell hypoplasia and increase in hematopoietic (myeloid) progenitor cells[a], Liver – Minimal proliferation of small bile ducts, small caliber vessels, and fibroblasts in the portal triads; Increased myeloid progenitor cells[a]/hematopoiesis, Spleen – Increased myeloid progenitor cells[a]/hematopoiesis

↑ = increased; ↓ = decreased.
[a] Terminology developed by the expert panel is used in this table rather than the terminology used by the study pathologist in the Study Report.
Source: Studiy TX-[redacted]-101348-046A; Study EXP0092

20/15 mg/kg 群の骨髄切片について、外部専門家委員会による再評価を実施した結果、「骨髄低形成」と本試験の病理組織学的検査担当者により報告された正常造血の減少の所見名及び変化の程度（グレード）が確認された（試験番号 EXP0092）。造血低下の程度は、死亡発見例及び状態悪化による早期剖検例で比較的高度であり、主に造血細胞（成熟骨髄系細胞、赤血球系細胞及び巨核球）の有糸分裂後細胞集団の減少による細胞密度の全体的な低下が認められた。造血低下に伴い初期段階の造血前駆細胞の増殖がみられたが、これらは後期段階（有糸分裂後）への限定的な成熟・分化の有無にかかわらず骨髄（顆粒球）系の細胞と考えられ、無効造血と一致した。ヘマトキシリン・エオシン染色のみによる胸骨骨髄切片の検査では分化段階を正確に特定できなかったが、当初診断された所見名の「幹細胞過形成」は、本試験の低形成骨髄で増加した細胞が骨髄幹細胞に通常みられる形態学的特徴を示していないことから初期段階の造血幹細胞ではなく顆粒球系の骨髄前駆細胞であると考えられ、骨髄に認められたフェドラチニブに関連した所見名として適切でないと結論された。このことに基づき、本概要では試験報告書で病理組織学的検査担当者による所見名ではなく、外部専門家委員会によって診断された所見名を使用する。さらに、フェドラチニブにより骨髄の変化が生じた数例の肝臓及び脾臓に認められた「幹細胞浸潤」の所見名についても、外部専門家委員会は、これらの肝臓及び脾臓の所見は骨髄で生じたものと同様の「骨髄性前駆細胞の増殖」と結論した。

この初期の前駆細胞の増殖は、フェドラチニブの全身曝露が残っている状態での骨髄・血液の回復傾向を示すものであり、腫瘍性所見ではないと考えられた。以上のことから、外部専門家委員会は、フェドラチニブのイヌを用いた 2 試験で認められた骨髄の変化は、造血低下の後に骨髄（顆粒球）系と考えられる初期の造血前駆細胞が増殖した二次的変化と判断した。

TK 測定値を Table 3.3.2-2 に要約する。

Table 3.3.2-2: イヌ 9 ヵ月間投与試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)			AUC(0-24h) (ng•h/mL)		
		Day 1	Day 26	Day 90	Day 1	Day 26	Day 90
Male	2	8.36	13.9	10.9	75.6	138	138
	6	58.9	95.6	73.0	495	910	873
	15	–	271	395	–	3150	5790
	20	428	–	–	4560	–	–
Female	2	9.82	12.0	9.59	83.4	125	116
	6	64.4	80.8	65.7	430	786	732
	15	–	200	279	–	1970	3020
	20	427	–	–	4450	–	–

Sex	Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
		Day 181	Day 271	Day 181	Day 271
Male	2	11.3	16.0	145	184
	6	88.1	117	1070	1200
	15	346	246	4920	2880
	20	–	–	–	–
Female	2	13.3	23.3	147	192
	6	64.0	76.4	697	836
	15	334	345[a]	3980	3840[a]
	20	–	–	–	–

– = not applicable
[a] Represents combined mean values for samples from Day 246 and Day 271.
Source: Study TX-[redacted]-101348-046A

フェドラチニブはすべての用量（2、6 及び 20/15 mg/kg）で雌雄全例の血漿中に検出された。吸収は比較的速やかでTmax 中央値は 1～4 時間であった。Cmax 及び AUC(0-24h)の用量比を上回る増加が、雌雄ともにいずれの採血時点でも認められた。雄の血漿中曝露量は概して雌よりわずかに高く、2 mg/kg の Day 1 及び Day 271 並びに 15 mg/kg の Day 271 を除くすべての採血日で高い傾向が認められた。反復投与後の血漿中曝露量は Day 1 よりも高く、反復投与により増加すると考えられたが、2

及び 6 mg/kg では Day 26 以降、15/20 mg/kg では Day 90 以降の更なる増加はみられなかった。Day 26 以降は、投与前にも検出可能な濃度のフェドラチニブが全試料で検出された。投与量の増加に伴い濃度が上昇し、Day 90 以降は定常状態と考えられた。

以上より、フェドラチニブを最長 9 ヵ月間反復投与したイヌにおける主な標的器官は、骨髄、リンパ組織、肝臓（主に胆管）、胆嚢及び脾臓と考えられた。さらに状態悪化例では、骨髄及びリンパ器官の変化に伴う免疫系への影響の二次的変化と考えられる肺炎及び膿瘍も観察された。高用量の 15/20 mg/kg は不耐であり、重篤な毒性及び死亡例が認められた。本試験の NOAEL は、当初 6 mg/kg と判断されたが、その後同用量での肝臓の変化が有害所見と判断された（試験番号 TX-[redacted]-101348-046A 報告書 Amendment No. 2）ことから、最終的に 2 mg/kg と決定された。

4 遺伝毒性試験

細菌を用いた復帰突然変異（Ames）試験、CHO 細胞を用いた in vitro 染色体異常試験及び in vivo ラット小核試験を実施した。各試験の結果を Table 4-1 に要約する。

Table 4-1: 遺伝毒性試験成績

Test system	Concentration or doses	Results
In vitro bacterial reverse mutation test (Ames assay); *Salmonella. typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia. coli* (WP2 *uvrA*)	1.5 to 5000 µg/plate	Negative (+/− S9)
In vitro chromosomal aberration assay in CHO cells	0.625 to 25 µg/mL (−S9) 1.25 to 45 µg/mL (+S9)	Negative (+/− S9)
In vivo rat micronucleus; chromosomal aberration assay (oral)	0 (vehicle), 5, 30, 80 mg/kg	Negative

Sources: Study TX-[redacted]-101348-084; Study TX-[redacted]-101348-050; Study TX-[redacted]-101348-051

Ames 試験（試験番号 TX-[redacted]-101348-084）において変異原性は認められなかった。ほ乳類培養細胞を用いた染色体異常試験（試験番号 TX-[redacted]-101348-050）において染色体異常誘発性は認められず、ラット骨髄小核試験（試験番号 TX-[redacted]-101348-051）においても多染性赤血球の統計学的に有意な増加は認められなかった。以上より、フェドラチニブは遺伝毒性を有さないと考えられた。

5 がん原性試験

5.1 マウス 29 日間投与用量設定試験

本試験は、CByB6F1-Tg(HRAS)2Jic マウスを用いた 26 週間がん原性試験の用量設定試験として実施した。野生型 CByB6F1（CByB6F1-Tg(HRAS)2Jic マウスと同腹の非トランスジェニック）マウス（1 群雌雄各 6 匹）に、フェドラチニブを 0（媒体対照）、100、200 及び 400/300 mg/kg の用量（投与容量 5 mL/kg）で 1 日 1 回、最長 29 日間強制経口投与した（試験番号 DDC0131）。TK 測定用サテライト群（対照群は雌雄各 6 匹、フェドラチニブ投与群は各用量雌雄各 18 匹）を別途に設けた。400

mg/kg で死亡例及び重篤な毒性症状の発生したことから、Day 3 に 300 mg/kg に減量した。しかし用量の減量後も死亡例及び毒性症状が発生したため、Day 6（毒性試験群）及び Day 7（TK 群）にそれぞれ最終投与した後、Day 7 に早期剖検した。TK 群の 400/300 mg/kg 群の雄 8 匹及び雌 2 匹を Day 4 に置き換え、300 mg/kg を Day 4～7 に投与した。

評価項目は、生死、一般状態、体重、摂餌量、血液学的検査及び血液生化学的検査並びに TK とした。投与期間終了時に毒性試験群の全例を剖検し、主要器官の重量を測定して組織試料を病理組織学的検査に供した。

フェドラチニブに関連する特記すべき所見を Table 5.1-1 に要約する。各投与群の死亡例に概してみられた臨床症状は、活動性低下、円背位、運動失調、斜視、努力性呼吸、粗毛及び皮温低下であった。

Table 5.1-1: マウス 29 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
100	Mortality (Found Dead and/or Euthanized): Toxicity group – 2 (1 male/1 female) on Day 9 or 20; TK group - 3 males on Day 24 or 25 Hematology: ↑ Platelet counts, ↓ Lymphocyte counts, ↓ Large unstained cells (males) Organ weights: ↓ Spleen (females)
200	Mortality (Found Dead and/or Euthanized): Toxicity group – 6 (3 males/3 females) on Day 25; TK group – 5 (4 males/1 female) on Day 25 Body weight: ↑ Days 15 (females only), 22, 29 (4% to 9%) Food consumption: ↑ Days 15 (females only), 22, 29 (8% to 24%) Hematology: ↑ Platelet counts, ↓ Lymphocyte counts, ↓ Large unstained cells, ↓ RBC, HGB and/or HCT Organ weights: ↓ Spleen; ↓Thymus (males); ↑ Heart (females) Gross pathology: Stomach (discolored or raised area) Histopathology: Bone marrow – hypoplasia (males), Thymus – lymphocyte depletion (males), necrosis (males), Mesenteric lymph node – necrosis (females), Urinary bladder – transitional cell vacuolation
400/300[a]	Mortality (Found Dead and/or Euthanized): Toxicity group – 12 (6 males/6 females) on Days 2 (400 mg/kg) and 4-7 (300 mg/kg); TK group – 19 (13 males/6 females) on Days 2 (400 mg/kg) and 4-7 (300 mg/kg) Gross pathology: Stomach (discolored or raised area) and spleen (discolored or small; males) Histopathology: Bone marrow – hypoplasia, Spleen – lymphocyte depletion, necrosis, ↓ extramedullary hematopoiesis, Thymus – lymphocyte depletion, necrosis, GALT/Peyer's patch – lymphocyte depletion; necrosis (females), Mesenteric lymph node – lymphocyte depletion, necrosis, Kidney – degeneration/necrosis renal tubules, Stomach – non-glandular – ulceration/inflammation; glandular – hypertrophy,

Table 5.1-1: マウス 29 日間投与試験における特記すべき所見

Dose (mg/kg)	Main Fedratinib-related Effects
	Vagina – asynchronous estrous cycle, Diaphragm muscle – degeneration/necrosis/inflammation

↑ = increased; ↓ = decreased.
[a] 400 mg/kg for 2 days followed by 300 mg/kg for 5 days; or 300 mg/kg for 4 days (Days 4-7).
Source: Study DDC0131

TK 測定値を Table 5.1-2 に要約する。

Table 5.1-2: マウス 29 日間投与試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
		Day 7	Day 28	Day 7	Day 28
Male	100	NA	3200	NA	30800
	200	NA	5020	NA	68200
	400/300 [a]	9620	NA	26600 [b]	NA
Female	100	NA	4470	NA	34400
	200	NA	6220	NA	100000
	400/300 [a]	12000	NA	34200 [b]	NA

[a] 400 mg/kg for 2 days followed by 300 mg/kg for 5 days; or 300 mg/kg for 4 days (Days 4-7).
[b] AUC(0-4) since toxicokinetic sampling was only done for 4 hours after dosing.
Source: Study DDC0131

フェドラチニブの曝露量は用量比をわずかに上回って増加した。100～200 mg/kg の間では、Day 28 での AUC の増加は雄で 2.21 倍、雌で 2.91 倍であり、雌の曝露量が雄よりわずかに高い傾向がみられた（Day 28 での雌／雄の曝露量比は、AUC で 1.12～1.47、Cmax で 1.24～1.40）。

以上より、野生型 CByB6F1（非トランスジェニック CByB6F1-Tg(HRAS)2Jic）マウスにフェドラチニブを 100、200 及び 400/300 mg/kg の用量で最長 29 日間経口投与した結果、用量に依存して状態悪化・死亡例が増加した。病理組織学的検査に基づく標的器官は、骨髄、リンパ組織［脾臓、胸腺、腸間膜リンパ節及び腸管関連リンパ組織（GALT）］、腎臓、膀胱、胃（前胃及び腺胃）、膣及び筋肉であった。また、心臓重量の統計学的有意な増加が認められた。TK の結果、全例で曝露が確認され、フェドラチニブの曝露量は用量比をわずかに上回って増加した。

5.2 マウス 26 週間投与がん原性試験

CByB6F1 Tg(HRAS)2Jic マウス（1 群雌雄各 25 匹）にフェドラチニブを 0（媒体対照）、3、10 及び 30 mg/kg の用量（投与容量 5 mL/kg）で 26 週間連日強制経口投与し、がん原性を評価した。また、野生型（非トランスジェニック）CByB6F1 マウス（1 群雌雄各 38～40 匹、媒体対照群は雌雄各 7 匹）

のサテライト群を設け、フェドラチニブを同様に投与して TK を測定した（試験番号 CAR0168）。陽性対照群には N−メチル−N−ニトロソ尿素（MNU）を 75 mg/kg の用量（投与容量 10 mL/kg）で Day 1 に腹腔内投与した。評価項目は、生死、一般状態、体重、体重増加量、摂餌量，剖検及び病理組織学的検査とした。TK 評価用の採血を Week 13 及び 26 に実施した。

計画剖検前に 12 例（雄 5 例、雌 7 例）が死亡発見又は状態悪化により早期剖検された（Table 5.2-1）。いずれの死亡例もフェドラチニブに起因するものではないと判断された。これらの 12 例中 2 例は偶発的事象によるものであり、2 例の死因は特定できなかった。残りの 8 例は多様な腫瘍の発生による死亡又は状態悪化であった（Table 5.2-1）。これらの各種腫瘍の発生頻度は低く、用量反応関係がみられなかったことから、いずれの腫瘍発生及び死亡もフェドラチニブに関連するものではないと考えられた。さらに、フェドラチニブ投与群の全生存率は、本試験に使用したマウスの系統で報告されている生存率（92%～100%）[1,2,3] の範囲内であった。

フェドラチニブ投与群の雌では死亡率の有意な増加傾向（Cox-Tarone 検定で p = 0.0453、Gehan-Breslow 検定で p = 0.0483）が認められ、30 mg/kg 群の死亡率の増加は媒体対照群と比較して Gehan-Breslow 検定で有意（p = 0.0396）であったが、Cox-Tarone 検定では有意ではなかった（p = 0.1177）。しかし、30 mg/kg 群の雌 3 例の計画外死亡のうち 2 例はフェドラチニブとの関連性がないと考えられる新生物による死亡であった。また、残り 1 例の死因は特定できずフェドラチニブとの関連性は不明であった。これらのことから、死亡率にフェドラチニブ投与との関連性はないと結論された。

TK 測定用サテライト群（野生型マウス）でも 2 例（30 mg/kg 雄 1 例、3 mg/kg 雌 1 例）が計画剖検前に死亡発見又は状態悪化により早期剖検されたが、これらの死亡もフェドラチニブとの関連性なしと判断された。

Table 5.2-1: マウス 26 週間投与がん原性試験における計画外死亡例

Sex	Dose (mg/kg)	Day of death	Cause of death
Male	3	127	Cage-related injury
Female	3	127	Mammary carcinoma
Male	10	127	Bronchioloalveolar carcinoma
Female	10	127	Gavage-related injury
Female	10	130	Nonglandular stomach carcinoma
Male	30	138	Undetermined
Female	30	139	Undetermined
Male	10	153	Lymphosarcoma
Female	10	173	Bronchioloalveolar carcinoma
Male	30	175	Hemangiosarcoma
Female	30	179	Sarcoma, origin unknown
Female	30	179	Hemangiosarcoma

Source: Study CAR0168

計画外死亡例では、状態悪化に関連した臨床症状（被毛粗剛、排糞量減少、円背位、不規則呼吸）がみられた。その他試験期間中にみられた臨床症状は、低頻度、一過性又は対照群にも同程度であったことから、フェドラチニブ投与との関連性はないと考えられた。

Day 29 以降、30 mg/kg 群の雌の体重は統計学的に有意な低値（対照群との差 10%未満）を示し、Day 183 での体重増加量に統計学的有意差が認められた。

摂餌量（週単位）は、各用量群の雄で対照群とおおむね同程度又はわずかに低値であり、関連した体重への影響はみられなかった。雌の摂餌量は 3 及び 10 mg/kg 群で対照群とおおむね同程度又はわずかに低値であったが、30 mg/kg 群では統計学的に有意な低値を示し、これに関連した体重の低値が認められた。

TK 測定値を Table 5.2-2 に示す。

Table 5.2-2: マウス 26 週間投与がん原性試験におけるトキシコキネティクス値

Sex	Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
		Week 13	Week 26	Week 13	Week 26
Male	3	26.4	15.7	214	114
	10	157	217	1640	2320
	30	1450	1280	15400	12700
Female	3	50.1	34.6	438	347
	10	249	165	2610	1600
	30	2060	2130	22100	22100

Source: Study CAR0168

TK 測定の結果、フェドラチニブを 3、10 及び 30 mg/kg の用量で最長 26 週間 1 日 1 回反復経口投与したマウス全例の曝露が確認された。フェドラチニブの曝露量は用量比を上回って増加した。3 mg/kg から 30 mg/kg への 10 倍の増加で、AUC(0-24h)は雄で 111 倍、雌で 63.7 倍増加した。Week 13～26 の曝露量は、10 mg/kg を除いて概して雌が雄より高く、Week 26 の雌／雄比は AUC(0-24h)で 1.74～3.04、Cmax で 1.66～2.20 であった。

剖検及び病理組織学的検査では、新生物を含めてフェドラチニブ投与に関連した所見は認められなかった。本試験で認められたすべての新生物の発生頻度を Table 5.2-3 に示す。認められた新生物の多くは HRAS2 マウスで自然発生が報告されている腫瘍[2,3,4,5,6]であったが、これら以外に良性星状細胞腫（10 mg/kg 雄 1 例）、乳腺癌（3 mg/kg 雌 1 例）及び原発不明の肉腫（10 mg/kg 雄 1 例及び 30 mg/kg 雌 1 例）の発生が認められた。星状細胞腫は本試験で用いた系統のトランスジェニックマウスでは報告されていないが、脳の混合型神経膠腫の発生が確認されている[4]ことから、神経膠由来

の腫瘍は本系統で観察されていることが示唆される。肉腫（組織球肉腫、平滑筋肉腫、横紋筋肉腫、骨肉腫、肉腫）の発生はHRAS2マウスでの報告があり[2,5]、間質由来の腫瘍は自然発生することが示されている。また、本試験で認められた原発不明の肉腫についても、上記の報告で原発組織を特定せず言及されている肉腫と同様であった。これらのことから、本試験で認められた腫瘍発生は、1）発現頻度が低いこと、2）統計学的に有意ではないこと、3）用量反応性がないことから、いずれもフェドラチニブに起因するものではないと考えられた。

Table 5.2-3: マウス 26 週間投与がん原性試験における新生物

Sex	Males				Females			
Dose (mg/kg)	**0**	**3**	**10**	**30**	**0**	**3**	**10**	**30**
Body, whole/cavity								
B-hemangioma	1	0	0	0	0	0	1	0
M-hemangiosarcoma	3	3	2	3	3	0	3	2
M-lymphosarcoma	0	0	1	0	0	0	0	0
M-sarcoma, origin unknown	0	0	1	0	0	0	0	1
Brain								
B-astrocytoma	0	0	1	0	0	0	0	0
Lung								
B-adenoma, bronchioloalveolar	0	2	1	2	0	1	1	1
M-carcinoma, bronchioloalveolar	1	0	1	0	0	1	2	1
Harderian gland								
B-adenoma	1	0	0	1	0	0	1	0
M-carcinoma	0	0	1	0	0	0	0	0
Liver								
M-carcinoma, hepatocellular	0	0	0	1	0	0	0	0
Nonglandular stomach								
M-carcinoma, squamous cell	0	0	0	0	0	0	1	0
Uterus								
B-polyp, endometrial stromal	NA	NA	NA	NA	1	0	0	0
Female mammary gland								
M-carcinoma	NA	NA	NA	NA	0	1	0	0

B = benign; M = malignant.
Source: Study CAR0168

陽性対照の MNU 投与群では死亡率が高く、雄で 17/25 例、雌で 19/25 例が計画剖検前に死亡発見又は状態悪化により早期剖検された。また、MNU の投与で知られている発がんが認められた。

以上より、フェドラチニブを 26 週間投与したトランスジェニックマウスにおいて、30 mg/kg の用量で雌に体重及び摂餌量の減少が認められた。フェドラチニブに関連した剖検所見及び病理組織学的所見は認められず、フェドラチニブに起因する腫瘍発生も認められなかった。

6 生殖発生毒性試験

6.1 受胎能及び着床までの初期胚発生に関する試験

Sprague-Dawley ラット（1 群雌雄各 24～25 匹）にフェドラチニブを 0（媒体対照）、3、10 及び 30 mg/kg の用量（投与容量 5 mL/kg）で 1 日 1 回強制経口投与した（試験番号 FER0500）。雄は、交配前の 70 日間以上から交配期間中（最長 6 日間）及び交配後を通して Week 14（対照群の数例は Week 21）の計画剖検前日まで投与した（総投与期間 91～142 日間）。雌は、交配前 14 日間から交配期間中及び交配後を通して妊娠 7 日まで投与した（総投与期間 22～27 日間）。

生死及び一般状態を毎日観察し、体重を定期的に測定した。摂餌量を雌雄の交配前期間は毎週、交配後の雌は妊娠 1、4、8 及び 14 日に測定した。

雄で 10 週間以上、雌で 2 週間以上の投与後、雌雄を最長 6 日間同居させ、交配が確認された雌は同居から除外した。交配期間中、膣塗抹標本観察を交配までの毎朝実施し、発情周期を観察して交配を確認した。

雄の剖検は、大部分を Day 92～96（Week 14）に、対照群の少数例を Day 129 又は 143（Week 21）に実施した。剖検時、精巣、精巣上体、前立腺及び精嚢の重量を測定した。これらの器官を採取して固定液に保存した。病理組織学的検査は実施しなかった。各群の雄 12 例について左精巣上体と左精巣（可能な場合）を採取して精子分析（精巣及び精巣上体の精子数、精子の運動性及び形態）に供した。

雌の剖検は妊娠 14 日に実施した。1 ヵ所以上の生存着床胚が確認された雌全例の妊娠子宮重量を測定し、子宮内容物、卵巣及び胎盤を観察して黄体数、着床数及び分布、着床状態（早期吸収胚、後期吸収胚、生存又は死亡胚・胎児）を記録した。非妊娠雌から卵巣、膣及び子宮を採取し、固定液中に保存した。病理組織学的検査は実施しなかった。

試験期間中に死亡例は認められず、一般状態の変化もみられなかった。

体重・体重増加量への影響が 30 mg/kg で雌雄に認められた （Table 6.1-1）。

Table 6.1-1: ラット生殖能及び初期胚発生に関する試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
30	Body Weight: Males: ↓ from study Day 43 [−8% on dosing Day 71 and −10% on dosing Day 92]; no change in food consumption Body Weight Gain: Females: ↓ during 1st week of gestation (−22% during GD 1-8); associated with minimal decreases in food consumption during GD 1-8 (up to −8%)

GD = gestation day; ↓ = decreased.
Source: Study FER0500

雌雄の体重及び摂餌量へのフェドラチニブに関連した影響は、3 及び 10 mg/kg では雌雄ともに認められなかった。

発情周期、交配所要日数、交尾行動、受胎能指数及び妊娠率へのフェドラチニブに関連した影響は認められなかった。精巣、精巣上体、前立腺、精嚢及び妊娠子宮重量のフェドラチニブに関連した変化並びに剖検所見はいずれの用量でもみられなかった。精巣上体精子数、精巣精子数、精子運動性及び形態学的解析所見にフェドラチニブに関連した影響はいずれの用量でも認められなかった。また、黄体数、着床数、着床前胚損失率、着床後胚損失率及び生存胚・胎児数への影響も認められなかった。

以上より、親動物の一般毒性として、30 mg/kg でわずかな体重減少又は体重増加抑制が雄で試験期間を通して、雌では軽微な摂餌量減少を伴って妊娠 1 週目にみられた。受胎能及び生殖能に関しては、フェドラチニブに関連した影響はいずれの用量でも認められなかった。したがって、親動物に関する無作用量（NOEL）は 10 mg/kg、雌雄の受胎能及び生殖能に関する NOEL は 30 mg/kg と考えられた。

6.2 胚・胎児発生に関する試験

6.2.1 ラット胚・胎児発生に関する用量設定試験

交配済み Crl:CD(SD)ラット（各群 5 匹）にフェドラチニブを 0（媒体対照）、3、10、30 及び 80 mg/kg の用量（投与容量 10 mL/kg）で妊娠 6 日～17 日に 1 日 1 回強制経口投与した（試験番号 TX-[redacted]-101348-055）。

本試験の評価項目は、一般状態、妊娠体重及び体重増加量、摂餌量とした。妊娠 20 日に全例を剖検して子宮内を検査し、全着床数、早期・後期吸収胚数、生存・死亡胎児数を記録した。また、各卵巣の黄体数及び妊娠子宮重量を記録した。胎児について体重測定、性別判定及び外表観察を実施した。

主な所見を Table 6.2.1-1 に示す。これらの所見に基づいて重要な試験（試験番号 TX-[redacted]-101348-057）の用量を設定した。

Table 6.2.1-1: ラット胚・胎児発生に関する用量設定試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
30	Developmental toxicity ↑ Post implantation loss ↓ Fetal body weight (7 to 9%, not statistically different from control)
80	Maternal toxicity ↓ Gestation body weight (13 to 17%, GD 12 to GD 20), body weight gain (59%, GD 6 to GD 18), and food consumption (23%, GD 6 to GD 18)
	Developmental toxicity ↑ Post implantation loss; ↓ fetal body weight (36 to 41%)

GD = gestation day; ↑ = increased; ↓ = decreased.
Source: Study TX-[redacted]-101348-055

6.2.2 ラット胚・胎児発生に関する試験

妊娠 Crl:CD(SD)ラット（各群 25 匹）にフェドラチニブを 0（媒体対照）、3、10 及び 30 mg/kg の用量（投与容量 10 mL/kg）で妊娠 6 日～17 日に 1 日 1 回強制経口投与した（試験番号 TX-[redacted]-101348-057）。また、TK 評価用サテライト群（媒体対照 3 匹、被験物質投与各群 6 匹）を設け、同様に投与した。

生死及び一般状態を観察し、妊娠体重、体重増加量及び摂餌量を測定した。妊娠 20 日に毒性試験群の全例について剖検及び子宮検査を実施し、全着床数、早期・後期吸収胚数、生存・死亡胎児数並びに胎児の性別及び体重を記録した。また、各卵巣の黄体数及び妊娠子宮重量を記録した。全胎児について外表検査、各同腹児の約 1/2 について内臓検査、残りの胎児について骨格検査を実施した。

主な所見を Table 6.2.2-1 に示す。

Table 6.2.2-1: ラット胚・胎児発生に関する試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
10	Maternal toxicity ↓ Gestation weight gain during the dosing period.
30	Maternal toxicity ↓ Gestation weight gain during the dosing period
	Developmental toxicity ↓ Fetal body weight ↑ Litter incidence of one type of skeletal variation (additional ossification centers on the cervical vertebral neural arches)

↑ = increased; ↓ = decreased.
Source: Study TX-[redacted]-101348-057

TK 測定値を Table 6.2.2-2 に要約する。

Table 6.2.2-2: ラット胚・胎児発生に関する試験のトキシコキネティクス値

Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
	GD 6	GD 17	GD 6	GD 17
3	8.23	2.76	60.5	26.1
10	42.3	46.8	349	419
30	265	294	3310	3250

GD = gestation day.
Source: Study TX-[redacted]-101348-057

以上より、母動物毒性に関する NOEL は、10 及び 30 mg/kg で妊娠体重の減少がみられたことから 3 mg/kg と考えられた。発生毒性に関する NOEL は、30 mg/kg で骨格変異の発生頻度が増加したことから 10 mg/kg と考えられた。奇形（外表、内臓又は骨格）の発生頻度増加は認められなかった。

6.2.3 ウサギ胚・胎児発生に関する用量設定試験

交配済み New Zealand White ウサギ（各群 6 匹）にフェドラチニブを 0（媒体対照）、3、10、30 及び 80 mg/kg の用量（投与容量 4 mL/kg）で妊娠 6 日～18 日に 1 日 1 回強制経口投与した（試験番号 TX-[redacted]-101348-056）。

80 mg/kg では母動物毒性の発現により投与を妊娠 10 日に中止し、生存例を妊娠 14 日に早期剖検した。

全例について生死及び一般状態を観察し、妊娠体重及び体重増加量、摂餌量を測定した。妊娠 29 日に生存例の全例について剖検及び子宮内検査を実施し、全着床数、早期・後期吸収胚数、生存・死亡胎児数を記録した。また、各卵巣の黄体数及び妊娠子宮重量を記録した。胎児について体重測定及び外表観察を実施した。

主な所見を Table 6.2.3-1 に示す。これらの所見に基づいて重要な試験（試験番号 TX-[redacted]-101348-058A）の用量を設定した。

Table 6.2.3-1: ウサギ胚・胎児発生に関する用量設定試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
80	Mortality 1 female died on GD 10; 1 female was euthanized in extremis on GD 13 Maternal toxicity Due to the mortality and toxicity in the remaining females (ie, weight loss and reduced food consumption), treatment was stopped on GD 10 and the group was terminated on GD 14.

GD = gestation day.
Source: Study TX-[redacted]-101348-056

6.2.4 ウサギ胚・胎児発生に関する試験

妊娠New Zealand Whiteウサギ（各群23匹）にフェドラチニブを0（媒体対照）、3、10及び30 mg/kgの用量（投与容量4 mL/kg）で妊娠6日～18日に1日1回強制経口投与した（試験番号TX-[redacted]-101348-058A）。また、TK評価用サテライト群（各群3匹）を設け、同様に投与した。

全例について生死及び一般状態を観察し、妊娠体重及び体重増加量、摂餌量を測定した。

妊娠29日に毒性試験群の全例について剖検及び子宮検査を実施し、全着床数、早期・後期吸収胚数、生存・死亡胎児数並びに胎児の性別及び体重を記録した。また、各卵巣の黄体数及び妊娠子宮重量を記録した。全胎児について外表検査、内臓検査及び骨格検査を実施した。

フェドラチニブに関連した死亡例はみられなかった。母動物の一般状態、妊娠体重、体重増加量、摂餌量及び剖検所見への影響はいずれの用量でも認められなかった。妊娠率は、対照群、10及び30 mg/kg群で100%、3 mg/kg群で95.7%であった。流産及び早産は対照群及びフェドラチニブ投与群のいずれでも認められなかったが、対照群の雌1例で全吸収胚が認められた。妊娠29日での対照群及び各投与群の生存胎児を有する母動物数は22例であった。TK群の妊娠率は対照群及び各投与群で100%であった。着床数、胎児体重及び性比、胎児の外表、内臓及び骨格所見にフェドラチニブに関連した影響は認められなかった。

TK測定値をTable 6.2.4-1に要約する。

Table 6.2.4-1: ウサギ胚・胎児発生に関する試験のトキシコキネティクス値

Dose (mg/kg)	Cmax (ng/mL)		AUC(0-24h) (ng•h/mL)	
	GD 6	GD 18	GD 6	GD 18
3	3.09	7.02	5.53	21.6
10	20.2	40.2	76.4	148
30	157	501	722	2320

GD = gestation day.
Source: Study TX-[redacted]-101348-058A

以上より、ウサギにおける母動物毒性及び胚・胎児発生に関するNOELは、評価した最高用量の30 mg/kgと考えられ、フェドラチニブはウサギにおいて胚・胎児毒性を示さなかった。

6.3 ラット出生前及び出生後の発生並びに母体の機能に関する試験

妊娠Crl:CD(SD)ラット（各群24匹）にフェドラチニブを0（媒体対照）、3、10及び30 mg/kgの用量（投与容量10 mL/kg）で妊娠6日から分娩を通して哺育20日まで、1日1回強制経口投与した（試験番号DPN0371）。

着床から離乳までの期間での妊娠及び哺育母動物並びに出生児の発達へのフェドラチニブの影響を評価した。F1出生児については、離乳までの発達及び成長への影響を評価した。離乳時に同腹児の

雌雄各 1 匹を選択し、成熟まで試験を継続した。成熟期間では F1 雌雄の成長、性成熟、自発運動及び反射、学習・記憶並びに生殖能（妊娠 13 日の帝王切開まで）を評価した。

主な所見を Table 6.3-1 に示す。

Table 6.3-1: ラット出生前及び出生後の発生に関する試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
30	Body weight gain F0 generation females Gestation – ↓mean weight gain during GD 6-8 (−48.1%), GD 16-18 (−17.0%), and GD 6-20 (−6.3%) F1 generation pups ↓ Mean body weight (pre-cull to weaning) ↓ Mean body weight and food consumption (males, during maturation) ↓ Mean body weight (females, MD 0 only)

GD = gestation day; MD = maturation day; ↓ = decreased.
Source: Study DPN0371

F0 雌の全例が計画剖検時まで生存した。妊娠及び哺育期間中にフェドラチニブに関連した一般状態及び摂餌量の変化は認められなかった。

30 mg/kg では雌 1 例が妊娠しなかった。フェドラチニブに関連した剖検所見はみられず、分娩数、妊娠率及び分娩児数などの生殖指標への影響も認められなかった。また、哺育期間中の生後 4 日生存率、離乳率などの各指標にもフェドラチニブに関連した影響は認められなかった。

離乳前の出生児の一般状態にフェドラチニブに関連した変化はいずれの用量でも認められなかった。

死亡児及び哺育 4 日の同腹児調整の剖検でフェドラチニブに関連した所見は認められなかった。

母動物の剖検ではフェドラチニブに関連した肉眼所見は認められなかった。

正向反射及び開眼の発達指標並びに瞳孔反射にフェドラチニブの影響は認められなかった。

F1 雄の亀頭包皮分離及び F1 雌の膣開口へのフェドラチニブの影響はいずれの用量でも認められなかった。

活動性（自発運動量及び聴覚性驚愕反応）並びに Water M-Maze による学習・記憶へのフェドラチニブの影響は、いずれの用量でも認められなかった。

離乳後の成熟期間評価に選択した F1 動物は全例が計画剖検まで生存し、F1 の成熟及び妊娠期間中にフェドラチニブに関連した一般状態の変化はみられなかった。

F1 の性周期、交尾率、受胎及び妊娠率にフェドラチニブの影響はみられず、F1 の帝王切開所見にも影響は認められなかった。F1 雌雄の剖検でもフェドラチニブに関連した肉眼所見は認められなかった。

以上より、妊娠 F0 ラットにフェドラチニブを 3、10 及び 30 mg/kg の用量で妊娠 6 日から分娩及び哺育 20 日まで経口投与した結果、30 mg/kg で妊娠中母動物の体重増加量が軽度に減少した。高用量 30 mg/kg 群の F1 出生児では、離乳前の雌雄、離乳後から成熟期の雄で体重の低値が認められた。発育分化及び行動発達にはフェドラチニブの影響は認められなかった。また、F1 の交尾率、交配率及び受胎率並びに妊娠 13 日の帝王切開所見のいずれにもフェドラチニブの影響はみられなかった。これらの結果に基づき、F0 母動物の一般毒性に関する NOAEL は 30 mg/kg、F1 出生児の発達に関する NOEL は 10 mg/kg と考えられた。

6.4 新生児を用いた試験

実施していない。

7 局所刺激性試験

実施していない。

8 その他の毒性試験

8.1 *不純物A のラット 1 ヵ月間投与試験

*不純物A （[redacted]、別名 [redacted]）の安全性確認のためのラット 1 ヵ月間投与試験を実施した（試験番号 TSA1485）。

Crl:CD(SD)ラット（6～7 週齢、1 群雌雄各 15 匹）に*不純物A を[redacted]%含有するフェドラチニブを 0（媒体対照）、5、30 及び 80 mg/kg の用量（投与容量 5 mL/kg）で 1 日 1 回 28 日間、強制経口投与した。28 日間の投与期間終了後に回復群（1 群雌雄各 5 匹）を 4 週間休薬し、回復性を評価した。

評価項目は、生死、一般状態、体重、摂餌量、眼科学的検査、臨床検査（血液学的検査、凝固検査、血液生化学的検査、尿検査）、剖検、器官重量及び病理組織学的検査とした。

主な所見を Table 8.1-1 に示す。

Table 8.1-1: *不純物A のラット 28 日間投与安全性確認試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
30	Body Weight ↓ Body weight (up to −7% and −5% in males and females, respectively) Food Consumption ↓ Mean food consumption (males) Clinical Pathology

＊新薬承認情報提供時に置き換え

Table 8.1-1: *不純物A のラット 28 日間投与安全性確認試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
	Hematology Day 29 ↓ Reticulocytes ↑ Platelets (males) ↓ Large unstained cells; ↑ neutrophils (females); ↑ monocytes After recovery, reticulocyte, platelet, and large unstained cell counts returned to ranges of concurrent controls. The following additional changes were noted: ↓ RBC (males) ↓ WBC, neutrophils, lymphocytes and monocytes (females)
	Clinical Chemistry Day 29 ↑ ALP (females) ↓ Cholesterol, bilirubin (females) All changes reversed after recovery (Day 57/58)
	Urine Chemistry ↓ Creatinine (−10%; males)
	Organ Weights (relative) ↓ Spleen and thymus
	Histopathology Day 29 Bone marrow – hypocellularity Lymphoid tissues – mesenteric lymph node (lymphocytic depletion); thymus (lymphocytic necrosis) Stomach (non-glandular) – submucosal edema Recovery – all above findings resolved; submucosal edema present in non-glandular stomach of 1 male recovery animal
80	Mortality 1 female (Day 21); cause of death was not determined
	Clinical Signs Piloerection, salivation, partly closed eyelids, and coat thinning; incoordination and noisy respiration (females); trend toward reversibility
	Body Weight ↓ Body weight (up to −17% and −11% in males and females, respectively) and body weight gain (up to −59% and −109% in males and females, respectively); trend toward reversibility
	Food Consumption ↓ Mean food consumption (males)
	Clinical Pathology
	Hematology Day 29 ↓ Reticulocytes ↑ Platelets ↓ Large unstained cells; ↓ WBC and lymphocytes (females); ↑ neutrophils; ↑ monocytes (males) After recovery, reticulocyte, platelet, and large unstained cell counts returned to ranges of concurrent controls. The following additional changes were noted: ↓ RBC (males) ↓ WBC, neutrophils, lymphocytes and monocytes (females)
	Coagulation ↓ Fibrinogen (males; reversed during recovery)

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Table 8.1-1: *不純物A のラット 28 日間投与安全性確認試験の主な所見

Dose (mg/kg)	Main Fedratinib-related Effects
	Clinical Chemistry Day 29 ↑ AST, ALT, ALP, potassium ↓ Cholesterol; ↓ bilirubin (females) All changes reversed after recovery (Day 57/58)
	Urine Chemistry
	↓ Creatinine
	↑ Protein
	All changes reversed after recovery (Day 57/58)
	Organ Weights (relative) ↑ Liver (females), heart and lung ↓ Spleen and thymus
	Histopathology Day 29 Bone marrow – hypocellularity Liver – hepatocellular hypertrophy and hypertrophy of bile duct epithelium Lymphoid tissues – thymus (lymphocytic necrosis and cortical atrophy); spleen (lymphocytic depletion); mesenteric lymph nodes (lymphocytic depletion) Lungs – alveolar macrophage accumulation Heart – myocardial degeneration & necrosis Stomach (non-glandular) – submucosal edema and squamous cell hyperplasia Muscle – degeneration and necrosis of quadriceps (females) Recovery (Day 57/58) – Microscopic findings reversible after 4-week recovery period

↑ = increased; ↓ = decreased.
Source: Study TSA1485

主な毒性の標的器官は、骨髄、肝臓（胆管）、リンパ組織（胸腺、脾臓、腸間膜リンパ節）、肺、心臓、前胃及び骨格筋であった。4 週間の休薬期間後、標的器官への影響には回復性が認められた。本試験の NOAEL は 5 mg/kg と判断された。

*不純物A の安全性確認のための 1 ヵ月間投与試験の結果は、フェドラチニブの 1 ヵ月間投与毒性試験の結果と同様であった。両試験での標的器官は、骨髄、胆管、リンパ組織（胸腺、脾臓、腸間膜リンパ節）、肺及び心臓であった。本試験では、前胃及び骨格筋にも変化が認められたほか、肝細胞肥大も認められた。いずれの試験でも休薬期間後、標的器官への影響は概して回復性を示した。

8.2 光毒性

3T3 細胞を用いた in vitro 試験を実施した（試験番号 PHV0056）。3T3 細胞をフェドラチニブ、陽性対照（塩酸クロルプロマジン）及び媒体に 1 時間曝露した。媒体は、フェドラチニブには酸性水、塩酸クロルプロマジンにはエタノールを用いた。3T3 細胞の半数について紫外線 A（UVA）を照射し、残りの半数は遮光した。照射終了後、照射細胞及び非照射細胞を 18～22 時間培養（37°C、5% CO_2）し、ニュートラルレッド染色により細胞生存率を評価した。

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相対生存率をフェドラチニブ（又は陽性対照）の吸光度と媒体対照の吸光度との比較により算出し、UVA 非照射 IC50（ニュートラルレッド取込 50%阻害濃度）と UVA 照射 IC50 との比較により光刺激係数（PIF）を算出した。

本試験系において、フェドラチニブは光毒性を示さなかった。

8.3 *不純物A の遺伝毒性試験

*不純物A は，5 種の *Salmonella typhimurium* 菌株（TA1535、TA1537、TA98、TA100 及び TA102）を用いた Ames 試験で代謝活性化 S9 の存在下及び非存在下のいずれでも最大濃度 5000 µg/plate まで遺伝毒性を示さなかった（試験番号 HIS1952）。また、ヒトリンパ球を用いた染色体異常試験（試験番号 MAF0133）でも、代謝活性化の存在下及び非存在下で最高濃度 10 mM（2950 µg/mL）まで、又は推奨される細胞毒性を示す濃度において、構造異常を有する細胞数の統計学的に有意な増加及び生物学的意義のある増加は認められなかった。以上の結果に基づき、*不純物A は染色体異常誘発性を有しないと結論された。

8.4 潜在的遺伝毒性不純物の安全性評価

In silico による変異原性予測で変異原性の警告が示された不純物のうち文献データがないものについては、単離した化合物を Ames 試験により評価した。変異原性が確認された不純物については、ICH M7「潜在的発がんリスクを低減するための医薬品中 DNA 反応性（変異原性）不純物の評価及び管理ガイドライン」の毒性学的懸念の閾値（TTC）に基づく許容摂取量 [redacted] µg/day から、フェドラチニブの最大 1 日投与量 400 mg における許容 1 日曝露量（PDE）は [redacted] ppm と算出された。

8.4.1 既知の遺伝毒性不純物

[redacted] はフェドラチニブの製造過程で生成される可能性があり、Ames 試験で変異原性を示すことが知られている[7]。既知の遺伝毒性不純物であることから遺伝毒性をさらに評価せず、ICH M7(R1) ガイドラインに基づいて TTC [redacted] µg/day を適用した。

8.4.2 警告構造を有するが遺伝毒性が確認されていない潜在的遺伝毒性不純物

以下に示すフェドラチニブの各不純物について *Salmonella typhimurium* の 5 種の菌株（TA1535、TA1537、TA98、TA100 及び TA102）を用いた Ames 試験を実施した結果、S9 mix 代謝活性化の存在下及び非存在下で変異原性は認められなかった（試験番号HIS2151、HIS2148、HIS2149、HIS2154、HIS2155、HIS2161、HIS2175 及び HIS2173）。これらの試験結果を Table 8.4.2-1 に示す。Ames 試験の最高用量は、ICH S2(R1)「医薬品の遺伝毒性試験及び解釈に関するガイダンス」に記載されている用量に基づき選択した。

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Table 8.4.2-1: フェドラチニブに関連する潜在的遺伝毒性不純物の Ames 試験

Impurity	Source	In vitro test/results	Study No.
*不純物B	Process intermediate	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2151
*不純物C	Process intermediate	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2148
*不純物D	Process intermediate	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2149
*不純物E	Process impurity	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2154
*不純物F	[redacted]	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2155
*不純物I	Process impurity	Ames: negative no GTI up to 500 µg/plate (+/− S9)	HIS2161
*不純物G	Process impurity	GLP Ames: negative no GTI up to 250 µg/plate (+/− S9)	HIS2175
*不純物H	[redacted]	GLP Ames: negative no GTI up to 5000 µg/plate (+/− S9)	HIS2173

GLP = regulatory assays conducted according to ICH S2(R1) guideline and under good laboratory practices.

9 考察及び結論

フェドラチニブの毒性評価として、一般毒性試験［単回投与試験並びにマウス（最長 1 ヵ月間）、ラット（最長 6 ヵ月間）及びイヌ（最長 9 ヵ月間）の反復投与試験］、in vitro 及び in vivo 遺伝毒性試験、ラット受胎能試験、ラット及びウサギ胚・胎児発生に関する試験、ラット出生前及び出生後の発生並びに母体の機能に関する試験、トランスジェニックマウス 6 ヵ月間がん原性試験、in vitro 光毒性試験を実施した。

マウスにおける主な標的器官は、骨髄（低形成）、リンパ組織（脾臓、胸腺、GALT 及び腸間膜リンパ節のリンパ球数減少・壊死）、腎臓（尿細管の変性・壊死）、胃（前胃の潰瘍・炎症、腺肥大）、膣（不完全性周期）、横隔膜筋（変性、壊死、炎症）及び膀胱（移行上皮空胞化）であった。

ラットの 1 ヵ月間及び 6 ヵ月間投与試験での主な標的器官は、骨髄（低形成）及び肝臓（胆管肥大及び壊死）であった。病理学的変化は、リンパ系組織（胸腺、脾臓及び腸間膜リンパ節の萎縮、腸間膜リンパ節の組織球浸潤）、肺（組織球浸潤）及び心臓（心筋症、心筋の変性・壊死）にも認められた。

イヌの 1 ヵ月間及び 9 ヵ月間投与試験での主な標的器官は、骨髄（低形成及び骨髄前駆細胞の増加、無効造血と一致）及び肝臓（胆管上皮の肥大及び増殖）であった。9 ヵ月間投与試験では、脾臓及び肝臓に骨髄前駆細胞の浸潤も認められた。この骨髄前駆細胞の増加は、骨髄・血液の回復傾向を

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示唆する所見と考えられた。1ヵ月間及び9ヵ月間投与試験で死亡例がみられた用量では、肝臓へのより重度な影響として、胆管上皮の変性・再生及び壊死（散発的に線維化及び炎症を伴う）、肝細胞壊死、クッパー細胞過形成、胆汁うっ滞及び動脈壁壊死が認められた。また、9 ヵ月間投与試験の状態悪化例では、食道及び胃の潰瘍及び慢性活動性炎症に関連した内出血、ストレス及び食欲不振に関連したリンパ組織のリンパ球減少などが認められた。さらに肺炎・膿瘍も両試験の死亡例で認められたが、骨髄及びリンパ系器官の変化に伴う免疫系への影響による二次的変化と考えられた。

フェドラチニブの遺伝毒性について、細菌を用いた Ames 試験、CHO 細胞を用いた in vitro 染色体異常試験、ラットを用いた in vivo 小核試験により評価した結果、いずれの試験でも陰性であった。

トランスジェニックマウスを用いた 6 ヵ月間投与がん原性試験では、フェドラチニブ投与に起因すると考えられる腫瘍発生は認められなかった。

ラットを用いた受胎能及び初期胚発生に関する試験では、いずれの用量においても、性周期、交尾行動、交配所要日数、受胎能、妊娠率などの生殖能指標にフェドラチニブの影響は認められなかった。

胚・胎児発生への影響に関する試験の結果、ラットにおいて胎児体重の減少や骨格変異（頚椎神経弓過剰骨化中心）などの胚・胎児発生への影響が認められた。ウサギにおいては、胚・胎児発生へのフェドラチニブの影響を示唆する所見は認められなかった。

ラットを用いた出生前及び出生後の発生に関する試験において、母動物の体重増加抑制、F1 出生児の体重及び摂餌量の減少がみられた。F1 出生児の身体発育分化及び行動、交尾率、生殖能、 受胎能指数及び妊娠 13 日の帝王切開所見にはフェドラチニブの投与による影響は認められなかった。

3T3 細胞を用いた in vitro 光毒性試験でフェドラチニブは光毒性を示さなかった。

*不純物A の安全性確認のためのラット 1 ヵ月間投与試験を実施した結果、標的器官はフェドラチニブの 1 ヵ月間投与毒性試験と概して同様であったが、さらに前胃の粘膜下浮腫及び扁平上皮過形成、大腿四頭筋壊死並びに肝細胞肥大が認められた。しかしながら、本試験では *不純物A を含有しないフェドラチニブ対照群を設定しなかったため、これらの所見が不純物に起因するか明らかでない。

1、6 及び 9 ヵ月間投与試験で認められたフェドラチニブに関連する主な影響及びこれらの影響に関連する曝露量を Table 9-1、Table 9-2 及び Table 9-3 に要約する。

Table 9-1: フェドラチニブのマウス 1 ヵ月間投与試験で認められた主な影響及びその曝露量（雌雄合算平均値）

Dose (mg/kg)	100	200	400/300[d]
Exposures[a]			
Cmax (ng/mL)[b]	3840	5620	NA[e]

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Table 9-1: フェドラチニブのマウス 1 ヵ月間投与試験で認められた主な影響及びその曝露量（雌雄合算平均値）

Dose (mg/kg)	100	200	400/300[d]
AUC(0-24h) (ng•h/mL)[b]	32600	84100	NA[e]
Main Effects[c]			
Lymphoid atrophy/necrosis (spleen, thymus, lymph nodes and/or GALT)	+	+	+
Bone marrow hypoplasia	−	+	+
Kidney (degeneration/necrosis renal tubules)	−	−	+
Stomach (non-glandular ulceration/ inflammation; glandular hypertrophy)	−	−	+
Mortality (main study)	2/12	6/12	12/12

[a] Average of male and female values.
[b] Cmax and AUC: Day 28.
[c] Effect (+) observed or (−) not observed.
[d] 400 mg/kg for 2 days followed by 300 mg/kg for 5 days; or 300 mg/kg for 4 days (Days 4-7).
[e] Not applicable; due to mortality.
Source: Study DDC0131

Table 9-2: フェドラチニブのラット 1 ヵ月間及び 6 ヵ月間投与試験で認められた主な影響及びその曝露量（雌雄合算平均値）

Dose (mg/kg)	5	3	30	10	80	30
	1-month	6-month	1-month	6-month	1-month	6-month
Exposures[a]						
Cmax (ng/mL)[b]	20	8	262	78	600	279
AUC(0-24h) (ng•h/mL)[b]	150	77	2860	721	8830	3760
Main Effects[c]						
Lymphoid tissue atrophy (spleen, thymus, lymph nodes)	−	−	+	−	+	−
Bone marrow hypoplasia	−	−	+	−	+	+
Bile duct (epithelial cell) hypertrophy and/or necrosis[d]	−	−	−	−	+	+
Stomach (non-glandular submucosal edema, squamous cell hyperplasia)	−	−	−	−	+[e]	−
Heart cardiomyopathy (degeneration/necrosis)	−	−	−	−	+	−
Skeletal muscle (degeneration/necrosis)	−	−	−	−	+[e]	−

Table 9-2: フェドラチニブのラット 1 ヵ月間及び 6 ヵ月間投与試験で認められた主な影響及びその曝露量（雌雄合算平均値）

Dose (mg/kg)	5	3	30	10	80	30
	1-month	6-month	1-month	6-month	1-month	6-month
Lung (histiocytic infiltration)	−	−	+	−	+	+
Mortality	−	−	−	−	−	−

[a] Average of male and female values.
[b] Cmax and AUC: Day 28 for 4-week study; Day 180 for 6-month study.
[c] Effect (+) observed or (−) not observed.
[d] Associated with increased liver enzymes and/or bilirubin.
[e] Only observed in 28-day rat study with SM3 impurity.
Source: Study TX-[redacted]-101348-074F; Study TX[redacted]-101348-044; Study TSA1485

Table 9-3: フェドラチニブのイヌ 1 ヵ月間及び 9 ヵ月間投与試験で認められた主な影響及びその曝露量（雌雄合算平均値）

Dose (mg/kg)	2	2	5	6	10	40/30	20/15
	1-month	9-month	1-month	9-month	1-month	1-month	9-month
Exposures[a]							
Cmax (ng/mL)[b]	21	20	105	97	244	1790	296
AUC(0-24h) (ng•h/mL)[b]	205	188	1040	1020	2760	18 600	3360
Main Selected Effects[c]							
Lymphoid tissue atrophy (spleen, thymus, lymph nodes)	+	−	+	−	+	+	+
Bone marrow							
hypoplasia	+	−	+	−	+	+	+
increased myeloid progenitor cells[d]	−	−	−	−	−	−	+
Liver[e]							
bile duct (epithelial cell) hypertrophy, proliferation, degeneration/regeneration, and/or necrosis	−	−	−	+	+	+	+
Mortality	−	−	−	−	−	6/10	9/20

[a] Average of male and female values.
[b] Cmax and AUC: Day 28 for 4-week study; Day 271 for 9-month study.
[c] Effect (+) observed or (−) not observed.
[d] Increased myeloid progenitor cells also observed in liver and spleen.
[e] Associated with increased liver enzymes and/or bilirubin.
Source: Study TX-[redacted]-101348-075F; Study TX-[redacted]-101348-046A

マウスでは、フェドラチニブの曝露量は用量比をわずかに上回って増加した。雌の曝露量は雄よりもわずかに高かった。ラットでは、1 ヵ月間及び 6 ヵ月間投与試験での曝露量は用量比を上回って増

加した。軽微から中程度の蓄積がみられ、曝露量は雌の方が雄よりわずかに高かった。イヌでは、1 ヵ月間及び 9 ヵ月間投与試験での曝露量は用量比を上回って増加し、軽微から中程度の蓄積がみられた。1 ヵ月間投与試験での雌雄の曝露量は同程度であったが、高用量の 30 mg/kg では雌の方が雄より低かった。9 ヵ月間投与試験では、雌の曝露量は雄と同程度又はわずかに低かった。

9.1 動物とヒトの曝露量比較

ラットを用いた 6 ヵ月間及びイヌを用いた 9 ヵ月間反復投与毒性試験、マウスを用いた 6 ヵ月間がん原性試験、ラット及びウサギを用いた生殖発生毒性試験における最高用量での曝露量と、臨床試験でのヒト曝露量を比較した（Table 9.1-1）。

Table 9.1-1: 動物とヒトとの曝露量比

Type of study	Species	Dose (mg/kg)	Cmax (ng/mL)	AUC(0-24h) (ng•h/mL)	Animal/Human Exposure Ratio[a]	
					Cmax	AUC(0-24h)
Repeat-dose toxicity	Rat (M)[b]	30[c]	200	3080	0.083	0.075
	Rat (F)[b]		357	4440	0.148	0.107
	Dog (M)[d]	15[c]	246	2880	0.102	0.070
	Dog (F)[d, g]		345	3840	0.143	0.093
Carcinogenicity	Mouse (M)	30[c]	1280	12700	0.530	0.307
	Mouse (F)		2130	22100	0.881	0.535
Reproductive function (fertility and mating)	Rat (M)[e]	30[h]	188	2910	0.078	0.070
	Rat (F)[f]		342	3840	0.141	0.093
Embryo-fetal developmental toxicity	Rat	30	294	3250	0.122	0.079
	Rabbit	30	501	2320	0.207	0.056
Pre- and post-natal developmental toxicity	Rat[f]	30	342	3840	0.141	0.093

[a] Values are animal/human ratios. Ratios are based on mean human exposure after repeated administration of 400 mg once daily: AUC(0-24h) = 41316 ng•h/mL, Cmax = 2417 ng/mL in adult Japanese subjects (popPK study FEDR-MPK-004).
[b] 6-month repeat-dose toxicity study in rats.
[c] Highest doses administered in mice, rats and dogs (6- or 9-month study).
[d] 9-month repeat-dose toxicity study in dogs.
[e] PK parameters estimated based on Day 90 toxicokinetic data from 6-month general toxicity study (Study TX-[redacted]-101348-044).
[f] PK parameters estimated based on Day 28 toxicokinetic data from 28-Day general toxicity study (Study TX-[redacted]-101348-074F).
[g] Represents combined mean values for samples from Day 246 and Day 271.
[h] Highest doses tested.
Source: Study TX-[redacted]-101348-044; Study TX-[redacted]-101348-046A; Study TX-[redacted]-101348-074F; Study CAR0168; Study FER0500; Study TX-[redacted]-101348-057; Study TX-[redacted]-101348-058A; Study DPN0371

動物とヒトとの曝露量比較から、ヒト曝露量はラット及びイヌの最高曝露量を上回ることが示された。予定臨床推奨用量の 400 mg を投与した日本人患者における定常状態 AUC は、ラット 6 ヵ月間及びイヌ 9 ヵ月間投与試験での AUC より約 9 倍～14 倍高い。

ヒト曝露量より高い曝露量が得られたマウス 1 ヵ月間投与試験の Cmax はヒトの約 4～5 倍（AUC は 0.6～0.8 倍）であったが、これらの曝露量では死亡例が発生した。また、ラット及びイヌの 1 ヵ月間試験では、ヒト曝露量はラットの最高 AUC より約 4 倍高く、イヌの最高 AUC の約 1.4 倍高い。

これらの比較から、ヒトは動物よりもフェドラチニブの毒性に対する感受性が低いことが示唆される。動物とヒトとの種差の要因については現時点では明らかでなく、ヤヌスキナーゼ 2（JAK2）を介する細胞内情報伝達を惹起する受容体の様々な組織における分布や、同受容体に関連するフェドラチニブの作用若しくは標的外作用に関する感受性の種差など、多くの原因が考えられる。

10 参考文献

[1] Nambiar PR, Turnquist SE, Morton D. Spontaneous tumor incidence in rasH2 mice: review of internal data and published literature. Toxicol Pathol. 2012; 40:614-23.

[2] Paranjpe M, Reem H, Shah S, et al. Historical Control Data of Spontaneous Tumors in Transgenic CByB6F1-Tg(HRAS)2Jic (tg.rasH2) Mice. Int J Toxicol. 2013; 32:48-57.

[3] Takaoka M, Sehata S, Maejima T, et al. Interlaboratory comparison of short-term carcinogenicity studies using CB6F1-rasH2 transgenic mice. Toxicol Pathol. 2003; 31:191-99.

[4] Kanno H, Tanakamaru Z, Ishimura Y, et al. Historical background data in CB6F1-Tg-rasH2 mice and CB6F1-nonTg-rasH2 mice over a 26-week experimental period. J Toxicol Pathol. 2003; 16:267-74.

[5] Mitsumori K, Koizumi H, Nomura T, et al. Pathological Features of Spontaneous and Induced Tumors in Transgenic Mice Carrying a Human Prototype c-Ha-ras Gene Used for Six-Month Carcinogenicity Studies. Toxicol Pathol. 1998; 26:520-31.

[6] Morton D, Alden CL, Roth AJ, et al. The Tg rasH2 mouse in cancer hazard identification. Toxicol Pathol. 2002; 30:139-46.

[7] Simmon VF, Kauhanen K, Tardiff RG. Mutagenic activity of chemicals identified in drinking water. Dev Toxicol Environ Sci. 1977; 2:249-58.

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1 毒性試験：一覧表

Table 2.6.7.1 Toxicology **Overview** **Test Article:** Fedratinib[a]

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses[b] (mg/kg)	GLP Compliance	Testing Facility	Study No.	Location in Dossier
Single-/repeat-dose Toxicity	Rat/Sprague Dawley	Oral gavage	1 day or 10 days	Single rising dose: 200, 400, 600, and 1000 10-day: 100 or 125	Yes	[redacted]	TX-[redacted]-101348-061	4.2.3.1-1
	Dog/Beagle	Oral gavage	1 day or 10 days	Single rising dose: 100, 150, 200, and 300 10-day: 50 or 75	Yes	[redacted]	TX-[redacted]-101348-062	4.2.3.1-2
Repeat-dose Toxicity	Mouse/BALB/c	Oral gavage (BID)	10 days	0, 200, 400, or 800 (0, 100, 200, or 400 BID)	No	[redacted]	PH-[redacted]-101348-023	4.2.3.2-1
	Rat/Sprague Dawley	Oral gavage	14 days	0, 35, 70, or 140	No	[redacted]	PH-[redacted]-101348-023	4.2.3.2-1
	Mouse/CByB6 F1	Oral gavage	29 days	0, 100, 200, or 400/300[c]	Yes	[redacted]	DDC0131	4.2.3.2-3
	Rat/Sprague Dawley	Oral gavage	28 days	0, 5, 30, or 80	Yes	[redacted]	TX-[redacted]-101348-074F	4.2.3.2-4
	Rat/Sprague Dawley	Oral gavage	3 or 6 months	0, 3, 10, or 30	Yes	[redacted]	TX-[redacted]-101348-044	4.2.3.2-5
	Dog/Beagle	Oral gavage	28 days	0, 2, 5, 10, or 40/30[d]	Yes	[redacted]	TX-[redacted]-101348-075F	4.2.3.2-6
	Dog/Beagle	Oral gavage	3, 6, or 9 months	0, 2, 6, or 20/15[e]	Yes	[redacted]	TX-[redacted]-101348-046A	4.2.3.2-7

Table 2.6.7.1 Toxicology Overview (Continued) **Test Article:** Fedratinib[a]

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses[b] (mg/kg)	GLP Compliance	Testing Facility	Study No.	Location in Dossier
Geno-toxicity	*S. typhimurium* and *E. coli*	In vitro	48 to 72 hr	1.5 to 5000 µg/plate	Yes	[redacted]	TX-[redacted]-101348-084	4.2.3.3.1-1
	CHO cells	In vitro	4 and 20 hr	Preliminary: 0.5 to 5000 µg/mL Main: 0.625 to 45 µg/mL	Yes	[redacted]	TX-[redacted]-101348-050	4.2.3.3.1-2
	Rat/Sprague Dawley	Oral gavage	single dose	0, 5, 30, or 80	Yes	[redacted]	TX-[redacted]-101348-051	4.2.3.3.2-1
Carcino-genicity	Mouse/ CByB6F1-Tg(HRAS)2Jic	Oral gavage	26 weeks	0, 3, 10, or 30	Yes	[redacted]	CAR0168	4.2.3.4.2-1
Reproductive and Developmental Toxicity								
FEED	Rat/Sprague Dawley	Oral gavage	M: 91 to 142 days F: 22 to 27 days	0, 3, 10, or 30	Yes	[redacted]	FER0500	4.2.3.5.1-1
DRF for EFD	Rat/Sprague Dawley	Oral gavage	GD 6 to 17	0, 3, 10, 30, or 80	No	[redacted]	TX-[redacted]-101348-055	4.2.3.5.2-1
EFD	Rat/Sprague Dawley	Oral gavage	GD 6 to 17	0, 3, 10, or 30	Yes	[redacted]	TX-[redacted]-101348-057	4.2.3.5.2-2
DRF for EFD	Rabbit/New Zealand White	Oral gavage	GD 6 to 18	0, 3, 10, 30, or 80	No	[redacted]	TX-[redacted]-101348-056	4.2.3.5.2-3
EFD	Rabbit/New Zealand White	Oral gavage	GD 6 to 18	0, 3, 10, or 30	Yes	[redacted]	TX-[redacted]-101348-058A	4.2.3.5.2-4
PPND	Rat/Sprague Dawley	Oral gavage	GD 6 to LD 20	0, 3, 10, or 30	Yes	[redacted]	DPN0371	4.2.3.5.3-1

Table 2.6.7.1 Toxicology **Overview (Continued)** **Test Article:** Fedratinib[a]

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses[b] (mg/kg)	GLP Compliance	Testing Facility	Study No.	Location in Dossier
Other Toxicity Studies								
Impurity Qualification (*不純物A)	Rat/Sprague Dawley	Oral gavage	28 days	0, 5, 30, or 80	Yes	[redacted]	TSA1485	4.2.3.7.6-1
Phototoxicity	BALB/c 3T3 mouse fibroblasts	In vitro	1 hr	up to 1000 µg/mL	Yes	[redacted]	PHV0056	4.2.3.7.7-1
Expert Panel Report[f]	Dog/Beagle	Oral gavage	28 days and 9 months	up to 40	No	[redacted]	EXP0092	4.2.3.7.7-2
*不純物B	*S. typhimurium*	In vitro	48 hr	*不純物B : 5 to 5000 µg/plate	Yes	[redacted]	HIS2151	4.2.3.7.6-2
*不純物C	*S. typhimurium*	In vitro	48 hr	*不純物C : 5 to 5000 µg/plate	Yes	[redacted]	HIS2148	4.2.3.7.6-3
*不純物D	*S. typhimurium*	In vitro	48 hr	*不純物D : 5 to 5000 µg/plate	Yes	[redacted]	HIS2149	4.2.3.7.6-4
*不純物E	*S. typhimurium*	In vitro	48 hr	*不純物E 1.6 to 5000 µg/plate	Yes	[redacted]	HIS2154	4.2.3.7.6-5
*不純物F	*S. typhimurium*	In vitro	48 hr	*不純物F : 5 to 5000 µg/plate	Yes	[redacted]	HIS2155	4.2.3.7.6-6
*不純物I	*S. typhimurium*	In vitro	48 hr	*不純物I : 0.5 to 500 µg/plate	No	[redacted]	HIS2161	4.2.3.7.6-7
*不純物G	*S. typhimurium*	In vitro	48 hr	*不純物G : 0.25 to 250 µg/plate	Yes	[redacted]	HIS2175	4.2.3.7.6-8
*不純物H	*S. typhimurium*	In vitro	48 hr	*不純物H : 0.16 to 5000 µg/plate	Yes	[redacted]	HIS2173	4.2.3.7.6-9
*不純物A	*S. typhimurium*	In vitro	48 hr	*不純物A : 5 to 5000 µg/plate	Yes	[redacted]	HIS1952	4.2.3.7.6-10

＊新薬承認情報提供時に置き換え

Table 2.6.7.1 Toxicology **Overview (Continued)** **Test Article:** Fedratinib[a]

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses[b] (mg/kg)	GLP Compliance	Testing Facility	Study No.	Location in Dossier
*不純物A	Cultured human peripheral blood lymphocytes	In vitro	3 hr or 20 hr	*不純物A : 2.5, 5, and 10 mM (3 hr) 0.23, 0.63, and 1.25 mM (20 hr)	No	[redacted]	MAF0133	4.2.3.7.6-11

BID = administered twice daily; CHO = Chinese hamster ovary; DRF = dose-range finding; EFD = embryo-fetal development; FEED = fertility and early embryonic development; GD = gestation day; LD = lactation day; PPND = pre-and postnatal development; +S9 = with metabolic activation; −S9 = without metabolic activation.

[redacted]

[a] Fedratinib (INN designation), the designation used in this document, is also known as SAR302503 (Sanofi group name) and TG101348 (TargeGen, Inc. name).
[b] Unless otherwise specified, for repeat-dose toxicity studies, the highest no observed adverse effect level is underlined.
[c] Due to mortality and toxicity observed at 400 mg/kg, the dose level was lowered to 300 mg/kg on Day 3 of the dosing phase.
[d] Due to unexpected toxicity, dosing was suspended in all dogs at 40 mg/kg from Days 12 to 15; on Day 16, dosing resumed at 30 mg/kg. On Day 24, dosing was terminated in the males but continued until Day 28 for the females at 30 mg/kg.
[e] Due to mortality noted at the 20 mg/kg level, the dose level was decreased to 15 mg/kg beginning on Day 26.
[f] Expert panel review of the 28-day and 9-month studies in dogs (TX-[redacted]-101348-075F and TX-[redacted]-101348-046A, respectively).

2 トキシコキネティクス：トキシコキネティクス試験の一覧表

Table 2.6.7.2 Toxicokinetics **Overview of Toxicokinetics Studies** **Test Article:** Fedratinib

Type of Study	Species/Strain	Method of Administration	Doses (mg/kg)	GLP Compliance	Study No.	Location in Dossier
10-day repeat-dose toxicity study	Dog/Beagle	Oral gavage	50 or 75	Yes	TX-[redacted]-101348-062	4.2.3.1-2
29-day repeat-dose toxicity study	Mouse/CByB6F1	Oral gavage	0, 100, 200, or 400/300[a]	Yes	DDC0131	4.2.3.4.2-1
14-day repeat-dose toxicity study	Rat/Sprague Dawley	Oral gavage	0, 35, 70, or 140	No	PDM-[redacted]-101348-021	4.2.3.2-2
28-day repeat-dose toxicity study	Rat/Sprague Dawley	Oral gavage	0, 5, 30, or 80	Yes	TX-[redacted]-101348-074F	4.2.3.2-3
6-month repeat-dose toxicity study	Rat/Sprague Dawley	Oral gavage	0, 3, 10, or 30	Yes	TX-[redacted]-101348-044	4.2.3.2-4
28-day repeat-dose toxicity study	Dog/Beagle	Oral gavage	0, 2, 5, 10, or 40/30[b]	Yes	TX-[redacted]-101348-075F	4.2.3.2-5
9-month repeat-dose toxicity study	Dog/Beagle	Oral gavage	0, 2, 6, or 20/15[c]	Yes	TX-[redacted]-101348-046A	4.2.3.2-6
26-week carcinogenicity study	Mouse/CByB6F1-Tg(HRAS)2Jic	Oral gavage	0, 3, 10, or 30	Yes	CAR0168	4.2.3.4.2-1
Embryo-fetal development study	Rat/Sprague Dawley	Oral gavage	0, 3, 10, or 30	Yes	TX-[redacted]-101348-057	4.2.3.5.2-2
Embryo-fetal development study	Rabbit/New Zealand White	Oral gavage	0, 3, 10, or 30	Yes	TX-[redacted]-101348-058A	4.2.3.5.2-4

[a] Due to mortality and observed toxicity at 400 mg/kg, the dose level was lowered to 300 mg/kg on Day 3 of the dosing phase.
[b] Due to unexpected toxicity, dosing was suspended in all dogs at 40 mg/kg from Days 12 to 15; on Day 16, dosing resumed at 30 mg/kg. On Day 24, dosing was terminated in the males but continued for the females at 30 mg/kg.
[c] Due to mortality noted at the 20 mg/kg level, the dose level was decreased to 15 mg/kg beginning on Day 26.

3 トキシコキネティクス：トキシコキネティクス試験成績の一覧

Table 2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** Fedratinib

Daily Dose (mg/kg)	Steady-state AUC(0-t) (ng•h/mL)									Study Duration (Study No.)	Sample Collection
	Mouse		Rat		Rabbit		Dog		Human[a]		
	Male	Female	Male	Female	Male	Female	Male	Female			
2	-	-	-	-	-	-	226	183		28 days (TX-[redacted]-101348-075F)	Day 28
2	-	-	-	-	-	-	138	125		9 months (TX-[redacted]-101348-046A)	Day 26
2	-	-	-	-	-	-	138	116		9 months (TX-[redacted]-101348-046A)	Day 90
2	-	-	-	-	-	-	145	147		9 months (TX-[redacted]-101348-046A)	Day 181
2	-	-	-	-	-	-	184	192		9 months (TX-[redacted]-101348-046A)	Day 271
3	214	438	-	-	-	-	-	-		26 weeks (CAR0168)	Week 13
3	114	347	-	-	-	-	-	-		26 weeks (CAR0168)	Week 26
3	-	-	92.4	83.1	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 90
3	-	-	76.9	76.6	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 180
3	-	-	-	26.1	-	-	-	-		GD 6-17 (TX-[redacted]-101348-057)	GD 17
3	-	-	-	-	-	21.6	-	-		GD 6-18 (TX-[redacted]-101348-058A)	GD 18
5	-	-	145	155	-	-	-	-		28 days (TX-[redacted]-101348-074F)	Day 28
5	-	-	-	-	-	-	1200	882		28 days (TX-[redacted]-101348-075F)	Day 28
6	-	-	-	-	-	-	910	786		9 months TX-[redacted]-101348-046A)	Day 26
6	-	-	-	-	-	-	873	732		9 months (TX-[redacted]-101348-046A)	Day 90
6	-	-	-	-	-	-	1070	697		9 months (TX-[redacted]-101348-046A)	Day 181
6	-	-	-	-	-	-	1200	836		9 months (TX-[redacted]-101348-046A)	Day 271
6.7									41316	-	Day 28
10	1640	2610	-	-	-	-	-	-		26 weeks (CAR0168)	Week 13
10	2320	1600	-	-	-	-	-	-		26 weeks (CAR0168)	Week 26

Table 2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** Fedratinib

Daily Dose (mg/kg)	Steady-state AUC(0-t) (ng•h/mL)								Human[a]	Study Duration (Study No.)	Sample Collection
	Mouse		Rat		Rabbit		Dog				
	Male	Female	Male	Female	Male	Female	Male	Female			
10	-	-	-	-	-	-	3230	2290		28 days (TX-[redacted]-101348-075F)	Day 28
10	-	-	560	711	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 90
10	-	-	716	725	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 180
10	-	-	-	419	-	-	-	-		GD 6-17 (TX-[redacted]-101348-057)	GD 17
10	-	-	-	-	-	148	-	-		GD 6-18 (TX-[redacted]-101348-058A)	GD 18
20[b]/15	-	-	-	-	-	-	3150	1970		9 months (TX-[redacted]-101348-046A)	Day 26
20[b]/15	-	-	-	-	-	-	5790	3020		9 months (TX-[redacted]-101348-046A)	Day 90
20[b]/15	-	-	-	-	-	-	4920	3980		9 months (TX-[redacted]-101348-046A)	Day 181
20[b]/15	-	-	-	-	-	-	2880	3840[c]		9 months (TX-[redacted]-101348-046A)	Day 271
30	-	-	1870	3840	-	-	-	-		28 days (TX-[redacted]-101348-074F)	Day 28
30	-	-	2910	4300	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 90
30	-	-	3080	4440	-	-	-	-		6 months (TX-[redacted]-101348-044)	Day 180
30	-	-	-	3250	-	-	-	-		GD 6-17 (TX-[redacted]-101348-057)	GD 17
30	-	-	-	-	-	2320	-	-		GD 6-18 (TX-[redacted]-101348-058A)	GD 18
30	15400	22100	-	-	-	-	-	-		26 weeks (CAR0168)	Week 13
30	12700	22100	-	-	-	-	-	-		26 weeks (CAR0168)	Week 26
35	-	-	10600	-	-	-	-	-		14 days (PDM-[redacted]-101348-021)	Day 14
40[d]/30	-	-	-	-	-	-	30100	7170		28 days (TX-[redacted]-101348-075F)	Day 24[d]/28
50	-	-	-	-	-	-	27700	55400		10 days (TX-[redacted]-101348-062)	Day 10
70	-	-	27600	-	-	-	-	-		14 days (PDM-[redacted]-101348-021)	Day 14
75	-	-	-	-	-	-	-	e		10 days (TX-[redacted]-101348-062)	Day 10
80	-	-	7250	10400	-	-	-	-		28 days (TX-[redacted]-101348-074F)	Day 28

Table 2.6.7.3 Toxicokinetics **Overview of Toxicokinetics Data** **Test Article:** Fedratinib

Daily Dose (mg/kg)	Steady-state AUC(0-t) (ng•h/mL)										
	Mouse		Rat		Rabbit		Dog		Human[a]	Study Duration (Study No.)	Sample Collection
	Male	Female	Male	Female	Male	Female	Male	Female			
100	30800	34400	-	-	-	-	-	-		29 days (DDC0131)	Day 28
140	-	-	9848[f]	-	-	-	-	-		14 days (PDM-[redacted]-101348-021)	Day 1[f]
200	68200	100000	-	-	-	-	-	-		29 days (DDC0131)	Day 28
400/300[g,h]	26600	34200	-	-	-	-	-	-		29 days (DDC0131)	Day 7[g]

AUC(0-t) = area under the plasma concentration-time curve from the time of dosing (T0) to the last quantifiable value (postdose); - = not applicable.

[a] Human exposure is based on mean human exposure after repeated administration of 400 mg once daily: AUC(0-24h) = 41316 ng•h/mL, maximum plasma concentration (Cmax) = 2417 ng/mL in adult Japanese subjects (popPK study FEDR-MPK-004).

[b] Due to mortality at 20 mg/kg, the dose level was decreased to 15 mg/kg on Day 26.

[c] Value represents combined mean values for Days 246 and 271.

[d] Due to toxicity at 40 mg/kg, dosing was suspended on Days 12 to 15 and resumed on Day 16 at a lower dose of 30 mg/kg. On Day 24, dosing was terminated for males but continued until Day 28 for females.

[e] Female was euthanized on Day 9 (trough plasma concentration prior to euthanasia was 3900 ng/mL).

[f] Due to mortality, complete plasma TK parameters were not determined for Day 14. Day 1 values are presented for reference.

[g] Due to mortality and observed toxicity at 400 mg/kg, the dose level was lowered to 300 mg/kg on Day 3. After continued mortality and signs of toxicity, animals in this group were given a final dose on Day 6 (surviving toxicity animals) or 7 (surviving toxicokinetic animals). AUC(0-4h) since toxicokinetic sampling was 4 hours after dosing.

[h] 400 mg/kg for 2 days followed by 300 mg/kg for 5 days; or 300 mg/kg for 4 days (Days 4 to 7).

4 毒性試験：被験物質（バッチ毎）一覧

Table 2.6.7.4 Toxicology **Drug Substance** **Test Article:** Fedratinib

Batch/Lot No.	Purity (%)	Specified Impurities (%)					Study No.	Type of Study
		*不純物A	Related Impurities (HPLC, % w/w) [redacted]	[redacted]	[redacted]	Unspecified Impurity		
Proposed specification	> 99.7	≤ 0.15	≤ 0.10	≤ 0.10	≤ 0.10	Total Impurities ≤ 0.30		
4	-	-	-	-	-	-	PH-[redacted]-101348-023	10-day BID repeat-dose study in mice
13	-	-	-	-	-	-	PH-[redacted]-101348-023	14-day repeat-dose study in rats
14	-	-	-	-	-	-	PH-[redacted]-101348-023	14-day repeat-dose study in rats
P213-3-4 (T1010994)	99.0	-	-	-	-	Total impurities 0.8	TSA1485	28-day repeat-dose study in rats -*不純物A qualification
P213-6-3 (C1011063)	99.5	0.13	< 0.05	< 0.02	< 0.05	Total impurities 0.13	PHV0056	3T3 in vitro phototoxicity study
C1020897	99.7	< 0.02	-	0.05	0.06	Total impurities 0.11	DDC0131	29-day repeat-dose study in mice
							CAR0168	26-week carcinogenicity study
							DPN0371	Pre- and postnatal development in rats
C1020898	100.4	< 0.02	-	< 0.05	0.06	Total impurities 0.06	FER0500	Fertility study in rats
K-22	98.25	-	-	-	-	-	TX-[redacted]-101348-061	Single/Repeat-dose study in rats
							TX-[redacted]-101348-062	Single/Repeat-dose study in dogs

＊新薬承認情報提供時に置き換え

Table 2.6.7.4 Toxicology **Drug Substance** **Test Article:** Fedratinib

Batch/Lot No.	Purity (%)	Specified Impurities (%)					Study No.	Type of Study
		*不純物A	Related Impurities (HPLC, % w/w)			Unspecified Impurity		
K-37	99.44	-	-	-	-	-	TX-[redacted]-101348-062	Single/Repeat-dose study in dogs
P00188-019 (K-45)	99.16	-	-	-	-	-	TX-[redacted]-101348-084	Bacterial reverse mutation assay
P188-82-3 (K-47)	98.5	0.11	0.12	0.23	0.39	Total impurities 0.98	TX-[redacted]-101348-084	Bacterial reverse mutation assay
							TX-[redacted]-101348-074F	28-day repeat-dose study in rats
							TX-[redacted]-101348-075F	28-day repeat-dose study in dogs
							TX-[redacted]-101348-050	Chromosomal aberrations assay
							TX-[redacted]-101348-051	Micronucleus study in rats
							TX-[redacted]-101348-044	6-month repeat-dose study in rats
							TX-[redacted]-101348-046A	9-month repeat-dose study in dogs
							TX-[redacted]-101348-055	DRF EFD study in rats
							TX-[redacted]-101348-056	DRF EFD study in rabbits
							TX-[redacted]-101348-057	EFD study in rats
							TX-[redacted]-101348-058A	EFD study in rabbits

BID = administered twice daily; DRF = dose-range finding; EFD = embryo-fetal development; - = not assayed/reported or data unavailable.

＊新薬承認情報提供時に置き換え

5 単回投与毒性試験

Table 2.6.7.5 Single-dose Toxicity **Test Article:** Fedratinib

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Gender and No. Per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings (mg/kg)	Study No.
Rat/ Sprague Dawley	Oral gavage (0.5% methylcellulose)	Single dose: 200, 400, 600, or 1000 Repeat-dose: 100 or 125	Single dose: 3M/3F Repeat-dose:5M/5F	200	400	Single dose: 200: gasping 400: 1F euthanized moribund on Day 2; gross necropsy (lung discoloration) suggested possible aspiration of test article; ↓ BW gain; gasping and abnormally colored urine 600: diarrhea, few feces, soft and/or mucoid stools; ↓ BW (up to 14%); stomach foci, and discoloration of the mesenteric lymph node and stomach (F) 1000: diarrhea, few feces, soft and/or mucoid stools; ↓ BW (up to 12%); abnormal content of the GI tract, distended stomach, stomach foci, and discoloration of the liver and mesenteric lymph node Repeat-dose: 100: ↓ BW (≤2%); small thymus (F) 125: few feces, soft stools, diarrhea; ↓ BW (≤8%) and FC (−7% to −32% compared to values at 100 mg/kg); stomach foci and small thymus	TX-[redacted]-101348-061
Dog/ Beagle	Oral gavage (0.5% methylcellulose)	Single rising dose: 100, 150, 200, or 300 Repeat-dose: 50 or 75	Single rising dose: 1M/1F Repeat-dose: 1M/1F	50	Single rising dose: >300 Repeat-dose: 75	Single dose: ≥ 100: vomiting, diarrhea, mucoid and soft stools Repeat-dose: 50: vomiting, diarrhea; ↓ BW (−8% to −14% compared to Day 1) and ↓ FC; gallbladder	TX-[redacted]-101348-062

Table 2.6.7.5 Single-dose Toxicity **Test Article:** Fedratinib

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Doses (mg/kg)	Gender and No. Per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings (mg/kg)	Study No.
						and ileal discoloration and jejunal abnormal contents 75: both dogs euthanized moribund (M on Day 8 and F on Day 9); vomiting, diarrhea; ↓ activity, wobbly gait, abnormal posturing, and breathing abnormalities (M); head tilt, ↑ activity, vocalization, and impaired mobility (F); ↓ BW (−5% to −9% compared to Day 1) and ↓ FC; distension, foci, and abnormal content of the gallbladder; discoloration of the mediastinal and mesenteric lymph nodes; stomach foci and abnormal stomach content; and abnormal content in the small and large intestine Mortality at 75 mg/kg precluded the determination of toxicokinetic parameters; however, the trough plasma concentration of the female on the day of sacrifice was 3900 ng/mL. After 10 days of dosing at 50 mg/kg, the AUC(0-24h) and Cmax were 27700 ng•h/mL and 3800 ng/mL (M) and 55400 ng•h/mL and 5400 ng/mL (F), respectively. The trough plasma concentration level was 1200 ng/mL (F) and 1900 ng/mL (M)	

AUC(0-24h) = area under the plasma concentration-time curve from time 0 to 24 hours; BW = body weight; Cmax = maximum plasma concentration; FC = food consumption; GI = gastrointestinal; ↓ = decreased; ↑ = increased.

6 反復投与毒性試験：重要な試験以外の試験

Table 2.6.7.6 Repeat-dose Toxicity **Non-pivotal Studies** **Test Article:** Fedratinib

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender/ No. Per Group	NOAEL (mg/kg)	Noteworthy Findings (mg/kg)	Study No.
Mouse/ BALB/c	Oral gavage (50% propylene glycol/10% Tween 80)	10 days BID	0, 200, 400, or 800 (0, 100, 200, or 400 mg/kg BID)	5M	Not defined	200: mild piloerection (starting on Day 5) and hypoactivity (starting on Day 9) 400: piloerection, hypoactivity, and signs of dehydration (dry, dark colored feces) starting on Day 3; mortality on Day 5 (all found dead by Day 9); cause of death unknown (histopathology not conducted) 800: piloerection, hypoactivity, and signs of dehydration (dry, dark colored feces) starting on Day 2; mortality on Day 3 (all found dead by Day 4); cause of death unknown (histopathology not conducted)	PH-[redacted]-101348-023[a]
Rat/ Sprague Dawley	Oral gavage (0.5% methylcellulose/ 0.05% Tween 80)	14 days	0, 35, 70, or 140	6M	Not defined	35 and 70: no fedratinib related effects 140: mortality (4M) on Days 6, 9, 10, and 14. On Day 14, an additional death occurred during plasma sampling; this death may have been due to or exacerbated by the anesthesia (the animal was considered to have survived to termination on Day 14); hypoactivity starting on Day 5; ↓ BW (up to 17%); in surviving animals marked BM depletion in sternabrae, and marked white pulp depletion in the spleen. In femoral BM smears, cellular dysmaturation (↑ band neutrophils, ↓ segmented neutrophils, a marked ↓ in erythroid cells, a marked ↑ in the myeloid:erythroid ratio, and a relatively ↑ lymphoid cell count)	PH-[redacted]-101348-023[a]

BM = bone marrow; BW = body weight; BID = administered twice daily; NOAEL = no observed adverse effect level; ↓ = decreased; ↑ = increased.

[a] Two sub-chronic toxicology studies were performed at TargeGen for initial toxicological assessment of fedratinib in rodents. TOX-024 and TOX-025 were the study numbers assigned to the mouse and rat studies, respectively. One study report (PH-[redacted]-101348-023) was used to summarize the data from both studies.

7 反復投与毒性試験：重要な試験

Table 2.6.7.7A Repeat-dose Toxicity in Mice **Test Article:** Fedratinib

Report Title: 4-week Oral Gavage Toxicity and Toxicokinetic Study with SAR302503 in Wild Type CByB6F1-Tg(HRAS)2Jic Mice

Species/Strain: Mouse/Wild Type RasH2 (CByB6F1-Tg[HRAS]2Jic)

Duration of Dosing: 29 days

Study No.: DDC0131

Initial Age: 8 to 9 weeks

Duration of Postdose: Not applicable

Location in Dossier: 4.2.3.2-3

Date of First Dose: [redacted], 20[redacted]

Method of Administration: Oral gavage

Vehicle/Formulation: 0.5% methylcellulose

GLP Compliance: Yes

Special Features: None

No Observed Adverse Effect Level: Not determined

Daily dose (mg/kg)		**0 (Control)**		**100**		**200**		**400/300[a]**	
No. of animals		**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Toxicokinetics:									
Day 7	No. evaluated	0	0	0	0	0	0	12	12
AUC(0-24h) (ng•h/mL)		NA	NA	NA	NA	NA	NA	26600[b,c]	34200[b,c]
Cmax (ng/mL)		NA	NA	NA	NA	NA	NA	9620[c]	12000[c]
Day 28	No. evaluated	6	6	15	18	14	17	0	0
AUC(0-24h) (ng•h/mL)		NA	NA	30800	34400	68200	100000	NA	NA
Cmax (ng/mL)		NA	NA	3200	4470	5020	6220	NA	NA
Noteworthy findings[d]:									
TK: No. found dead/sacrificed moribund		0	0	3[e]	0	4[e]	1[e]	13[e]	6[e]
Main: No. found dead/sacrificed moribund		0	0	1[e]	1[e]	3[e]	3[e]	6[e]	6[e]

Table 2.6.7.7A Repeat-dose Toxicity in Mice **Study No. DDC0131 (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**100**		**200**		**400/300[a]**	
No. of animals		**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Mortality evaluation	No. evaluated	0	0	1	1	3	3	6	6
Gross pathology									
Spleen									
Discolored and/or small		NA	NA	-	-	-	-	4	-
Stomach									
Discolored		NA	NA	-	-	-	-	3	1
Raised area		NA	NA	-	-	-	2	1	-
Histopathology									
GALT/Peyer's patch									
Depletion, lymphocytes									
	Minimal to moderate	NA	NA	-	-	-	-	3	4
Necrosis, lymphocytes									
	Slight	NA	NA	-	-	-	-	-	1
Kidney									
Degeneration/necrosis, tubule, corticomedullary junction									
	Minimal to moderate	NA	NA	-	-	-	-	6	6
Mesenteric lymph nodes									
Depletion, lymphocytes									
	Minimal to slight	NA	NA	-	-	-	-	4	4
Necrosis, lymphocytes									
	Minimal	NA	NA	-	-	-	1	1	1

Table 2.6.7.7A Repeat-dose Toxicity in Mice **Study No. DDC0131 (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**100**		**200**		**400/300[a]**	
No. of animals	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Bone marrow, femur								
Hypocellular								
Minimal to moderate	NA	NA	-	-	1	-	6	5
Bone marrow, sternum								
Hypocellular								
Minimal to moderate	NA	NA	-	-	1	-	6	5
Muscle, diaphragm								
Degeneration/necrosis/inflammation								
Minimal to moderate	NA	NA	-	-	-	-	3	4
Spleen								
Depletion, lymphocyte								
Minimal to moderate	NA	NA	-	-	-	-	6	6
Hematopoiesis, extramedullary, decreased								
Minimal to moderate	NA	NA	-	-	-	-	4	5
Necrosis, lymphocytes, increased								
Minimal to slight	NA	NA	-	-	-	-	2	1
Stomach (glandular)								
Hypertrophy, mucin cell, fovea								
Minimal to slight	NA	NA	-	-	-	-	1	5
Stomach (nonglandular)								
Ulcer/inflammation								
Slight to marked	NA	NA	-	-	-	-	4	1

Table 2.6.7.7A Repeat-dose Toxicity in Mice **Study No. DDC0131 (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**100**		**200**		**400/300[a]**	
No. of animals		**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Thymus									
Depletion, lymphocytes									
	Minimal to marked	NA	NA	2	-		-		4
Necrosis, lymphocyte									
	Minimal to moderate	NA	NA	1	-	2	-	1	1
Urinary bladder									
Vacuolation, transitional cell									
	Minimal to slight	NA	NA	-	-	3	2	-	-
Vagina									
Asynchronous estrous cycle		NA	NA	NA	-	NA	-	NA	4
Diestrus		NA	NA	NA	-	NA	-	NA	-
Estrus		NA	NA	NA	-	NA	-	NA	1
Metestrus		NA	NA	NA	-	NA	-	NA	1
Dosing phase evaluation	No. evaluated	6	6	6	6	6	6	0	0
Noteworthy findings[d]:									
Clinical observations		-	-	-	-	-	-	NA	NA
Body weight[f]									
Day 15		-	21.9 g	-	-	-	5.0%	NA	NA
Day 22		28.0 g	22.4 g	-	-	3.6%	8.9%*	NA	NA
Day 29		28.4 g	22.9 g	-	-	4.9%	7.9%	NA	NA
Food consumption[f]									
Day 8 to 15		-	32.3 g	-	-	-	8.0%*	NA	NA
Day 15 to 22		-	26.2 g	-	-	24.0%*	16.0%*	NA	NA

Table 2.6.7.7A Repeat-dose Toxicity in Mice **Study No. DDC0131 (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**100**		**200**		**400/300[a]**	
No. of animals		**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Day 22 to 29		30.8 g	32.1 g	-	-	16.6%	10.0%	NA	NA
Hematology[f] (Day 30)									
Red blood cells (10^6/μL)		10.2	9.83	-	-	−10.0%*	−16.4%	NA	NA
Hemoglobin (g/dL)		15.5	15.7	-	-	−10.3%*	−15.3%	NA	NA
Hematocrit (%)		55.5	55.8	-	-	−5.2%	−12.7%	NA	NA
Platelets (10^3/μL)		907	808	78.5%*	67.6%	157%*	31.9%	NA	NA
Lymphocytes (10^3/μL)		2.30	2.21	−19.6%	−22.6%	−55.7%*	−41.6%	NA	NA
Large unstained cells (10^3/μL)		0.02	0.05	−50.0%	-	−50.0%	−80.0%	NA	NA
Serum chemistry		-	-	-	-	-	-	-	-
Organ weights[f] (Day 30)	No. evaluated	6	6	5	5	3	3	0	0
Heart									
Absolute wt		-	0.1344 g	-	-	-	22.2%*	NA	NA
Relative to body wt ratio		-	0.6035	-	-	-	12.6%*	NA	NA
Relative to brain wt ratio		-	26.7606	-	-	-	23.3%*	NA	NA
Spleen									
Absolute wt		0.0767 g	0.0903 g	-	−27.1%*	−28.7%	−33.7%*	NA	NA
Relative to body wt ratio		0.2776	0.4050	-	−27.2%*	−31.3%	−38.7%*	NA	NA
Relative to brain wt ratio		15.3798	17.9652	-	−25.2%*	−29.9%*	−33.0%*	NA	NA
Thymus									
Absolute wt		0.0426 g	-	-	-	−39.4%*	-	NA	NA
Relative to body wt ratio		0.1544	-	-	-	−41.7%*	-	NA	NA
Relative to brain wt ratio		8.5508	-	-	-	−40.8%*	-	NA	NA

Table 2.6.7.7A Repeat-dose Toxicity in Mice Study No. DDC0131 (Continued)

Daily dose (mg/kg)		0 (Control)		100		200		400/300[a]	
No. of animals		**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M: 6**	**F: 6**
Gross pathology	No. evaluated	6	6	5	5	3	3	0	0
Stomach									
Raised area		0	-	-	-	1	-	NA	NA
Histopathology	No. evaluated	6	6	5	5	3	3	0	0
Thymus									
Depletion, lymphocytes									
	Slight	0	-	-	-	1	-	NA	NA
Urinary bladder									
Vacuolation, transitional cell									
	Minimal	0	0	-	-	2	2	NA	NA

AUC(0-24h) = AUC from time 0 to 24 hours; Cmax = maximum plasma concentration; GALT = gut-associated lymphoid tissue; NA = not applicable; wt = weight; TK = toxicokinetic; - = no noteworthy findings; * = statistically significant at $p \leq 0.05$ (ANOVA/Dunnett's test; rank-transformed data for spleen absolute and relative values in males, thymus relative values in males).

[a] Due to mortality and observed toxicity at 400 mg/kg, the dose level was lowered to 300 mg/kg on Day 3. After continued mortality and signs of toxicity, animals in this group were given a final dose on Day 6 (surviving toxicity animals) or Day 7 (surviving toxicokinetic animals).

[b] AUC(0-4h) since toxicokinetic sampling was only done for 4 hours after dosing.

[c] 400 mg/kg for 2 days followed by 300 mg/kg for 5 days; or 300 mg/kg for 4 days (Days 4 to 7).

[d] Only treatment-related findings are presented.

[e] Death of 1M at 400 mg/kg (Day 2) was attributed to slight gastric ulcer/inflammation; the remaining animals euthanized or found moribund cause of death was undetermined histologically but were considered test article-related. In addition, TK animals (3M at 100 mg/kg, 4M/1F at 200 mg/kg, 13M/6F at 400/300 mg/kg) were found dead or euthanized during the study. In general, clinical signs observed in moribund animals in all dose groups included hypoactivity, hunched posture, ataxia, squinted eyes, labored respiration, rough hair coat, and hypothermia.

[f] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences. (N = 6 or less; main study animals).

Table 2.6.7.7B Repeat-dose Toxicity in Rats **Test Article:** Fedratinib

Report Title: A 28-day Toxicity Study of TG101348 Administered by Oral Gavage to Rats with a 14-day Recovery Period

Species/Strain: Rat/Sprague Dawley
Duration of Dosing: 28 days
Study No.: TX-[redacted]-101348-074F

Initial Age: Approximately 8 weeks
Duration of Postdose: 14 days
Location in Dossier: 4.2.3.2-4

Date of First Dose: [redacted], 20[redacted]
Method of Administration: Oral gavage

Vehicle/Formulation: 0.5% methylcellulose
GLP Compliance: Yes

Special Features: None

No Observed Adverse Effect Level: Not determined

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
Toxicokinetics:	No. evaluated	6	6	9	9	9	9	9	9
Day 1									
AUC(0-24h) (ng•h/mL)		NA	NA	127	177	1450	3670	2830	7550
Cmax (ng/mL)		NA	NA	15.6	23.4	153	376	257	618
Day 28									
AUC(0-24h) (ng•h/mL)		NA	NA	145	155	1870	3840	7250	10400
Cmax (ng/mL)		NA	NA	19.3	20.7	182	342	509	691
Noteworthy findings[b]**:**									
No. evaluated		15	15	10	10	10	10	15	15
No. found dead/sacrificed moribund		0	0	0	0	0	0	0	1[a]
Body weight[d]									
Day 28		410 g	272 g	−2.5%	-	−3.9%	−6.6%*	−12.6%**	−10.8%**
Food consumption		-	-	-	-	-	-	-	-

Table 2.6.7.7B Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-074F (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
Clinical observations[c]									
Hypothermia (cool to touch)		0/0	0/0	-	-	-	-	2/2	3/3
Salivation prior to dose		0/0	0/0	-	-	-	1/1	2/1	9/5
Salivation		0/0	0/0	-	-	-	-	2/1	5/4
Ophthalmology		-	-	-	-	-	-	-	-
Hematology		-	-	-	-	-	-	-	-
Serum chemistry[d] (Day 29)									
Aspartate aminotransferase (IU/L)		85	106	-	-	-	-	119%**[e]	172%**[e]
Alanine aminotransferase (IU/L)		26	33	-	-	25.1%*	44.5%	43.5%**	60.9%*
Alkaline phosphatase (IU/L)		-	82	-	-	-	-	-	207%**[e]
Gamma glutamyl transferase (IU/L)		-	1.34	-	-	-	-	-	108%**
Bilirubin (mg/dL)		-	0.60	-	-	-	18.6%*	-	33.0%**
Phosphorus (mg/dL)		7.2	6.4	8.3%*	16.7%**	15.1%**	26.8%**	24.1%**	41.2%**
Urinalysis		-	-	-	-	-	-	-	-
Organ weights[d] (Day 29)	No. evaluated	10	10	10	10	10	10	10	9
Prostate									
Absolute wt		0.90 g	NA	-	NA	-	NA	−20.1%**	NA
Relative to brain wt ratio		41.5	NA	-	NA	-	NA	−18.1%*	NA
Seminal vesicles									
Absolute wt		1.62 g	NA	-	NA	-	NA	−29.9%**	NA
Relative to brain wt ratio		75.0	NA	-	NA	-	NA	−27.8%*	NA
Salivary gland									
Absolute wt		0.67 g	0.45 g	-	-	-	−13.4*	−18.4**	−26.3**

Table 2.6.7.7B Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-074F (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
Relative to brain wt ratio		31.2	22.0	-	-	-	−12.6*	−16.4**	−25.4**
Spleen									
Absolute wt		0.71 g	0.54 g	-	-	-	−17.8**	−38.1**	−48.6**
Relative to brain wt ratio		32.7	26.5	-	-	-	−17.3**	−36.2**	−48.2**
Thymus									
Absolute wt		0.42 g	0.37 g	-	-	-	−21.5*	−44.8**	−59.7**
Relative to brain wt ratio		19.6	18.3	-	-	-	−21.3*	−43.5**	−59.4**
Lung									
Absolute wt		-	1.10 g	-	-	-	-	-	34.1**[e]
Relative to brain wt ratio		-	54.2	-	-	-	-	-	35.1**[e]
Gross pathology	No. evaluated	10	10	10	10	10	10	10	9
Small thymus		0	0	-	-	-	-	3	7
Histopathology (Day 29)									
Bone marrow (sternum)	No. evaluated	9	10	10	10	10	10	10	10
Hypoplasia									
	Minimal to moderate	0	0	-	-	1	8	9	10
Heart	No. evaluated	10	10	0	10	0	10	10	10
Cardiomyopathy									
	Minimal to mild	-	0	-	-	-	-	-	7
Spleen	No. evaluated	10	10	10	10	10	10	10	10
Lymphoid atrophy									
	Mild	0	0	-	-	-	2	10	9

Table 2.6.7.7B Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-074F (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
Liver	No. evaluated	10	10	10	10	10	10	10	10
Bile duct epithelial cell necrosis - focal									
	Minimal	-	0	-	-	-	-	-	1
Bile duct epithelial cell necrosis - multifocal									
	Minimal	-	0	-	-	-	-	-	2
Periductular fibrosis - focal									
	Mild	-	0	-	-	-	-	-	1
Periductular fibrosis - multifocal									
	Mild	-	0	-	-	-	-	-	2
Mononuclear cell inflammation									
	Minimal	-	0	-	-	-	-	-	3
Diffuse hypertrophy of bile duct epithelial cells									
	Mild	0	0	-	-	-	-	10	10
Mixed cell infiltrates (decreased)									
	Minimal	9	10	-	-	-	-	5	0
Lung	No. evaluated	10	10	10	10	10	10	10	10
Histiocytic infiltrates									
	Minimal to mild	0	0	-	-	1	6	2	9
Eosinophilic material									
	Mild	-	0	-	-	-	-	-	9
Thymus	No. evaluated	10	10	10	10	10	10	10	10
Lymphoid atrophy									
	Minimal to mild	0	0	-	-	2	1	10	10

Table 2.6.7.7B Repeat-dose Toxicity in Rats Study No. TX-[redacted]-101348-074F (Continued)

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 15**	**F: 15**
Mesenteric LN	No. evaluated	10	10	10	10	10	10	10	10
Histiocytosis									
	Minimal to moderate	0	0	-	-	-	-	10	9
Erythrophagocytosis									
	Mild to moderate	0	-	-	-	-	-	3	-
Lymphoid atrophy									
	Minimal to mild	0	0	-	-	-	1	8	8
Postdose evaluation	No. evaluated	5	5	0	0	0	0	5	5
Body weight gain (%)[d]									
Days 35 to 42		25 g	-	NA	NA	NA	NA	43%	-
Histopathology									
Lungs									
Histiocytic infiltrates									
	Minimal to mild	-	0	NA	NA	NA	NA	-	5
Spleen									
Hematopoiesis									
	Minimal to mild	-	0	NA	NA	NA	NA	-	5

AUC(0-24h) = AUC from time 0 to 24 hours; Cmax = maximum plasma concentration; LN = lymph node; NA = not applicable; wt = weight; - = no noteworthy findings; * = statistically significant at $p < 0.05$; ** = statistically significant at $p < 0.01$ (ANOVA/Dunnett-test).

[a] Euthanized on Day 23; not related to administration with fedratinib (gavage accident).

[b] Only treatment-related findings are presented.

[c] Total incidence/no. of animals.

[d] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences.

[e] Kruskal-Wallis/Dunn's test.

Table 2.6.7.7C Repeat-dose Toxicity in Rats **Test Article:** Fedratinib

Report Title: A 6-month Toxicity Study of TG101348 Administered by Oral Gavage to Rats

Species/Strain: Rat/Sprague Dawley **Duration of Dosing:** 3 or 6 months **Study No.:** TX-[redacted]-101348-044

Initial Age: Approximately 8 weeks **Duration of Postdose:** Not applicable **Location in Dossier:** 4.2.3.2-5

Date of First Dose: [redacted], 20[redacted] **Method of Administration:** Oral gavage

Vehicle/Formulation: 0.5% methylcellulose **GLP Compliance:** Yes

Special Features: None

No Observed Adverse Effect Level: 10 mg/kg

Daily dose (mg/kg)		**0 (Control)**		**3**		**10**		**30**	
Total no. of animals on study		**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
No. evaluated (3 months)		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
No. evaluated (6 months)		**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Toxicokinetics:	No. evaluated	0	0	12	12	12	12	12	12
Day 1									
AUC(0-24h) (ng•h/mL)		NA	NA	42.5	66.3	363	680	1430	3210
Cmax (ng/mL)		NA	NA	7.03	9.65	62.1	86.5	150	302
Day 90									
AUC(0-24h) (ng•h /mL)		NA	NA	92.4	83.1	560	711	2910	4300
Cmax (ng/mL)		NA	NA	10.4	9.72	58.2	60.7	188	349
Day 180									
AUC(0-24h) (ng•h/mL)		NA	NA	76.9	76.6	716	725	3080	4440
Cmax (ng/mL)		NA	NA	6.25	10.6	87.8	67.8	200	357
Noteworthy findings[a]:									
No. evaluated		30	30	30	30	30	30	30	30
No. found dead/sacrificed moribund[b]		0	1	0	0	1	0	1	2

Table 2.6.7.7C Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-044 (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Total no. of animals on study	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Clinical observations	-	-	-	-	-	-	-	-
Body weight[c]								
Day 90	591 g	304 g	-	-	-	-	−12.0%*	−3.3%
Day 182	679 g	347 g	-	-	-	-	−11.2%*	−7.6%
Body weight gain[c]								
Day 85 to 90	12 g	3 g	-	-	-	-	−25.0%	−33.3%
Day 174 to 182	7 g	6 g	-	-	-	-	−71.4%	-
Food consumption (g/animal/day)[c]								
Day 1 to 8	32	-	-	-	-	-	−8.5%*	-
Day 29 to 36	33	-	-	-	-	-	−7.5%	-
Day 57 to 64	34	-	-	-	-	-	−7.4%*	-
Day 85 to 90	32	-	-	-	-	-	−4.9%	-
Ophthalmology	-	-	-	-	-	-	-	-
Hematology[c]								
Platelets (10^3 cmm)								
Day 91	1140	-	-	-	-	-	26.6%*	-
Day 183	1160	1040	-	-	-	-	20.4%*	20.2%*
Leukocytes (10^3 cmm)								
Day 91	5.79	4.23	-	-	-	-	−22.7%	−26.4%
Day 183	7.74	-	-	-	-	-	−7.6%	-
Lymphocytes (10^3 cmm)								
Day 91	4.00	3.21	-	-	-	−21.5%	−43.8%*	−40.8%
Day 183	5.82	3.26	-	-	-	-	−21.5%*[d]	−12.5%

Table 2.6.7.7C Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-044 (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**3**		**10**		**30**	
Total no. of animals on study		**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Erythrocytes (10^6 cmm)									
Day 183		8.43	7.38	-	-	-	-	−4.4%*	−4.4%*
Hematocrit (%)									
Day 183		41.3	38.8	-	-	-	-	−2.1%	−5.7%*
Hemoglobin (g/dL)									
Day 183		14.4	13.8	-	-	-	-	−1.8%	−7.2%*
Serum chemistry[c]									
Aspartate aminotransferase (IU/L)									
Day 91		-	103	-	-	-	-	-	33.9%*[d]
Alanine aminotransferase (IU/L)									
Day 91		-	34	-	-	-	-	-	27.9%
Alkaline phosphatase (IU/L)									
Day 91		-	47	-	-	-	-	-	81.9%*[d]
Day 183		-	27	-	-	-	-	-	119%*[d]
Gamma glutamyl transferase (IU/L)									
Day 91		-	0.07	-	-	-	-	-	71.6%
Day 183		-	0.60	-	-	-	-	-	14.8%*[d]
Coagulation		-	-	-	-	-	-	-	-
Urinalysis		-	-	-	-	-	-	-	-
Organ weights[c] (Day 91)	No. evaluated	10	10	10	10	10	10	9	9
Salivary gland									
Absolute wt		0.82 g	0.48 g	−5.7%	−4.8%	−9.7%	−9.1%	−18.7%*	−12.2%
Relative to brain wt ratio		36.1	23.4	−4.3%	−4.9%	−9.1%	−6.8%	−16.9%*	−13.6%*

Table 2.6.7.7C Repeat-dose Toxicity in Rats **Study No. TX-[redacted]-101348-044 (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**3**		**10**		**30**	
Total no. of animals on study		**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Spleen									
Absolute wt		0.84 g	0.50 g	-	-	-	-	−24.8%*	−19.0%*
Relative to brain wt ratio		36.9	24.3	-	-	-	-	−23.5%*	−20.7%*
Thymus									
Absolute wt		0.321 g	0.229 g	−17.0%	-	−24.2%*	-	−28.8%*	−5.0%
Relative to brain wt ratio		14.2	11.2	−15.8%	-	−24.5%*	-	−27.0%*	−8.0%
Organ weights[c] (Day 183)	No. evaluated	20	19	20	20	19	20	20	19
Salivary gland									
Absolute wt		0.83 g	0.51 g	-	-	-	-	−14.8%*	−14.9%*
Relative to brain wt ratio		35.3	24.2	-	-	-	-	−14.1%*	−14.2%*
Spleen									
Absolute wt		1.00 g	0.61 g	-	-	-	-	−26.0%*	−32.1%*
Relative to brain wt ratio		42.2	29.0	-	-	-	-	−25.2%*	−31.4%*
Gross pathology (Day 91)		-	-	-	-	-	-	-	-
Histopathology (Day 91)[e]									
Bone marrow (sternum)	No. evaluated	10	10	0	10	0	10	10	10
Hypoplasia									
	Minimal	-	0	NA	-	NA	-	-	2
Liver	No. evaluated	10	10	0	10	0	10	10	10
Hypertrophy; epithelium; bile duct									
	Minimal	-	0	NA	-	NA	-	-	4
Gross pathology (Day 183)		-	-	-	-	-	-	-	-

Table 2.6.7.7C Repeat-dose Toxicity in Rats Study No. TX-[redacted]-101348-044 (Continued)

Daily dose (mg/kg)		**0 (Control)**		**3**		**10**		**30**	
Total no. of animals on study		**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Histopathology (Day 183)[e]									
Bone marrow (sternum)	No. evaluated	20	20	0	20	1	20	20	20
Hypoplasia									
	Minimal	-	0	NA	-	-	-	-	7
Liver	No. evaluated	20	20	20	20	20	20	20	20
Hypertrophy; epithelium; bile duct									
	Minimal	0	0	-	-	-	-	8	20
Necrosis; bile duct; epithelium									
	Minimal	-	0	-	-	-	-	-	1

AUC(0-24h) = AUC from time 0 to 24 hours; Cmax = maximum plasma concentration; NA = not applicable; wt = weight; - = no noteworthy findings; * = statistically significant at $p < 0.05$ (ANOVA/Dunnett-test).

[a] Only treatment-related findings are presented.

[b] None were considered test article-related.

[c] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences.

[d] Kruskal-Wallis/Dunn's test.

[e] Scheduled euthanasia and moribund euthanasia.

Table 2.6.7.7D Repeat-dose Toxicity in Dogs **Test Article:** Fedratinib

Report Title: A 28-day Toxicity Study of TG101348 Administered by Oral Gavage to Dogs with a 14-day Recovery Period

Species/Strain: Dog/Beagle **Duration of Dosing:** 28 days **Study No.:** TX-[redacted]-101348-075F

Initial Age: Approximately 6 months **Duration of Postdose:** 14 days **Location in Dossier:** 4.2.3.2-6

Date of First Dose: [redacted], 20[redacted] **Method of Administration:** Oral gavage

Vehicle/Formulation: 0.5% methylcellulose **GLP Compliance:** Yes

Special Features: None

No Observed Adverse Effect Level: Not determined

Daily dose (mg/kg)	**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Toxicokinetics: No. evaluated	5	5	3	3	3	3	3	3	5	5
Day 1										
AUC(0-24h) (ng•h/mL)	NA	NA	86.0	77.4	550	439	1230	1000	4970	3730
Cmax (ng/mL)	NA	NA	8.8	10.6	69.7	62.1	178	166	756	529
Day 28										
AUC(0-24h) (ng•h/mL)	NA	NA	226	183	1200	882	3230	2290	30100[b,c]	7170
Cmax (ng/mL)	NA	NA	19.8	21.6	104	106	271	216	2800[b,c]	777
Noteworthy findings[d]:										
No. evaluated	5	5	3	3	3	3	3	3	5	5
No. found dead/sacrificed moribund	0	0	0	0	0	0	0	0	4[e]	2[f]
Clinical observations[g]										
Mucoid stools	0	5	1	2	4	4	3	20	18	14
Diarrhea	0	4	2	-	2	4	5	6	29	29
Soft stools	4	36	9	16	9	13	11	21	19	33
Vomitus	5	5	6	8	8	21	18	24	58	74
No feces/few feces	1	0	-	-	-	1	-	-	10	3

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)	**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Shallow breathing	0	0	-	-	-	-	-	-	1	2
Rapid breathing	0	0	-	-	-	-	-	-	1	3
Labored breathing	0	0	-	-	-	-	-	-	1	2
Rales	-	0	-	-	-	-	-	-	-	1
Decreased activity	0	0	-	-	-	-	1	3	17	12
Tremors	0	0	-	-	-	-	-	-	18	36
Wobbly gait	0	0	-	-	-	-	-	-	2	2
Abnormal posture	0	-	-	-	-	-	-	-	2	-
Impaired mobility	0	-	-	-	-	-	-	-	3	-
Thin appearance	0	-	-	-	-	-	-	-	5	-
Cool to touch	0	0	-	-	-	-	-	-	2	1
Dehydration	0	0	-	-	-	-	-	-	4	2
Partially closed eyelids	0	0	-	-	-	-	-	-	1	2
Ocular discharge	-	0	-	-	-	-	-	-	-	4
Salivation	5	0	-	-	-	-	-	-	78	157
Body weight[h]										
Day 15	8592 g	7215 g	-	-	-	-	−1.3%	−4.6%	−17.8%	−3.7%
Day 28	8972 g	7467 g	-	-	-	-	−1.9%	−4.8%	−24.4%	−5.4%
Body weight gain[h]										
Day 8 to 15	229 g	246 g	-	-	-	-	−108%	−37.9%	−274%*	−87.8%
Day 1 to 28	1451 g	1162 g	-	-	-	-	−36.6%	−31.6%	−83.3%	−12.2%
Food consumption (g/animal/day)[h]										
Week 2	300	-	-	-	-	-	-	-	−56.8%**	-

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)		**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals		**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Week 4		302	-	-	-	-	-	-	-	−79.5%**	-
Ophthalmology		-	-	-	-	-	-	-	-	-	-
Electrocardiography		-	-	-	-	-	-	-	-	-	-
Blood pressure parameters		-	-	-	-	-	-	-	-	-	-
Hematology[h]											
Day 14	No. evaluated	5	5	3	3	3	3	3	3	3	4
Day 29	No. evaluated	5	5	3	3	3	3	3	3	0	3
Red blood cells (10^6 cmm)											
Day 14		6.26	-	-	-	-	-	-	-	−20.8%**	-
Day 29		-	5.87	-	-	-	-	-	-	NA	−12.5%
Hemoglobin (g/dL)											
Day 14		14.7	-	-	-	-	-	-	-	−18.9%**	-
Day 29		-	13.8	-	-	-	-	-	-	NA	−13.0%*
Hematocrit (%)											
Day 14		42.9	-	-	-	-	-	-	-	−21.1%**	-
Day 29		-	39.7	-	-	-	-	-	-	NA	−13.5%*
Platelets (10^3 cmm)											
Day 14		314	-	-	-	-	-	-	-	−30.4%	-
Day 29		-	326	-	-	-	-	-	−34.4%*	NA	−32.9%*
White blood cells (10^3 cmm)											
Day 29		-	8.46	-	-	-	-	-	−9.8%	NA	−40.9%
Lymphocytes (10^3 cmm)											
Day 29		-	3.06	-	-	-	-	-	-	NA	−11.2%

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)	**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Neutrophils (10^3 cmm)										
Day 29	-	4.65	-	-	-	-	-	-	NA	−71.3%**
Eosinophils (10^3 cmm)										
Day 14	0.51	-	-	-	-	-	-	-	−85.7%	-
Day 29	-	0.19	-	-	-	-	-	-	NA	−53.9%
Basophils (10^3 cmm)										
Day 29	-	0.11	-	-	-	-	-	-	NA	−69.7%
Monocytes (10^3 cmm)										
Day 14	0.82	-	-	-	-	-	-	-	84.1%*	-
Day 29	-	0.42	-	-	-	-	-	-	NA	96.3%*
Reticulocytes (%RBC)										
Day 14	1.30	-	-	-	-	-	-	-	−75.7%**	-
Day 29	-	0.80	-	-	-	-	-	-	NA	70.4%
Macro platelets (slight)										
Day 14	0	-	-	-	-	-	-	-	2	-
Day 29	-	0	-	-	-	-	-	-	NA	2
Serum chemistry[h]										
Day 29 No. evaluated	5	5	3	3	3	3	3	3	0	3
Aspartate aminotransferase (IU/L)	-	28	-	78.8%**	-	45.0%*	-	73.4%**	NA	51.9%**
Alanine aminotransferase (IU/L)	30	26	-	-	-	-	172%*[i]	126%**	NA	66.0%*
Total protein (g/dL)	-	5.17	-	-	-	-	-	-	NA	−17.8%**
Albumin (g/dL)	-	2.99	-	-	-	-	-	-	NA	−19.4%**
Albumin/globulin ratio	-	1.38	-	-	-	-	-	-	NA	−4.5%

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)		0 (Control)		2		5		10		40/30[a]	
No. of animals		**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Urinalysis		-	-	-	-	-	-	-	-	-	-
Organ weights[h]	No. evaluated	3	3	3	3	3	3	3	3	0	1
Spleen											
Absolute wt		70.8 g	73.6 g	-	-	-	-	−20.6%	−45.9%	NA	−48.0%
Relative to body wt ratio		0.882	1.03	-	-	-	-	−24.2%	−42.9%	NA	−44.2%
Thymus											
Absolute wt		10.1 g	9.64 g	-	-	-	−38.6%	−30.9%	−21.2%	NA	−67.7%
Relative to body wt ratio		0.125	0.131	-	-	-	−34.9%	−33.8%	−15.3%	NA	−64.4%
Gross pathology		-	-	-	-	-	-	-	-	-	-
Histopathology											
Bone marrow (sternum)	No. evaluated	3	3	3	3	3	3	3	3	4	3
Hypoplasia											
	Minimal to marked	0	0	-	1	1	2	2	3	4	3
Epididymides	No. evaluated	3	NA	3	NA	3	NA	3	NA	4	NA
Aspermia		0	NA	-	NA	-	NA	-	NA	2	NA
Oligospermia											
	Mild	0	NA	-	NA	-	NA	-	NA	1	NA
Testis	No. evaluated	3	NA	3	NA	3	NA	3	NA	4	NA
Aspermia		0	NA	-	NA	-	NA	-	NA	1	NA
Degeneration - seminiferous tubule											
	Mild	0	NA	-	NA	-	NA	-	NA	3	NA
Oligospermia											
	Mild to moderate	0	NA	-	NA	-	NA	-	NA	2	NA

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)		0 (Control)		2		5		10		40/30[a]	
No. of animals		**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Thymus	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - lymphoid											
	Minimal to marked	0	0	2	-	1	1	2	-	4	3
Intestine - cecum	No. evaluated	3	3	3	3	3	3	3	2	4	3
Atrophy - glandular											
	Minimal to moderate	0	0	-	-	-	-	-	-	3	2
Intestine - colon	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - glandular											
	Minimal to moderate	0	0	-	-	-	-	-	-	4	2
Intestine - duodenum	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - glandular											
	Minimal to moderate	0	0	-	-	-	-	-	-	3	2
Intestine - ileum	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - glandular											
	Minimal to mild	0	0	-	-	-	-	-	-	2	1
Atrophy - Peyer’s patch											
	Minimal to mild	0	0	-	-	-	-	-	-	3	3
Intestine - rectum	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - glandular											
	Minimal to moderate	0	0	-	-	-	-	-	-	4	2
Spleen	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - lymphoid											
	Minimal to moderate	0	0	-	-	-	-	-	-	4	3

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)		0 (Control)		2		5		10		40/30[a]	
No. of animals		M: 5	F: 5	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 5	F: 5
Liver	No. evaluated	3	3	3	3	3	3	3	3	4	3
Hypertrophy - bile duct epithelium											
	Minimal to mild	0	0	-	-	-	-	2	-	4	3
Inflammation - mononuclear											
	Mild to moderate	0	-	-	-	-	-	-	-	2	-
Necrosis - bile duct - focal											
	Mild	-	0	-	-	-	-	-	-	-	1
Necrosis - bile duct - multifocal											
	Moderate	0	-	-	-	-	-	-	-	2	-
Necrosis - hepatocellular - focal											
	Minimal	0	-	-	-	-	-	-	-	1	-
Necrosis - hepatocellular - multifocal											
	Moderate	0	-	-	-	-	-	-	-	1	-
Hyperplasia - Kupffer cell											
	Mild to moderate	0	0	-	-	-	-	-	-	2	1
Fibrosis - multifocal											
	Moderate	0	-	-	-	-	-	-	-	2	-
Cholestasis											
	Moderate	0	-	-	-	-	-	-	-	1	-
Basophilic particulate material - bile duct epithelium											
	Minimal	0	0	-	-	-	-	-	-	2	1
Proliferation - small bile ducts - small caliber vessels and fibroblasts											
	Minimal to moderate	0	0	-	-	-	-	-	-	4	3

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)		**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals		**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Lung	No. evaluated	3	3	3	3	3	3	3	3	4	3
Bronchopneumonia - bacterial											
	Marked	0	0	-	-	-	-	-	-	1	2
Pleuritis											
	Marked	0	-	-	-	-	-	-	-	1	-
LN - mediastinal	No. evaluated	0	0	0	0	0	0	0	0	0	1
Atrophy - lymphoid											
	Moderate	NA	NA	NA	NA	NA	NA	NA	NA	NA	1
LN - mesenteric	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - lymphoid											
	Minimal to moderate	0	0	-	-	-	-	-	-	4	3
LN - mandibular	No. evaluated	3	3	3	3	3	3	3	3	4	3
Atrophy - lymphoid											
	Mild	-	0	-	-	-	-	-	-	-	1
Postdose evaluation											
Day 38 Sacrifice	No. evaluated	0	0	0	0	0	0	0	0	1	0
Day 43 Sacrifice	No. evaluated	2	2	0	0	0	0	0	0	0	2
Body weight[h]											
Day 42		-	7463 g	NA	NA	NA	NA	NA	NA	NA	2.8%
Body weight gain[h]											
Day 35 to 42		-	333 g	NA	NA	NA	NA	NA	NA	NA	10.7%
Hematology											
Day 38	No. evaluated	0	0	0	0	0	0	0	0	1	0

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)	**0 (Control)**		**2**		**5**		**10**		**40/30[a]**	
No. of animals	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Platelets (10^3 cmm)	NA	NA	NA	NA	NA	NA	NA	NA	672	NA
Reticulocytes (% RBC)	NA	NA	NA	NA	NA	NA	NA	NA	6.34	NA
Day 43[h] No. evaluated	2	2	0	0	0	0	0	0	0	2
Platelets (10^3 cmm)	-	336	NA	NA	NA	NA	NA	NA	NA	17.0%
Monocytes (10^3 cmm)	-	0.40	NA	NA	NA	NA	NA	NA	NA	6.3%
Reticulocytes (% RBC)	-	1.31	NA	NA	NA	NA	NA	NA	NA	120%
Organ weights[h] (Day 38/43)										
Spleen										
Absolute wt	99.6 g	70.1 g	NA	NA	NA	NA	NA	NA	−56.4%	−15.6%
Relative to body wt ratio	1.03	0.999	NA	NA	NA	NA	NA	NA	−44.8%	−16.2%
Thymus										
Absolute wt	14.5 g	-	NA	NA	NA	NA	NA	NA	−29.2%	-
Relative to body wt ratio	0.150	-	NA	NA	NA	NA	NA	NA	−10.3%	-
Gross pathology (Day 38/43) No. evaluated	2	2	0	0	0	0	0	0	1	2
Ileum - discoloration	-	1	NA	NA	NA	NA	NA	NA	-	2
Histopathology (Day 38/43)										
Bone marrow (sternum)										
Hyperplasia										
Minimal	0	0	NA	NA	NA	NA	NA	NA	1	2
Epididymides										
Aspermia	0	NA	NA	NA	NA	NA	NA	NA	1	NA
Liver										

Table 2.6.7.7D Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-075F (Continued)

Daily dose (mg/kg)	0 (Control)		2		5		10		40/30[a]	
No. of animals	**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Hypertrophy - bile duct epithelium										
Mild	0	0	NA	NA	NA	NA	NA	NA	1	2
Macrophage infiltration										
Moderate	-	0	NA	NA	NA	NA	NA	NA	-	1
Neutrophil infiltration										
Minimal	-	0	NA	NA	NA	NA	NA	NA	-	1
Moderate	0	0	NA	NA	NA	NA	NA	NA	1	1
Hematopoiesis										
Minimal	-	0	NA	NA	NA	NA	NA	NA	-	1
Mild	0	0	NA	NA	NA	NA	NA	NA	1	1
Proliferation: small bile ducts, small caliber cells and fibroblasts										
Mild	-	0	NA	NA	NA	NA	NA	NA	-	1
LN - mesenteric										
Atrophy - lymphoid										
Minimal	-	0	NA	NA	NA	NA	NA	NA	-	1
Spleen										
Atrophy - lymphoid										
Mild	0	0	NA	NA	NA	NA	NA	NA	1	2
Testis										
Aspermia	0	NA	NA	NA	NA	NA	NA	NA	1	NA
Degeneration - seminiferous tubule										
Mild	0	NA	NA	NA	NA	NA	NA	NA	1	NA

AUC(0-24h) = AUC from time 0 to 24 hours; A/G = albumin/globulin ratio; Cmax = maximum plasma concentration; LN = lymph node; NA = not applicable; wt = weight; - = no noteworthy findings; * = statistically significant at $p < 0.05$ (ANOVA/Dunnett-test); ** = statistically significant at $p < 0.01$ (ANOVA/Dunnett-test).

[a] Due to unexpected toxicity, dosing was suspended for all dogs at 40 mg/kg from Days 12 to 15; on Day 16, dosing resumed at 30 mg/kg. On Day 24, dosing was terminated in the males but continued until Day 28 for the females at 30 mg/kg.

[b] Day 24.

[c] n = 2.

[d] Only treatment-related findings are presented.

[e] Euthanized moribund on Days 12, 13, 22, and 26.

[f] Euthanized moribund on Days 11 and 25.

[g] Total number of incidences.

[h] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences. Statistical difference not performed when $n \leq 2$.

[i] Kruskal-Wallis/Dunn's test.

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Test Article:** Fedratinib

Report Title: A 9-month Toxicity Study of TG101348 Administered by Oral Gavage to Dogs

Species/Strain: Dog/Beagle **Duration of Dosing:** 3, 6, or 9 months **Study No.:** TX-[redacted]-101348-046A

Initial Age: Approximately 6 months **Duration of Postdose:** Not applicable **Location in Dossier:** 4.2.3.2-7

Date of First Dose: [redacted], 20[redacted] **Method of Administration:** Oral gavage

Vehicle/Formulation: 0.5% methylcellulose **GLP Compliance:** Yes

Special Features: None

No Observed Adverse Effect Level: 2 mg/kg

Daily dose (mg/kg)		**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
No. evaluated (3 months)		**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
No. evaluated (6 months)		**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
No. evaluated (9 months)		**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 4**	**F: 4**
Toxicokinetics:									
Day 1	No. evaluated	10	10	10	10	10	10	11	12
AUC(0-24h) (ng•h/mL)		NA	NA	75.6	83.4	495	430	4560	4450
Cmax (ng/mL)		NA	NA	8.36	9.82	58.9	64.4	428	427
Day 26	No. evaluated	10	10	10	10	10	10	9	7
AUC(0-24h) (ng•h/mL)		NA	NA	138	125	910	786	3150	1970
Cmax (ng/mL)		NA	NA	13.9	12.0	95.6	80.8	271	200
Day 90	No. evaluated	10	10	10	10	10	10	7	7
AUC(0-24h) (ng•h/mL)		NA	NA	138	116	873	732	5790	3020
Cmax (ng/mL)		NA	NA	10.9	9.59	73.0	65.7	395	279
Day 181	No. evaluated	7	7	7	7	7	7	6	7
AUC(0-24h) (ng•h/mL)		NA	NA	145	147	1070	697	4920	3980
Cmax (ng/mL)		NA	NA	11.3	13.3	88.1	64.0	346	334

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Day 271	No. evaluated	4	4	4	4	4	4	2	4
AUC(0-24h) (ng•h/mL)		NA	NA	184	192	1200	836	2880	3840[b]
Cmax (ng/mL)		NA	NA	16.0	23.3	117	76.4	246	345[b]
Noteworthy findings[c]:									
No. evaluated		10	10	10	10	10	10	10	10
No. found dead/sacrificed moribund[d]		0	0	0	0	0	0	6	3
Clinical signs[e]									
Vomiting		28	21	19	35	25	25	42	44
Soft stools		332	108	296	134	270	126	361	129
Mucoid material in cage/tray		8	9	10	14	9	8	15	12
Mucoid stools		121	87	179	111	79	52	157	103
Diarrhea		54	9	41	12	29	5	33	17
Body weight[f]									
Day 85		9370 g	-	-	-	-	-	−7.5%	-
Day 174		9982 g	-	-	-	-	-	−10.7%	-
Day 271		10700 g	-	-	-	-	-	−18.5%	-
Food consumption (g/animal/day)[f]									
Day 37		337	-	-	-	-	-	−53.8%*	-
Day 71		356	-	-	-	-	-	−21.5%	-
Ophthalmology		-	-	-	-	-	-	-	-
Electrocardiography		-	-	-	-	-	-	-	-
Hematology[f]									
Reticulocytes (10^9/L)									

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Day 24	55.4	-	32.7%	-	31.2%	-	-	-
Day 91	34.1	37.5	33.1%	-	127%*[g]	37.7%	128%*[g]	114%*
Day 182	43.1	56.9	-	-	63.0%*	-	59.5%*	32.8%
Day 272	28.3	-	-	-	90.0%*	-	138%*	-
White blood cells (10^3/cmm)								
Day 24	9.35	9.09	-	-	−11.7%	−6.4%	−19.4%	−10.6%
Day 91	9.30	10.7	-	-	−5.5%	−15.6%	−16.4%	−25.3%*
Day 182	9.28	9.15	-	-	−6.5%	10.2%	−28.0%	−18.5%
Day 272	10.2	8.22	-	-	−13.1%	−14.4%	−24.3%	−25.4%
Neutrophils (10^3/cmm)								
Day 24	5.38	5.40	-	-	−16.5%	−9.9%	−40.8%*	−25.6%
Day 91	5.43	6.87	-	-	−8.1%	−26.1%	−34.6%	−43.2%*
Day 182	5.46	5.66	-	-	-	-	−46.7%*	−32.9%*[g]
Day 272	6.42	5.06	-	-	−15.5%	−24.6%	−38.6%	−46.8%*
Eosinophils (10^3/cmm)								
Day 24	0.23	0.20	-	-	−14.9%	−31.1%	−63.4%*	−30.8%
Day 91	0.24	0.18	-	-	−20.9%	-	−57.8%*	−5.8%
Day 182	0.27	0.26	-	-	−9.5%	−14.5%	−51.2%	−43.0%
Day 272	0.37	0.25	-	-	−19.5%	−13.3%	−16.8%	-
Red blood cells (10^6/cmm)								
Day 24	6.15	6.22	-	-	-	-	−13.7%*	−16.6%*
Day 91	6.09	6.41	-	-	-	-	−13.5%*	−14.4%*
Day 182	7.08	6.80	-	-	−10.9%*	−9.4%*	−18.5%*	−12.5%*

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Day 272	6.75	6.90	-	-	−5.2%	−10.1%*	−7.9%	−12.6%*
Hemoglobin (g/dL)								
Day 24	13.8	13.9	-	-	-	-	−12.3%*	−14.8%*
Day 91	13.9	14.5	-	-	-	-	−12.9%*	−11.4%*
Day 182	16.2	15.9	-	-	−7.4%	−7.5%	−19.2%*	−14.0%*
Day 272	15.7	15.9	-	-	−4.6%	−9.1%*	−12.0%	−12.5%*
Hematocrit (%)								
Day 24	40.4	40.7	-	-	-	-	−13.6%*	−17.0%*
Day 91	40.0	42.0	-	-	-	-	−11.0%*	−11.7%*
Day 182	45.9	45.1	-	-	−7.6%	−8.6%*	−17.5%*	−12.7%*
Day 272	45.2	45.8	-	-	−3.8%	−7.9%	−9.9%	−10.9%*
Serum chemistry[f]								
Aspartate aminotransferase (IU/L)								
Day 24	28	27	-	-	17.8%	18.2%	30.4%*	14.7%
Day 91	28	27	-	-	34.2%*	27.8%	68.3%*	54.9 %*[g]
Day 182	27	26	-	-	38.5%*	-	72.6%*	47.0%*
Day 272	24	26	-	-	64.9%*	-	123%*	71.6%*
Alanine aminotransferase (IU/L)								
Day 24	25	23	-	-	92.1%*[g]	79.7%	514%*[g]	227%*[g]
Day 91	33	25	-	-	165%*[g]	121%	433%*[g]	288%*[g]
Day 182	36	27	-	-	74.6%	47.1%	403%*[g]	110%*[g]
Day 272	32	26	-	-	171%	50.5%	246%	117%
Alkaline phosphatase (IU/L)								

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Day 24	105	-	-	-	-	-	94.3%*[g]	-
Day 91	72	-	-	-	-	-	85.7%*[g]	-
Day 182	45	-	-	-	-	-	174%*[g]	-
Day 272	35	-	-	-	-	-	151%*	-
Gamma glutamyl transferase (IU/L)								
Day 24	2.39	2.08	-	-	-	-	89.1%	43.1%
Day 91	1.61	2.04	-	-	-	-	50.9%	26.4%
Cholesterol (mg/dL)								
Day 24	150	144	-	-	-	-	−11.9%	−25.4%*
Day 91	154	159	-	-	-	-	−29.2%*	−34.4%*
Day 182	122	151	-	-	-	-	−29.8%*	−37.3%*
Day 272	126	171	-	-	-	-	−31.9%*	−45.5%*
Albumin (g/dL)								
Day 24	2.78	2.96	-	-	-	-	−7.9%*	−12.1%*
Day 91	2.85	2.99	-	-	-	-	−13.1%*	−10.4%*
Day 182	3.20	3.26	-	-	-	-	−17.3%*	−13.2%*
Day 272	3.13	3.19	-	-	-	-	−16.2%*	−6.3%
Globulin (g/dL)								
Day 24	2.42	-	-	-	-	-	4.2%	-
Day 91	2.42	-	-	-	-	-	26.1%*[g]	-
Day 182	2.31	-	-	-	-	-	27.3%*	-
Day 272	2.33	-	-	-	-	-	37.3%	-

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Albumin/Globulin ratio									
Day 24		1.15	1.27	-	-	-	-	−9.6%	−7.9%
Day 91		1.18	1.32	-	-	-	-	−30.1%*[g]	−12.5%*
Day 182		1.39	1.44	-	-	-	-	−34.2%*	−15.5%
Day 272		1.35	1.31	-	-	-	-	−37.4%*	−8.6%
Urinalysis		-	-	-	-	-	-	-	-
Organ weights[f] - Day 91	No. evaluated	3	3	3	3	3	3	1[h]	2
Salivary gland									
Absolute wt		-	7.91 g	-	-	-	−21.6%*	-	−24.6%*
Relative to body wt ratio		-	0.110	-	-	-	−22.8%*	-	−21.5%*
Spleen									
Absolute wt		68.6 g	94.2 g	-	-	−18.9%	−40.4%*	−39.6%	−56.4%*
Relative to body wt ratio		0.722	1.31	-	-	−5.3%	−41.3%*	−30.2%	−54.8%*
Organ weights[f]- Day 182	No. evaluated	3	3	3	3	3	3	2	3
Spleen									
Absolute wt		88.5 g	63.7 g	-	-	−28.4%	−21.4%	−32.6%	−30.3%
Relative to body wt ratio		0.940	0.897	-	-	−30.0%	−25.9%	−30.1%	−31.7%
Organ weights[f] - Day 272	No. evaluated	4	4	4	4	4	4	2	4
Spleen									
Absolute wt		105 g	-	-	-	−49.8%*	-	−57.6%*	-
Relative to body wt ratio		0.972	-	-	-	−49.1%*	-	−48.5%*	-
Gross pathology (Day 91)		-	-	-	-	-	-	-	-
Histopathology (Day 91)[i]	No. evaluated	3	3	3	3	3	3	4	5

Table 2.6.7.7E Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-046A (Continued)

Daily dose (mg/kg)	0 (Control)		2		6		20/15[a]	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Bone marrow (sternum)								
Increased myeloid progenitor cells[j]								
Mild to marked	0	0	-	-	-	-	4	3
Hypoplasia; hematopoietic								
Mild to marked	0	0	-	-	-	-	4	3
Liver								
Increased myeloid progenitor cells[j]								
Minimal to marked	0	0	-	-	-	-	3	3
Hematopoiesis								
Mild	0	-	-	-	-	-	1	-
Infiltration; lymphoplasmacytic; periductal								
Moderate	-	0	-	-	-	-	-	1
Necrosis; bile duct; multifocal								
Moderate	-	0	-	-	-	-	-	1
Necrosis; periductal								
Minimal	-	0	-	-	-	-	-	1
Necrosis; hepatocyte; multifocal								
Mild	-	0	-	-	-	-	-	1
Necrosis; arterial mural; multifocal								
Mild	-	0	-	-	-	-	-	1
Proliferation; small bile ducts; small caliber vessels and fibroblasts								
Minimal	0	0	-	-	1	1	3	1

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)	**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Epithelial degeneration/regeneration; bile duct; multifocal								
Mild to moderate	-	0	-	-	-	-	-	3
Stasis; bile								
Minimal to mild	-	0	-	-	-	-	-	2
Fibrosis; periductal; bile duct								
Moderate	-	0	-	-	-	-	-	1
Spleen								
Depletion, lymphoid								
Mild to marked	-	0	-	-	-	-	-	3
Increased myeloid progenitor cells[j]								
Minimal to marked	0	0	-	-	-	-	2	3
Hematopoiesis								
Mild	0	-	-	-	-	-	1	-
Gross pathology (Day 182)	-	-	-	-	-	-	-	-
Histopathology (Day 182)[i] No. evaluated	3	3	3	3	3	3	3	3
Bone marrow (sternum)								
Increased myeloid progenitor cells[j]								
Mild to marked	0	-	-	-	-	-	2	-
Hypoplasia; hematopoietic								
Marked	0	-	-	-	-	-	1	-
Hyperplasia								
Minimal	0	-	-	-	-	-	1	-
Hyperplasia; megakaryocyte								

Table 2.6.7.7E Repeat-dose Toxicity in Dogs **Study No. TX-[redacted]-101348-046A (Continued)**

Daily dose (mg/kg)		**0 (Control)**		**2**		**6**		**20/15[a]**	
Total no. of animals on study		**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
	Minimal	0	-	-	-	-	-	1	-
Liver									
Increased myeloid progenitor cells[j]									
	Minimal	0	-	-	-	-	-	1	-
Spleen									
Depletion; lymphoid									
	Moderate	0	-	-	-	-	-	1	-
Increased myeloid progenitor cells[j]									
	Mild	0	-	-	-	-	-	1	-
Gross pathology (Day 272)		-	-	-	-	-	-	-	-
Histopathology (Day 272)[i]	No. evaluated	4	4	4	4	4	4	4	4
Bone marrow (sternum)									
Increased myeloid progenitor cells[j]									
	Mild to marked	0	-	-	-	-	-	3	-
Hypoplasia; hematopoietic									
	Mild to marked	0	-	-	-	-	-	3	-
Hyperplasia									
	Moderate	-	0	-	-	-	1	-	-
Liver									
Increased myeloid progenitor cells[j]									
	Minimal	0	-	-	-	-	-	1	-
Proliferation; small bile ducts; small caliber vessels and fibroblasts									
	Minimal	-	0	-	-	-	-	-	2

Table 2.6.7.7E Repeat-dose Toxicity in Dogs Study No. TX-[redacted]-101348-046A (Continued)

Daily dose (mg/kg)	0 (Control)		2		6		20/15[a]	
Total no. of animals on study	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Spleen								
Increased myeloid progenitor cells[j]								
Minimal	0	-	-	-	-	-	1	-

A/G = albumin/globulin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC(0-24h) = AUC from time 0 to 24 hours; Cmax = maximum plasma concentration; GGT = gamma glutamyl transferase; GI = gastrointestinal; NA = not applicable; wt = weight; - = no noteworthy findings; * = statistically significant at $p < 0.05$ (ANOVA/Dunnett-test unless noted otherwise).

[a] Due to mortality noted at the 20 mg/kg level, the dose level was decreased to 15 mg/kg beginning on Day 26.

[b] Represents combined mean values for samples from Day 246 and 271.

[c] Only treatment-related findings are presented.

[d] At 20 mg/kg, 1 male and 3 females were euthanized moribund (Days 18 to 26); following the reduction in the dose to 15 mg/kg, 4 additional males were euthanized on Days 61, 89, 109, and 232. One 15 mg/kg male was found dead on Day 188.

[e] No. of incidences (all animals including moribund sacrifices).

[f] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences.

[g] Kruskal-Wallis/Dunn's test.

[h] Excluded from statistical analysis ($N < 2$).

[i] Scheduled euthanasia plus moribund.

[j] Terminology developed by the Expert Panel (Study Report EXP0092) is used in this table rather than the terminology (hyperplasia or infiltration of stem cells) used by the study pathologist in the study report of TX-[redacted]-101348-046A.

8 *In Vitro* 遺伝毒性試験

Table 2.6.7.8A Genotoxicity: In Vitro (Bacterial Reverse Mutation) **Test Article:** Fedratinib

Report Title: Bacterial Reverse Mutation (Ames) Assay with TG101348

Test for Induction of: Reverse mutation in bacterial cells | **No. of Independent Assays:** 3 | **Study No.:** TX-[redacted]-101348-084

Test System: *Salmonella typhimurium* and *Escherichia coli* | **No. of Independent Cultures:** 3 | **Location in Dossier:** 4.2.3.3.1-1

Metabolizing System: Aroclor 1254-induced rat liver S9 | **No. of Cells Analyzed/Culture:** 1.6-10.1 x 10^8

Vehicle: Test Article: Sterile distilled water | **Positive Controls:** DMSO or water | **GLP Compliance:** Yes

Treatment: 48 to 72 hours | **Dates of Treatment:** [redacted], 20[redacted]

Cytotoxic Effects: Yes | **Genotoxic Effects:** None

Metabolic Activation	Test Article	Dose Level (µg/plate)	Initial Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 *uvr*A
Without Activation	Water	0	14 ± 4	157 ± 11	13 ± 2	10 ± 6	32 ± 4
	Fedratinib	1.5	13 ± 6	149 ± 7	15 ± 10	7 ± 1	34 ± 3
		5.0	15 ± 5	155 ± 4	17 ± 9	8 ± 1	29 ± 4
		15	13 ± 3	160 ± 11	11 ± 1	8 ± 1	29 ± 9
		50	22 ± 6	145 ± 16	10 ± 4	7 ± 3	35 ± 13
		150	12 ± 3	139 ± 3	13 ± 6	7 ± 1	40 ± 2
		500	16 ± 1	170 ± 6	17 ± 6	6 ± 3	45 ± 1
		1500	16 ± 3	0 ± 0	7 ± 2	4 ± 2	19 ± 1
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	Sodium azide	1.0	NA	636 ± 48	813 ± 14	NA	NA
	9-aminoacridine	75	NA	NA	NA	445 ± 40	NA
	2-nitrofluorene	1.0	229 ± 26	NA	NA	NA	NA
	Methyl methanesulfonate	1000	NA	NA	NA	NA	403 ± 58

Table 2.6.7.8A Genotoxicity: In Vitro **Study No.: TX-[redacted]-101348-084 (Continued)**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Initial Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 *uvr*A
With Activation	Water	0	24 ± 2	180 ± 4	14 ± 1	6 ± 2	30 ± 5
	Fedratinib	1.5	17 ± 1	152 ± 11	12 ± 3	5 ± 2	31 ± 16
		5.0	15 ± 1	168 ± 1	14 ± 2	6 ± 2	27 ± 4
		15	17 ± 8	168 ± 6	14 ± 2	4 ± 2	40 ± 1
		50	15 ± 3	148 ± 3	17 ± 4	4 ± 2	41 ± 2
		150	25 ± 1	169 ± 22	11 ± 4	7 ± 1	40 ± 11
		500	23 ± 3	177 ± 6	13 ± 5	6 ± 3	31 ± 2
		1500	25 ± 4	186 ± 18	6 ± 1	6 ± 4	34 ± 1
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2-aminoanthracene	1.0	587 ± 33	609 ± 1	108 ± 14	187 ±117	NA
		10.0	NA	NA	NA	NA	233 ± 128

Table 2.6.7.8A Genotoxicity: In Vitro **Study No.: TX-[redacted]-101348-084 (Continued)**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Confirmatory Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 *uvr*A
Without Activation	Water	0	24 ± 6	186 ± 10	30 ± 7	8 ± 3	53 ± 8
	Fedratinib	15	24 ± 4	193 ± 7	29 ± 4	9 ± 2	50 ± 2
		50	20 ± 6	192 ± 14	32 ± 5	10 ± 4	60 ± 1
		150	26 ± 5	168 ± 7	31 ± 8	8 ± 2	60 ± 4
		500	26 ± 8	192 ± 26	31 ± 1	11 ± 5	57 ± 11
		1500	18 ± 8	0 ± 0	0 ± 0	9 ± 2	45 ± 5
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	Sodium azide	1.0	NA	640 ± 23	740 ± 53	NA	NA
	9-aminoacridine	75	NA	NA	NA	869 ± 387	NA
	2-nitrofluorene	1.0	129 ± 2	NA	NA	NA	NA
	Methyl methanesulfonate	1000	NA	NA	NA	NA	456 ± 31
With Activation	Water	0	31 ± 10	201 ± 18	19 ± 2	14 ± 4	46 ± 6
	Fedratinib	15	26 ± 7	177 ± 82	12 ± 3	7 ± 2	48 ± 4
		50	34 ± 10	200 ± 9	20 ± 6	14 ± 5	55 ± 7
		150	33 ± 2	188 ± 6	19 ± 4	11 ± 2	60 ± 3
		500	30 ± 14	193 ± 18	16 ± 2	12 ± 1	48 ± 1
		1500	45 ± 1	243 ± 23	10 ± 2	13 ± 1	41 ± 11
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2-aminoanthracene	1.0	431 ± 60	614 ± 80	82 ± 40	64 ± 8	NA
		10.0	NA	NA	NA	NA	225 ± 33

Table 2.6.7.8A Genotoxicity: In Vitro **Study No.: TX-[redacted]-101348-084 (Continued)**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Confirmatory Mutation assay (retest): Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 *uvr*A
Without Activation	Water	0	13 ± 2	149 ± 37	17 ± 2	6 ± 1	28 ± 1
	Fedratinib	15	12 ± 2	158 ± 7	20 ± 4	4 ± 2	27 ± 2
		50	13 ± 3	151 ± 26	21 ± 3	7 ± 3	27 ± 3
		150	14 ± 4	151 ± 15	19 ± 2	6 ± 2	28 ± 3
		500	17 ± 1	185 ± 22	14 ± 3	6 ± 3	33 ± 6
		1500	10 ± 2	0 ± 0	0 ± 0	2 ± 1	21 ± 11
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	Sodium azide	1.0	NA	566 ± 88	460 ± 66	NA	NA
	9-aminoacridine	75	NA	NA	NA	1325 ± 100	NA
	2-nitrofluorene	1.0	145 ± 10	NA	NA	NA	NA
	Methyl methanesulfonate	1000	NA	NA	NA	NA	1030 ± 89
With Activation	Water	0	19 ± 5	163 ± 20	11 ± 1	9 ± 3	31 ± 4
	Fedratinib	15	19 ± 1	158 ± 7	12 ± 1	6 ± 1	29 ± 4
		50	28 ± 4	199 ± 12	10 ± 3	5 ± 2	33 ± 4
		150	33 ± 6	180 ± 8	13 ± 1	10 ± 3	33 ± 3
		500	29 ± 7	196 ± 21	11 ± 3	10 ± 3	34 ± 6
		1500	27 ± 2	173 ± 25	4 ± 2	10 ± 4	27 ± 2
		5000	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	2-aminoanthracene	1.0	295 ± 37	616 ± 62	97 ± 6	94 ± 4	NA
		10.0	NA	NA	NA	NA	1078 ± 91

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.

Table 2.6.7.8B Genotoxicity: In Vitro (Chromosomal Aberrations) **Test Article:** Fedratinib

Report Title: TG101348: In vitro Mammalian Chromosome Aberration Test in Chinese Hamster Ovary (CHO) Cells

Test for Induction of: Chromosomal aberrations **No. of Independent Assays:** 3[a] **Study No.:** TX-[redacted]-101348-050

Test System: Chinese hamster ovary cells **No. of Independent Cultures:** 2 **Location in Dossier:** 4.2.3.3.1-2

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** 200 (100 for structural aberrations in positive control)

Vehicle: Test Article: De-ionized water **Positive Controls:** Sterile distilled water **GLP Compliance:** Yes

Treatment: 4 hours ±S9, 20 hours −S9 **Dates of Treatment:** [redacted], 20[redacted]

Cytotoxic Effects: Yes

Genotoxic Effects: None

Treatment Metabolic Activation	Test Article	Concentration (µg/mL)	Mean Mitotic Index	Aberrations/cell[c] (mean ± SD)	Cells with Aberrations	
					Numerical (%)	Structural (%)
20-hour[b] **Without Activation**	Water	0	10.9	0.005 ± 0.071	0.0	0.5
	Fedratinib[d]	0.625	10.6	0.005 ± 0.071	0.0	0.5
		1.25	9.8	0.000 ± 0.000	0.0	0.0
		2.5	5.9	0.005 ± 0.071	0.0	0.5
	Mitomycin C	0.1	5.8	0.300 ± 0.644	0.0	20.0**

Table 2.6.7.8B Genotoxicity: In Vitro **Study No. TX-[redacted]-101348-050 (Continued)**

Treatment Metabolic Activation	Test Article	Concentration (µg/mL)	Mean Mitotic Index	Aberrations/cell[c] (mean ± SD)	Cells with Aberrations	
					Numerical (%)	Structural (%)
4-hour[b] Without Activation	Water	0	9.1	0.000 ± 0.000	1.0	0.0
	Fedratinib[e]	2.5	8.9	0.005 ± 0.071	0.5	0.5
		5	8.6	0.000 ± 0.000	0.5	0.0
		7.5	8.6	0.000 ± 0.000	0.5	0.0
	Mitomycin C	0.2	5.4	0.340 ± 0.794	0.0	21.0**
4-hour[b] With Activation	Water	0	11.5	0.000 ± 0.000	0.5	0.0
	Fedratinib[f]	2.5	11.0	0.000 ± 0.000	0.0	0.0
		5	11.0	0.005 ± 0.071	0.5	0.5
		15	10.9	0.005 ± 0.071	2.0	0.5
	Cyclophosphamide	10	2.1	0.310 ± 0.706	0.0	19.0**

SD = standard deviation; ** = $p \leq 0.01$ (Fisher's Exact test).

[a] In addition, a range finding assay was conducted with and without metabolic activation.

[b] Cells from all treatment conditions were harvested 20 hours after initiation of the treatments.

[c] Severely damaged cells were counted as 10 aberrations.

[d] Concentrations of 0.625 to 10 µg/mL were tested but 3.5, 5, 7.5 and 10 µg/mL were not analyzed due to excessive toxicity.

[e] Concentrations of 1.25 to 25 µg/mL were tested but 15 and 25 µg/mL were not analyzed due to excessive toxicity.

[f] Concentrations of 1.25 to 45 µg/mL were tested but 25, 35 and 45 µg/mL were not analyzed due to excessive toxicity.

9 *In Vivo* 遺伝毒性試験

Table 2.6.7.9 Genotoxicity: In Vivo (Bone Marrow Micronucleus in Rats) **Test Article:** Fedratinib

Report Title: Rat Bone Marrow Micronucleus Test Following Oral Administration of TG101348

Test for Induction of: Micronuclei
Treatment Schedule: Single dose
Study No.: TX-[redacted]-101348-051
Test System/Strains: Rat/Sprague Dawley
Sampling Time: 24 and 48 hr
Location in Dossier: 4.2.3.3.2-1
Age: 6 to 8 weeks
Method of Administration: Oral gavage
Cells Evaluated: Bone marrow erythrocytes
Vehicle/Formulation: 0.5% Methylcellulose
GLP Compliance: Yes
No. of Cells Analyzed/Animal: MPCE/2000 PCE
Dates of Treatment: [redacted], 20[redacted]
Special Features: None
Toxic/Cytotoxic Effects: At ≥ 30 mg/kg, clinical sign (piloerection) in all males.
Genotoxic Effects: None

Test Article	Dose (mg/kg)	No. of Animals		Time (hr)	PCE/total erythrocytes (Mean ± SD)		MPCE/1000 PCE (Mean ± SD)		Number of MPCE/ 10000 PCE scored	
		M	F		M	F	M	F	M	F
Vehicle	0	5	5	24	0.544 ± 0.04	0.521 ± 0.05	0.1 ± 0.22	0.5 ± 0.35	1	5
	0	5	5	48	0.560 ± 0.02	0.536 ± 0.02	0.2 ± 0.27	0.2 ± 0.27	2	2
Fedratinib	5	5	5	24	0.493 ± 0.04	0.505 ± 0.05	0.1 ± 0.22	0.3 ± 0.27	1	3
	30	5	5	24	0.519 ± 0.03	0.489 ± 0.04	0.2 ± 0.27	0.3 ± 0.27	2	3
	80	5	5	24	0.502 ± 0.07	0.498 ± 0.08	0.2 ± 0.27	0.2 ± 0.27	2	2
	80	5	5	48	0.494 ± 0.05	0.484 ± 0.04	0.3 ± 0.27	0.2 ± 0.27	3	2
Cyclophosphamide	40	5	5	24	0.352 ± 0.05	0.360 ± 0.05	15.1 ± 3.09	10.3 ± 1.35	151*	103*

MPCE = micronucleated polychromatic erythrocytes; PCE = polychromatic erythrocytes; SD = standard deviation; * = $p \leq 0.05$ (Kastenbaum-Bowman Tables).

10 がん原性試験

Table 2.6.7.10 Carcinogenicity in Mice **Test Article:** Fedratinib

Report Title: 26-week Oral Gavage Carcinogenicity and Toxicokinetic Study with SAR302503 in CByB6F1-Tg(HRAS)2Jic Mice

Species/Strain: Mouse/CByB6F1-Tg(HRAS)2Jic | **Duration of Dosing:** 26 weeks | **Study No.:** CAR0168

Initial Age: 8 weeks | **Method of Administration:** Oral gavage | **Location in Dossier:** 4.2.3.4.2-1

Date of First Dose: [redacted], 20[redacted] | **Vehicle/Formulation:** 0.5% methylcellulose

Treatment of Controls: Vehicle control: 0.5% methylcellulose daily; Positive control: single intraperitoneal dose of MNU (75 mg/kg, 7.5 mg/mL) on Day 1. **GLP Compliance:** Yes

Basis for High-Dose Selection: The high dose of 30 mg/kg was selected based on mortality observed at 100 mg/kg in a 1-month mouse study (Study No. DDC0131).

Special Features: None

Daily dose (mg/kg)		**0 (Vehicle Control)**		**3**		**10**		**30**		**MNU: 75 (Positive Control)**	
No. of animals		**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Toxicokinetics:	No. evaluated	6	6	36	36	36	36	36	36	0	0
Week 13											
AUC(0-24h) (ng•h/mL)		NA	NA	214	438	1640	2610	15400	22100	NA	NA
Cmax (ng/mL)		NA	NA	26.4	50.1	157	249	1450	2060	NA	NA
Week 26											
AUC(0-24h) (ng•h/mL)		NA	NA	114	347	2320	1600	12700	22100	NA	NA
Cmax (ng/mL)		NA	NA	15.7	34.6	217	165	1280	2130	NA	NA
No. of animals (Main study)											
At Start		25	25	25	25	25	25	25	25	25	25
Died/sacrificed moribund		0	0	1	1	2	3	2	3	17	19
Terminal sacrifice		25	25	24	24	23	22	23	22	8	6
Survival (%)		100	100	96	96	92	88	92	88[b]	32	24

Table 2.6.7.10 Carcinogenicity in Mice **Study No. CAR0168 (Continued)**

Daily dose (mg/kg)	**0 (Vehicle Control)**		**3**		**10**		**30**		**MNU: 75 (Positive Control)**	
No. of animals	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Clinical observations	-	-	-	-	-	-	-	-	-	-
Body weight[c,d]										
Day 29	-	19.9 g	-	-	-	-	-	−4.02%*	NA	NA
Day 57	-	20.6 g	-	-	-	-	-	−4.37%*	NA	NA
Day 85	-	21.1 g	-	-	-	-	-	−2.37%	NA	NA
Day 113	-	21.8 g	-	-	-	-	-	−5.50%*	NA	NA
Day 141	-	21.9 g	-	-	-	-	-	−2.74%	NA	NA
Day 169	-	22.1 g	-	-	-	-	-	−4.07%*	NA	NA
Day 183	-	22.1 g	-	-	-	-	-	−3.62%	NA	NA
Body weight gain[c]										
Day 1 to 183	-	3.7 g	-	-	-	-	-	−27%*	NA	NA
Food consumption[c]										
Day 1 to 8	-	26.5 g	-	-	-	-	-	−3.40%	NA	NA
Day 29 to 36	-	26.5 g	-	-	-	-	-	−7.55%*	NA	NA
Day 57 to 64	-	27.3 g	-	-	-	-	-	−9.16%*	NA	NA
Day 85 to 92	-	32.8 g	-	-	-	-	-	−24.1%*	NA	NA
Day 113 to 120	-	32.2 g	-	-	-	-	-	−19.9%*	NA	NA
Day 141 to 148	-	28.0 g	-	-	-	-	-	−9.29%*	NA	NA
Day 176 to 183	-	27.4 g	-	-	-	-	-	−5.84%	NA	NA
Gross pathology	-	-	-	-	-	-	-	-	e	e
Histopathology (Neoplastic lesions)										
No. evaluated	25	25	25	25	25	25	25	25	25[f]	25[f]
Body, whole/cavity										

Table 2.6.7.10 Carcinogenicity in Mice **Study No. CAR0168 (Continued)**

Daily dose (mg/kg)	**0 (Vehicle Control)**		**3**		**10**		**30**		**MNU: 75 (Positive Control)**	
No. of animals	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Benign hemangioma	1	0	-	-	-	1	-	-	-	-
Malignant hemangiosarcoma	3	3	3	-	2	3	3	2	4	4
Malignant lymphosarcoma	0	0	-	-	1	-	-	-	19	14
Malignant sarcoma, origin unknown	0	0	-	-	1	-	-	1	-	-
Malignant mesothelioma	-	0	-	-	-	-	-	-	-	1
Skin basal tumor	-	0	-	-	-	-	-	-	-	1
Brain										
Benign astrocytoma	0	-	-	-	1	-	-	-	-	-
Liver										
Malignant carcinoma, hepatocellular	0	-	-	-	-	-	1	-	-	-
Harderian gland										
Benign adenoma	1	0	-	-	-	1	1	-	-	-
Malignant carcinoma	0	-	-	-	1	-	-	-	-	-
Lung										
Benign adenoma, bronchioloalveolar	0	0	2	1	1	1	2	1	1	5
Malignant carcinoma, bronchiolo-alveolar	1	0	-	1	1	2	-	1	-	-
Nonglandular stomach										
Malignant carcinoma, squamous cell	0	0	-	-	-	1	-	-	7	5
Benign papilloma, squamous cell	0	0	-	-	-	-	-	-	9	12
Spleen										
Malignant mesothelioma	-	0	-	-	-	-	-	-	-	1
Skin/Subcutis										

Table 2.6.7.10 Carcinogenicity in Mice **Study No. CAR0168 (Continued)**

Daily dose (mg/kg)	0 (Vehicle Control)		3		10		30		MNU: 75 (Positive Control)	
No. of animals	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Benign keratoacanthoma	0	0	-	-	-	-	-	-	2	3
Benign papilloma, squamous cell	0	0	-	-	-	-	-	-	3	3
Benign basal cell tumor	-	0	-	-	-	-	-	-	-	1
Uterus										
Benign polyp, endometrial stromal	NA	1	NA	-	NA	-	NA	-	NA	2
Female mammary gland										
Malignant carcinoma	NA	0	NA	1	NA	-	NA	-	NA	-

AUC(0-24h) = AUC from time 0 to 24 hour; Cmax = maximum plasma concentration; NA = not applicable; NMU = N-methyl-N-nitrosourea; - = no noteworthy findings; * = statistically significant at p ≤0.05 (AVOVA and Dunnett's, Rank-transformed data).

[a] Includes an extra animal/sex for possible replacements.

[b] In test article treated-females, a significant positive trend for higher mortality was noted (P = 0.0453 by Cox-Tarone and p = 0.0483 by Gehan-Breslow), with the 30 mg/kg group having a significant increase compared to the vehicle control group as analyzed by the Gehan-Breslow test (p = 0.0396) but not by the Cox-Tarone test (p = 0.1177). However, two of the three unscheduled deaths in females at 30 mg/kg were caused by fatal neoplasms that were not considered as fedratinib-related. The third female had an undetermined cause of death with no known relationship to fedratinib. Based on these observations, it was concluded that there was no fedratinib-related effect on mortality.

[c] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences). Data for positive control not included since they were excluded from statistical analyses.

[d] Data presented is a sampling of data collected; additional data points are presented in the final report.

[e] Macroscopic masses were observed for 7/25 males and 10/25 females in the positive control group. The masses were generally wart-like lesions observed on the abdomen or perianal areas.

[f] The neoplasms observed in positive control animals have been associated with the carcinogenic effect reported with administration of MNU in this mouse strain[1,2]

11 生殖発生毒性試験：重要な試験以外の試験

Table 2.6.7.11 Reproductive and Developmental Toxicity **Non-pivotal Studies** **Test Article:** Fedratinib

Species/ Strain	Method of Administration (Vehicle/Formulation)	Dosing Period	Doses (mg/kg)	No. per Group	Noteworthy Findings (mg/kg)	Study No.
Rat/ Sprague Dawley	Oral gavage (0.5% methylcellulose)	GD 6 to 17	0, 3, 10, 30, or 80	5F	Maternal toxicity: 3, 10, 30: No effects 80: ↓ gestation bw (−13 to −17%, GD 12 to GD 20); ↓ bw gain (−59% GD 6 to GD 18); ↓ FC (−23%, GD 6 to GD 18) Developmental toxicity: 3, 10: No effects 30: ↑ postimplantation loss and ↓ fetal bw (−7 to −9% compared to controls) 80: ↑ postimplantation loss and significantly ↓ fetal bw (−36 to −41%). One litter had malformations: edema, omphalocele, brachydactyly, and missing nail (paw); the significance of this finding is unclear. Dose levels of 3, 10, and 30 mg/kg were selected for the definitive study.	TX-[redacted]-101348-055
Rabbit/ New Zealand White	Oral gavage (0.5% methylcellulose)	GD 6 to 18	0, 3, 10, 30, or 80	6F	Maternal toxicity: 3, 10: No effects 30: 1F had bw loss and ↓ FC beginning on GD 13 (aborted on GD 26). The significance of this finding is unclear. 80: 1F found dead on GD 10 and 1F was euthanized in extremis on GD 13. Due to the mortality and the toxicity in the remaining F (i.e. bw loss and ↓ FC), treatment was stopped on GD 10. These F continued to be monitored (observed, weighed and FC recorded) until the group was terminated (GD 14).	TX-[redacted]-101348-056

Table 2.6.7.11 Reproductive and Developmental Toxicity **Non-pivotal Studies** **Test Article:** Fedratinib

Species/ Strain	Method of Administration (Vehicle/Formulation)	Dosing Period	Doses (mg/kg)	No. per Group	Noteworthy Findings (mg/kg)	Study No.
					Developmental toxicity: 3, 10 or 30: No effects 80: Does only received 4 doses (GD 6-9) and were terminated early on GD 14. Dose levels of 3, 10, and 30 mg/kg were selected for the definitive study.	

bw = body weight; FC = food consumption; GD = gestation day; ↓ = decreased.

12 生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

Table 2.6.7.12 Reproductive and Developmental Toxicity - Study of Effects on Fertility and Early Embryonic Development to Implantation

Test Article: Fedratinib

Report Title: SAR302503A - Oral male and female fertility study in rats

Design similar to ICH 4.1.1? Yes

Duration of Dosing: 91 to 142 days (M)
22 to 27 days (F)

Study No.: FER0500

Species/Strain: Rat/Sprague Dawley

Day of Mating: GD 0

Location in Dossier: 4.2.3.5.1-1

Initial Age: 9 weeks (M); 10 weeks (F)

Day of C-Section: [redacted], 20[redacted] to [redacted], 20[redacted]

Date of First Dose: [redacted], 20[redacted] (M) and [redacted], 20[redacted] (F)

Method of Administration: Oral gavage

GLP Compliance: Yes

Special Features: None

Vehicle/Formulation: 0.5% methylcellulose

No Observed Effect Level: F0 Male and Female: 10 mg/kg

Male and Female fertility: 30 mg/kg

Daily dose (mg/kg)		0 (Control)	3	10	30
Males	No. evaluated	24	24	24	24
No. found dead or sacrificed moribund		0	0	0	0
Clinical observations		-	-	-	-
Premating body weight[a]					
Day 43		480 g	-	-	−5.2%
Day 71		526 g	-	-	−8.2%*[b]
Postmating body weight[a]					
Day 92		561 g	-	-	−9.8%
Premating food consumption		-	-	-	-
Females	No. evaluated	25	24	24	24
No. found dead or sacrificed moribund		0	0	0	0
Clinical observations		-	-	-	-
Premating body weight		-	-	-	-

Table 2.6.7.12: Reproductive and Developmental Toxicity (Continued) **Study No. FER0500**

Daily dose (mg/kg)	**0 (Control)**	3	10	**30**
Gestation body weight[a]				
Day 8	295 g	-	-	−4.5%*[b]
Gestation body weight gain[a]				
GD 1 to 4	20.4 g	-	-	−21.6%
GD 4 to 8	17.1 g	-	-	−22.2%
Premating food consumption	-	-	-	-
Gestation food consumption[a,c]				
GD 1 to 4	26.2	-	-	−7.6%*[d]
GD 4 to 8	27.0	-	-	−7.0%*[d]
Mean No. Estrous Cycles/14 days	-	-	-	-
Cohabited Pairs	25	24	24	24
Mated Females	25	24	24	24
Mean No. Days Prior to Mating	3.0	2.7	2.9	2.8
% Females Sperm-Positive	100.0	100.0	100.0	100.0
% Pregnant Females	100.0	95.8	87.5	95.8
Litters: No. evaluated	25	23	21	23
Corpora lutea	-	-	-	-
Implantation sites	-	-	-	-
Pre-implantation loss (% corpora lutea)	-	-	-	-
Viable fetuses	-	-	-	-
Dead fetuses	-	-	-	-
Resorptions	-	-	-	-

C-Sec = Caesarean section; GD = gestation day; - = no noteworthy findings.

[a] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent difference).

[b] Significant trend (* = p ≤ 0.05) through indicated dose level by average and/or linear response test.
[c] Control values presented in g/animal/day.
[d] Statistically significant (* = p ≤ 0.05) using a Jonckheere-Terpstra test associated to the step-down ordinal test procedure.

13 生殖発生毒性試験：胚・胎児発生に関する試験

Table 2.6.7.13A Reproductive and Developmental Toxicity in Rats - Effects on Embryo-Fetal Development **Test Article:** Fedratinib

Report Title: TG101348: Study for Effects on Embryo-Fetal Development in Rats

Design similar to ICH 4.1.3? Yes | **Duration of Dosing:** 12 days (GD 6 to 17) | **Study No.:** TX-[redacted]-101348-057

Species/Strain: Rat/Sprague Dawley | **Day of Mating:** GD 0 | **Location in Dossier:** 4.2.3.5.2-2

Initial Age: 8 to 10 weeks | **Day of C-Sec:** GD 20

Date of First Dose: [redacted], 20[redacted] | **Method of Administration:** Oral gavage | **GLP Compliance:** Yes

Special Features: None | **Vehicle/Formulation:** 0.5% methylcellulose

No Observed Effect Level: F0 Females (maternal toxicity): 3 mg/kg **F1 Litters (developmental toxicity):** 10 mg/kg

Daily dose (mg/kg)		**0 (Control)**	**3**	**10**	**30**
No. of animals		**F: 25**	**F: 25**	**F: 25**	**F: 25**
F0 Females					
Toxicokinetics:	No. evaluated	3	6	6	6
AUC(0-24h) (ng•h/mL)					
Day 1 (GD 6)		NA	60.5	349	3310
Day 12 (GD 17)		NA	26.1	419	3250
Cmax (ng/mL)					
Day 1 (GD 6)		NA	8.23	42.3	265
Day 12 (GD 17)		NA	2.76	46.8	294
No. inseminated		25	25	25	25
No. pregnant		24	25	25	25
No. found dead or sacrificed moribund		0	0	0	0
No. with live fetus(es)		24	25	25	25
No. with total litter loss		0	0	0	0
Pregnancy index (%)		96	100	100	100

Table 2.6.7.13A Reproductive and Developmental Toxicity (Continued) **Study No. TX-[redacted]-101348-057**

Daily dose (mg/kg)	**0 (Control)**	3	10	**30**
No. of animals	**F: 25**	**F: 25**	**F: 25**	**F: 25**
Clinical observations	-	-	-	-
Body weight[a]				
GD 15	303 g	-	−1.78%	−3.63%
GD 18	339 g	-	−2.72%	−4.93%
GD 20	375 g	-	−3.04%	−5.06%
Body weight gain[a]				
GD 6-9	13.9 g	-	−5.76%	−24.5%*
GD 9-12	22.5 g	-	−15.1%*	−16.9%*
GD 18-20	36.8 g	-	−6.25%	−5.98%
GD 6-18	93.2 g	-	−9.44%*	−15.7%**
Food consumption	-	-	-	-
Gross pathology	-	-	-	-
F_1 Litters				
Corpora lutea	-	-	-	-
Implantation sites	-	-	-	-
Preimplantation loss (% implants/animal)	-	-	-	-
Viable fetuses	-	-	-	-
Sex ratio of fetuses (% male)	-	-	-	-
Postimplantation loss (% implants/animal)	-	-	-	-
Nonviable fetuses	-	-	-	-
Litter size	-	-	-	-
Mean no. resorptions	-	-	-	-
Gravid uterine weight (g)	-	-	-	-

Table 2.6.7.13A Reproductive and Developmental Toxicity (Continued) **Study No. TX-[redacted]-101348-057**

Daily dose (mg/kg)	**0 (Control)**	3	1**0**	**30**
No. of animals	**F: 25**	**F: 25**	**F: 25**	**F: 25**
Fetal weight (g) - males (mean ± SD)	4.30 ± 0.19	-	-	3.86**± 0.20
Fetal weight (g) - females (mean ± SD)	4.05 ± 0.22	-	-	3.69**± 0.24
Fetal weight (g) - males + females (mean ± SD)	4.18 ± 0.18	-	-	3.77**± 0.20
Fetal gross external anomalies	-	-	-	-
Fetal visceral anomalies	-	-	-	-
Fetal skeletal variation				
Cervical vertebra - neural arches, additional ossification center				
Litter incidence (%)	0	-	-	28**
Fetal incidence (%)	0	-	-	8

AUC(0-24h) = AUC from time 0 to 24 hours; C-Sec = Caesarean section; Cmax = maximum plasma concentration; GD = gestation day; NA = not applicable; SD = standard deviation; - = no noteworthy findings; * = statistically significant at $p < 0.05$; ** = statistically significant at $p < 0.01$.

[a] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences**.**

Table 2.6.7.13B Reproductive and Developmental Toxicity in Rabbits - Effects on Embryo-fetal Development **Test Article:** Fedratinib

Report Title: TG101348: Study for Effects on Embryo-Fetal Development in Rabbits

Design similar to ICH 4.1.3? Yes | **Duration of Dosing:** 13 days (GD 6 to 18) | **Study No.:** TX-[redacted]-101348-058A

Species/Strain: Rabbit/New Zealand White | **Day of Mating:** GD 0 | **Location in Dossier:** 4.2.3.5.2-4

Initial Age: 7 months | **Day of C-Sec:** GD 29

Date of First Dose: [redacted], 20[redacted] | **Method of Administration:** Oral gavage | **GLP Compliance:** Yes

Special Features: None | **Vehicle/Formulation:** 0.5% methylcellulose

No Observed Effect Level: F0 Females (maternal toxicity): 30 mg/kg **F1 Litters (developmental toxicity):** 30 mg/kg

Daily dose (mg/kg)	**0 (Control)**	**3**	**10**	**30**
No. of animals	**F: 23**	**F: 23**	**F: 23**	**F: 23**
F0 Females				
Toxicokinetics: No. females evaluated	3	3	3	3
AUC(0-24h) (ng•h/mL)				
Day 1 (GD 6)	NA	5.53	76.4	722
Day 13 (GD 18)	NA	21.6	148	2320
Cmax (ng/mL)				
Day 1 (GD 6)	NA	3.09	20.2	157
Day 13 (GD 18)	NA	7.02	40.2	501
No. inseminated	23	23	23	23
No. pregnant	23	22	23	23
No. found dead or sacrificed moribund	0	0	1[a]	1[b]
No. with live fetus(es)	22	22	22	22
No. with total litter loss	1	0	0	0
Pregnancy index (%)	100	95.7	100	100
Clinical observations	-	-	-	-

Table 2.6.7.13B Reproductive and Developmental Toxicity (Continued) **Study No. TX-[redacted]-101348-058A**

Daily dose (mg/kg)	**0 (Control)**	**3**	**10**	**30**
No. of animals	**F: 23**	**F: 23**	**F: 23**	**F: 23**
F1 Litters:				
Corpora lutea	-	-	-	-
Implantation sites	-	-	-	-
Preimplantation loss (% implants/animal)	-	-	-	-
Viable fetuses	-	-	-	-
Sex ratio of fetuses (% male)	-	-	-	-
Postimplantation loss (% implants/animal)	-	-	-	-
Nonviable fetuses	-	-	-	-
Litter size	-	-	-	-
Mean no. resorptions	-	-	-	-
Gravid uterine weight (g)	-	-	-	-
Fetal weight (g) - males	-	-	-	-
Fetal weight (g) - females	-	-	-	-
Fetal weight (g) - males + females	-	-	-	-
Fetal gross external anomalies	-	-	-	-
Fetal visceral anomalies	-	-	-	-
Fetal skeletal anomalies	-	-	-	-

AUC(0-24h) = AUC from time 0 to 24 hours; C-Sec = Caesarean section; Cmax = maximum plasma concentration; GD = gestation day; NA = not applicable; - = no noteworthy findings.

[a] Died on GD 16; death was not related to administration with fedratinib (attributed to a dosing-related injury).

[b] Euthanized in extremis on GD 21 due to impaired right forelimb function, unrelated to fedratinib administration.

14 生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

Table 2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

Test Article: Fedratinib

Report Title: Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function with SAR302503 in Rats

Design similar to ICH 4.1.2? Yes

Duration of Dosing: GD 6 thru LD 20

Day of Mating: GD 0

Study No.: DPN0371

Location in Dossier: 4.2.3.5.3-1

Species/Strain: Rat/Sprague Dawley

Method of Administration: Oral gavage

Initial Age: 11 weeks (F0 females)

Vehicle/Formulation: 0.5% methylcellulose

GLP Compliance: Yes

Date of First Dose: [redacted], 20[redacted]

Litters Culled/Not Culled: Culled to 4/sex/litter

Special Features: At weaning, 1 male and 1 female per litter were selected to continue on study during maturation phase which assessed growth, sexual development, locomotor activity, reflex development, learning and memory, and reproductive capability (through GD 13 cesarean sections).

No Observed Adverse Effect Level: F0 Females (maternal toxicity): 30 mg/kg; **No Observed Effect Level: F1 (developmental toxicity):** 10 mg/kg

Daily dose (mg/kg)		**0 (Control)**	**3**	**10**	**30**
F0 Females	No. evaluated	24	24	24	24
No. pregnant		24	24	24	23
No. inseminated		24	24	24	24
No. found dead or sacrificed moribund		0	0	0	0
No. with live fetus(es)		24	24	24	23
No. with total litter loss		0	0	0	0
Clinical observations		-	-	-	-
Necropsy observations		-	-	-	-
Gestation body weight		-	-	-	-
Lactation body weight		-	-	-	-
Gestation body weight gain[a]					
GD 6-8		10.8 g	-	-	−48.1%***
GD 16-18		28.9 g	-	-	−17.0%**

Table 2.6.7.14 Reproductive and Developmental Toxicity (Continued) **Study No. DPN0371**

Daily dose (mg/kg)		**0 (Control)**	3	10	**30**
Lactation body weight gain		-	-	-	-
Gestation food consumption		-	-	-	-
Lactation food consumption		-	-	-	-
Mean duration of gestation (days)		-	-	-	-
No. with live pups		-	-	-	-
No. with total litter loss		-	-	-	-
Gestation index (%)		-	-	-	-
Mean no. implantations		-	-	-	-
Live born pups (total number)		-	-	-	-
Still born pups (total number)		-	-	-	-
Live birth index (%)		-	-	-	-
Sex ratios (% males) - Day 0		-	-	-	-
Post implantation loss (%)		-	-	-	-
Pups delivered		-	-	-	-
Dead pups		-	-	-	-
F1 Litters (Preweaning)	No. evaluated	24	24	24	23
Viability index at PND 4 (pre-culling) (%)		-	-	-	-
Viability index at PND 21 (weaning) (%)		-	-	-	-
Viable pups (total number)					
PND 1-4		-	-	-	-
PND 4-21		-	-	-	-
Body weight[a]					
PND 0[b]	Males	6.85 g	-	-	−10.7%***
	Females	6.47 g	-	-	−12.4%***

Table 2.6.7.14 Reproductive and Developmental Toxicity (Continued) **Study No. DPN0371**

Daily dose (mg/kg)		**0 (Control)**	3	10	**30**
PND 4[b] (precull)	Males	10.28 g	-	-	−10.7%**
	Females	9.84 g	-	-	−11.7%**
PND 4 (postcull)	Males	10.24 g	-	-	−11.3%
	Females	9.79 g	-	-	−12.9%
PND 21[b]	Males	54.99 g	-	-	−4.60%
	Females	53.81 g	-	-	−5.59%*
Clinical observations		-	-	-	-
Pup necropsy observations		-	-	-	-
Landmark development					
Eye opening		-	-	-	-
Surface righting		-	-	-	-
Pupillary reflex		-	-	-	-
Balanopreputial separation		-	-	-	-
Vaginal opening		-	-	-	-
Sensory evaluation and behavioral testing					
Auditory startle - Males and Females (PND 31 or 66)		-	-	-	-
Locomotor activity - Males and Females (PND 22 or 59)		-	-	-	-
Learning (Water Maze) - Males and Females (PND 43)		-	-	-	-
F1 Males (Postweaning)	No. evaluated	24	24	24	23
No. found dead or sacrificed moribund		-	-	-	-
Clinical observations		-	-	-	-
Body weight (%)[a]					

Table 2.6.7.14 Reproductive and Developmental Toxicity (Continued) **Study No. DPN0371**

Daily dose (mg/kg)	**0 (Control)**	3	10	**30**
Post weaning Day 0	93 g	-	-	−9.68%
Post weaning Day 56	534 g	-	-	−10.7%**
Pairing Day 7	558 g	-	-	−10.8%***
Post pairing Day 14	629 g	-	-	−10.7%**
Body weight gain[a]				
Post weaning Days 28-35	66.0 g	-	-	−16.7%***
Pairing Day 14-Post pairing Day 7	25.3 g	-	-	−19.4%
Food consumption[a]				
Pairing Days 49-56	242.8 g	-	-	−4.74%
Post pairing Days 7-14	254.3 g	-	-	−8.61%*
Male reproductive indices				
Mating index %	-	-	-	-
Fecundity index %	-	-	-	-
Fertility index %	-	-	-	-
F1 Females (Postweaning) No. evaluated	24	23	24	23
No. found dead or sacrificed moribund	-	-	-	-
Clinical observations	-	-	-	-
Body weight[a]				
Post weaning Day 0	87 g	-	-	−9.20%*
Gestation	-	-	-	-
Food consumption	-	-	-	-
Average times in estrus	-	-	-	-
No. of days to inseminate	-	-	-	-
No. females placed into cohabitation	24	23	24	23

Table 2.6.7.14 Reproductive and Developmental Toxicity (Continued) **Study No. DPN0371**

Daily dose (mg/kg)		**0 (Control)**	3	1**0**	**30**
Mating index (%)		-	-	-	-
Fecundity index (%)		-	-	-	-
Fertility index (%)		-	-	-	-
No. with viable litter (Pregnant females)		21	20	18	19
No. with total litter loss		-	-	-	-
No. corpora lutea		-	-	-	-
No. implantations		-	-	-	-
Pre-implantation loss (%)		-	-	-	-
F1 Litters	No. evaluated	21	19	18	19
Live		-	-	-	-
No. dead		0	0	0	0
Early resorptions		-	-	-	-
Late resorptions		-	-	-	-
Post-implantation loss (%)		-	-	-	-

GD = gestation day; LD = lactation day; PND = postnatal day; - = no noteworthy findings; * = statistically significant at $p < 0.05$; ** = statistically significant at $p < 0.01$; *** = statistically significant at $p < 0.001$ (Dunnett Exact Homogenous Test or Wilcoxon Rank Sum Test).

[a] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences**.**

[b] Covariate adjusted mean.

15 新生児を用いた試験

該当なし。

16 局所刺激性試験

該当なし。

17 その他の毒性試験

Table 2.6.7.17A Other Toxicity Studies – *不純物A **Qualification – 1-month Rat Study** **Test Article:** Fedratinib

Report Title: SAR302503 - 1-month Oral Toxicity Study in Rats with a 4-week Recovery Period

Species/Strain: Rat/Sprague Dawley | **Duration of Dosing:** 28 days | **Study No.:** TSA1485

Initial Age: Approximately 6 to 7 weeks | **Duration of Postdose:** 4 weeks | **Location in Dossier:** 4.2.3.7.6-1

Date of First Dose: [redacted] (M)/[redacted] (F), 20[redacted] | **Method of Administration:** Oral gavage

Special Features: None | **Vehicle/Formulation:** 0.5% methylcellulose | **GLP Compliance:** Yes

No Observed Adverse Effect Level: 5 mg/kg

Daily dose (mg/kg)	**0 (Control)**		**5**		**30**		**80**	
No. of animals	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Noteworthy findings[a]								
No. found dead/moribund sacrifice	0	0	0	0	0	0	0	1[b]
Clinical observations[c]								
Incoordination (gait)	0/0	0/0	-	-	-	-	3/1	7/4
Increased resistance to dosing	0/0	0/0	-	-	-	-	5/9	11/9
Piloerection; whole body (mild)	0/0	0/0	-	-	-	-	5/9	8/11
Piloerection; whole body (moderate)	0/0	0/0	-	-	-	-	2/2	8/2
Salivation (mild)	0/0	0/0	-	-	-	-	2/9	2/14
Salivation (moderate)	0/0	0/0	-	-	-	-	5/10	3/11
Salivation (marked)	-	0/0	-	-	-	-	-	2/3
Coat thinning; abdomen (mild)	0/0	0/0	-	-	-	-	2/3	8/7
Coat thinning; abdomen (moderate)	0/0	0/0	-	-	-	-	2/2	4/2
Coat thinning; ventral neck (mild)	0/0	-	-	-	-	-	3/1	-
Coat thinning; chest (mild)	-	0/0	-	-	-	-	-	7/5
Coat thinning; chest (moderate)	-	0/0	-	-	-	-	-	4/1

Table 2.6.7.17A Other Toxicity Studies – *不純物A Qualification (Continued) **Study No. TSA1485**

Daily dose (mg/kg)	**0 (Control)**		**5**		**30**		**80**	
No. of animals	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Noisy respiration	-	0/0	-	-	-	-	-	2/1
Partially closed eyelids	0/0	0/0	-	-	-	-	4/2	8/13
Body weight[d]								
Day 8	285 g	186 g	-	-	−3%*	−1%	−4%*	−1%
Day 28	391 g	237 g	-	-	−7%*	−5%*	−17%*	−7%*
Body weight gain[d]								
Day 1 to 8	54.5 g	19.7 g	-	-	-	-	−18%	−20%
Day 22 to 28	28.5 g	14.5 g	-	-	-	-	−56%	−33%
Food consumption[d]								
Day 1 to 8	29.3 g	-	-	-	−8%	-	−4%	-
Day 22 to 28	30.6 g	-	-	-	−8%*	-	−14%*	-
Ophthalmology	-	-	-	-	-	-	-	-
Hematology[d] (Day 29)								
Reticulocytes (%)	2.36	2.77	-	-	−11%*	−30%*	−36%*	−27%*
Platelets (10^9/L)	952	1090	-	-	24%*	-	28%*	29%*
White blood cells (10^9/L)	-	10.2	-	-	-	-	-	−22%*
Neutrophils (10^9/L)	1.71	1.32	-	-	-	21%*	46%*	45%*
Lymphocytes (10^9/L)	-	8.47	-	-	-	-	-	−32%*
Monocytes (10^9/L)	0.225	0.243	-	-	44%*	16%	37%*	-
Large unstained cell counts (10^9/L)	0.066	0.075	-	-	−15%	−33%*	−61%*	−62%*
Serum chemistry[d] (Day 29)								
Aspartate aminotransferase (U/L)	99.4	111	-	-	-	-	158*	243%*
Alanine aminotransferase (U/L)	35.1	40.6	-	-	-	-	125%*	112%*

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Table 2.6.7.17A Other Toxicity Studies – *不純物A Qualification (Continued) **Study No. TSA1485**

Daily dose (mg/kg)		**0 (Control)**		**5**		**30**		**80**	
No. of animals		**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Alkaline phosphatase (U/L)		197	122	-	-	-	56%*	35%*	164%*
Bilirubin (µmol/L)		-	1.14	-	-	-	−23%*	-	−49%*
Cholesterol (mmol/L)		1.44	1.64	-	-	-	−34%*	−45%*	−61%*
Potassium (mmol/L)		6.71	6.45	-	-	-	-	9%*	12%*
Fibrinogen (g/L)		3.95	-	-	-	-	-	−17%*	-
Urinalysis[d] (Day 29)									
Creatinine (µmol)		73.9	48.3	-	-	−10%*	-	−20%*	−16%*
Protein (mg)		6.7	2.1	-	-	-	-	51%*	125%*
Organ weights[d]	No. evaluated	10	10	10	10	10	10	10	10
Heart									
Absolute wt		1.36 g	0.91 g	-	-	−7.18 %	−0.07%	−2.10%	11.1%
Relative to brain wt ratio		65.3	47.6	-	-	−4.97%	−1.67%	1.48%	10.9%*
Liver									
Absolute wt		10.5 g	7.03 g	-	-	−6.99%	−2.37%	−6.88%	12.1%**
Relative to brain wt ratio		505	369	-	-	−4.79%	−4.21%	−3.76%	11.8%**
Lung									
Absolute wt		1.65 g	1.21 g	-	-	7.20%	−5.73%	1.47%	31.4%**
Relative to brain wt ratio		79.0	63.3	-	-	9.88%	−7.42%	5.24%	31.2%**
Spleen									
Absolute wt		0.580 g	0.516 g	-	-	−16.5%*	−16.8%**	−37.7%**	−37.2%**
Relative to brain wt ratio		27.8	27.0	-	-	−14.6%*	−18.1%**	−35.4%**	−37.2%**
Thymus									
Absolute wt		0.465 g	0.433 g	-	-	−2.64%	−14.2%	−44.1%**	−44.7%**

＊新薬承認情報提供時に置き換え

Table 2.6.7.17A Other Toxicity Studies – *不純物A Qualification (Continued) **Study No. TSA1485**

Daily dose (mg/kg)	**0 (Control)**		**5**		**30**		**80**	
No. of animals	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Relative to brain wt ratio	22.3	22.7	-	-	−0.48%	−15.6%	−41.9%**	−44.8%**
Gross pathology	-	-	-	-	-	-	-	-
Histopathology								
Bone marrow (femur) No. evaluated	10	10	9	10	10	10	10	11
Hypocellularity								
Minimal to mild	0	0	-	-	2	1	9	11
Bone marrow (sternum) No. evaluated	10	10	10	10	10	10	10	8
Hypocellularity								
Minimal to moderate	0	0	-	-	5	8	6	8
Heart No. evaluated	10	10	10	10	10	10	10	11
Degeneration/necrosis: myocardium								
Minimal to mild	5	3	-	-	-	-	9	8
Liver No. evaluated	10	10	10	10	10	10	10	11
Hypertrophy: hepatocellular, diffuse								
Minimal	0	0	-	-	-	-	10	10
Hypertrophy: bile duct epithelium								
Mild	0	0	-	-	-	-	10	10
Mesenteric lymph nodes No. evaluated	10	10	9	9	10	10	9	9
Depletion: lymphocyte								
Minimal to moderate	0	0	-	-	3	2	8	9
Lung No. evaluated	10	10	10	10	10	10	10	11
Macrophages: alveolar								

＊新薬承認情報提供時に置き換え

Table 2.6.7.17A Other Toxicity Studies – *不純物A Qualification (Continued) Study No. TSA1485

Daily dose (mg/kg)		0 (Control)		5		30		80	
No. of animals		**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
	Minimal to mild	8	3	-	-	-	-	10	11
Muscle - quadriceps	No. evaluated	10	10	10	10	10	10	10	11
Degeneration/necrosis									
	Minimal to mild	-	8	-	-	-	-	-	8
Spleen	No. evaluated	10	10	10	10	10	10	10	11
Depletion: lymphocyte									
	Minimal to mild	0	0	-	-	-	-	3	8
Stomach - nonglandular	No. evaluated	10	10	10	10	10	10	10	11
Edema									
	Minimal to mild	0	0	-	-	1	-	10	4
Hyperplasia: squamous cell									
	Mild to moderate	0	0	-	-	-	-	4	2
Thymus	No. evaluated	10	10	10	10	10	9	9	11
Atrophy: cortex									
	Minimal to mild	0	0	-	-	-	-	3	4
Necrosis: lymphocyte									
	Minimal to moderate	0	0	-	-	2	-	4	9
Postdose evaluation									
Body weight[d]									
Day 36		412 g	253 g	-	-	−3%	−7%*	−16%*	−8%*
Day 56/57		482 g	275 g	-	-	-	-	−11%*	−10%*
Body weight gain[d]									
Day 29 to 36		47.4 g	28.0 g	-	-	-	-	−17%	7%

Table 2.6.7.17A Other Toxicity Studies – *不純物A Qualification (Continued) **Study No. TSA1485**

Daily dose (mg/kg)	**0 (Control)**		**5**		**30**		**80**	
No. of animals	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Day 36 to 43	27.0 g	8.4 g	-	-	-	-	4%	−109%
Food consumption[d]								
Day 29 to 36	29.8	-	-	-	−9%	-	−7%	-
Day 50 to 56/57	30.9	-	-	-	−3%	-	−7%	-
Hematology[d] (Day 57/58)								
Red blood cells (10^{12}/L)	8.47	-	-	-	−5%*	-	−7%*	-
White blood cells (10^9/L)	-	10.1	-	-	-	−26%*	-	−19%*
Neutrophils (10^9/L)	-	1.24	-	-	-	−29%	-	−24%
Lymphocytes (10^9/L)	-	8.32	-	-	-	−24%	-	−17%
Monocytes (10^9/L)	-	0.326	-	−45%	-	−46%	-	−18%
Histopathology								
Stomach: nonglandular No. evaluated	5	5	5	5	5	5	5	4
Edema								
Minimal	0	-	-	-	1	-	-	-

wt = weight; * = statistically significant at $p \leq 0.05$; ** = statistically significant at $p \leq 0.01$.

[a] Only treatment-related findings presented.

[b] One female was found dead on Day 21; death was preceded by clinical signs of salivation on Days 19 and 20; cause of death was undetermined.

[c] Mean number of days with sign/no. of animals with finding.

[d] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical difference is based on actual data not percent differences.

＊新薬承認情報提供時に置き換え

Table 2.6.7.17B Other Toxicity Studies – Phototoxicity **Test Article:** Fedratinib

Species/ Strain	Method of Administration	Dosing Period	Doses	No. per Group	Noteworthy Findings	Study No.
3T3 cells (mouse BALB/c fibroblasts)	In vitro	1 hour	Experiment 1: 0.3 to 1000 µg/mL Experiment 2: 10 to 300 µg/mL	6 wells/ dose	**Experiment 1:** IC50 = 94.07 µg/mL and 64.91 µg/mL, without and with UVA irradiation respectively. PIF = 1.45 (non-phototoxic) **Experiment 2:** IC50 = 78.69 µg/mL and 80.91 µg/mL, without and with UVA irradiation respectively. PIF = 0.97 (non-phototoxic) Fedratinib did not show any in vitro phototoxic potential in 3T3 cells.	PHV0056

IC50 = the concentration of the test article that inhibits the uptake of Neutral Red by 50%; PIF = photo irritation factor; UVA = ultraviolet light A.

Table 2.6.7.17C Other Toxicity Studies – Expert Panel Report **Test Article:** Fedratinib

Species/ Strain	Method of Administration	Dosing Period	Doses (mg/kg)	Sex/No. per Group	Noteworthy Findings	Study No.
Dog/ Beagle	Oral gavage	28 days or 9-months	28-day study: 0, 2, 5, 10, or 40/30[a] 9-month study: 0, 2, 6, or 20/15[b]	28-day study: Main study: 3M/3F Recovery: 2M/2F in control and 40/30 mg/kg 9-month study: 3-month interim: 3M/3F in control, 2 and 6 mg/kg; 1M/2F in 20/15 mg/kg 6-month interim: 3M/3F in control, 2 and 6 mg/kg; 2M/3F in 20/15 mg/kg 9-month: 4M/4F	28-day study (TX-[redacted]-101348-075F): A review by a panel of external experts was conducted on the bone marrow sections of dogs from all groups with the diagnosis of bone marrow hypoplasia plus selected controls. The Expert Panel confirmed the presence of decreased hematopoiesis, termed “hypoplasia” by the Study Pathologist, in the bone marrow of dogs treated at 40/30 mg/kg. This decrease was characterized by a loss of cellularity due primarily to a decrease in the post-mitotic pool of hematopoietic cells (i.e., mature, differentiated myeloid and erythroid cells). In some dogs with decreased hematopoiesis at 40/30 mg/kg, the Expert Panel observed an apparent increase in early stage hematopoietic progenitor cells in the bone marrow. 9-month study (TX-[redacted]-101348-046A): A review by a panel of external experts was conducted on bone marrow sections from dogs treated at 20/15 mg/kg and selected controls. The Expert Panel noted decreased hematopoiesis was more severe in dogs sacrificed moribund or found dead, and was characterized by a loss of cellularity due primarily to a decrease in the post-mitotic pool of hematopoietic cells (i.e., mature myeloid and erythroid cells and megakaryocytes). The decreased hematopoiesis was accompanied by proliferation of early stage hematopoietic progenitor cells, likely of myeloid (granulocytic) lineage with or without limited maturation/differentiation into later stage (post-mitotic) cells and was consistent with “ineffective myelopoiesis.”	EXP0092

Table 2.6.7.17C Other Toxicity Studies – Expert Panel Report **Test Article:** Fedratinib

Species/ Strain	Method of Administration	Dosing Period	Doses (mg/kg)	Sex/No. per Group	Noteworthy Findings	Study No.
					The panel concluded that the nomenclature "stem cell hyperplasia" used by the Study Pathologist was not appropriate, as the cells that increased in the hypocellular bone marrow did not have morphologic features generally associated with bone marrow stem cells. Based on this, the terminology developed by the Expert Panel is used in the Written and Tabular Summaries. The Study Pathologist also diagnosed "stem cell infiltration" in the liver and spleen of some dogs with bone marrow changes. The Expert Panel considered these changes to be a proliferation of hematopoietic (myeloid) progenitor cells similar to that occurring in the bone marrow. This proliferation of early progenitor cells was considered a putative attempt at bone marrow/hematologic recovery in animals and was considered non-neoplastic. The Expert Panel considered the changes in the bone marrow to start as a decrease in hematopoiesis followed by a proliferation of early stage hematopoietic progenitor cells of myeloid (granulocytic) lineage.	

[a] Due to unexpected toxicity, dosing was suspended in all dogs at 40 mg/kg from Days 12 to 15; on Day 16, dosing resumed at 30 mg/kg. On Day 24, dosing was terminated in the males but continued until Day 28 for the females at 30 mg/kg.
[b] Due to mortality noted at 20 mg/kg, the dose level was decreased to 15 mg/kg beginning on Day 26.

Table 2.6.7.17D Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物B

Report Title: *不純物B - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.:** HIS2151

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-2

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted] and [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	11.7 ± 1.2	91.7 ± 11.9	6.7 ±1.5	4.7 ± 2.3	137.3 ± 8.6
	*不純物B	5	17.7 ± 4.0	85.7 ± 2.1	7.3 ± 1.5	3.7 ± 1.2	122.0 ± 15.6
		16	14.0 ± 7.2	90.0 ± 6.0	8.3 ± 1.2	5.0 ± 1.0	128.0 ± 6.1
		50	13.0 ± 1.0	84.3 ± 4.7	6.7 ± 2.1	6.0 ± 1.7	116.7 ± 7.5
		160	15.3 ± 2.1	78.3 ± 6.4	2.7 ± 2.5	7.7 ± 1.5	117.3 ± 3.1
		500	15.0 ± 1.7	79.0 ± 2.6	6.3 ± 2.1	6.7 ± 0.6	128.7 ± 5.5
		1600	17.3 ± 3.2	79.7 ± 0.6	7.3 ± 0.6	7.7 ± 4.2	83.7 ± 20.0
		5000	18.7 ± 1.5	66.7 ± 7.2	4.0 ± 4.4	6.0 ± 1.0	6.3 ± 6.5[a]
	Sodium azide	1.0	NA	NA	280.3 ± 12.7	NA	NA
		2.0	NA	547.0 ± 33.8	NA	NA	NA
	ICR191[b]	0.3	NA	NA	NA	188.0 ± 34.1	NA
	2-nitrofluorene	2.5	386.7 ± 47.1	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	NA	NA	681.3 ± 50.2

Table 2.6.7.17D Other Toxicity Studies - Genotoxicity Study on *不純物B **(Continued)** **Study No. HIS2151**

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	DMSO	0	17.3 ± 2.5	96.7 ± 1.2	6.3 ± 1.5	6.0 ± 2.0	184.3 ± 5.7
	*不純物B	5	22.0 ± 5.6	82.3 ± 24.1	9.0 ± 2.6	6.3 ± 3.2	162.7 ± 8.7
		16	18.7 ± 5.0	91.7 ± 5.1	5.3 ± 1.5	10.7 ± 2.1	176.7 ± 14.3
		50	21.0 ± 3.5	86.3 ± 5.0	4.0 ± 2.6	7.3 ± 4.0	187.3 ± 15.3
		160	20.7 ± 0.6	86.0 ± 6.6	5.7 ± 1.2	5.7 ± 4.0	185.3 ± 11.0
		500	22.3 ± 4.7	81.3 ± 8.6	6.0 ± 2.0	7.7 ± 0.6	176.3 ± 20.8
		1600	25.0 ± 4.4	80.0 ± 6.6	8.0 ± 4.0	7.3 ± 3.5	154.7 ± 17.7
		5000	15.7 ± 5.0	65.3 ± 7.4	4.3 ± 3.2	7.3 ± 2.3	15.3 ± 5.7[a]
	2-aminoanthracene	1.5	1115.0 ± 104.1	1389.3 ± 43.7	180.3 ± 18.9	104.0 ± 10.5	NA
		8.0	NA	NA	NA	NA	1114.7 ± 125.3

Table 2.6.7.17D Other Toxicity Studies - Genotoxicity Study on *不純物B **(Continued)** **Study No. HIS2151**

First repeat of TA98 & TA102

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	17.0 ± 2.6	NA	NA	NA	133.0 ± 10.8
	*不純物B	5	16.0 ± 1.0	NA	NA	NA	129.7 ± 13.3
		16	12.7 ± 6.1	NA	NA	NA	135.7 ± 21.1
		50	15.0 ± 3.0	NA	NA	NA	135.7 ± 12.1
		160	13.7 ± 0.6	NA	NA	NA	130.3 ± 3.5
		500	16.3 ± 4.0	NA	NA	NA	121.3 ± 10.1
		1600	12.3 ± 5.1	NA	NA	NA	97.0 ± 12.0
		5000	18.3 ± 4.5	NA	NA	NA	2.7 ± 1.2[a]
	2-nitrofluorene	2.5	388.0 ± 22.5	NA	NA	NA	NA
	Mitocmycin C	0.3	NA	NA	NA	NA	628.3 ± 21.9

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] Toxicity indicated by clearing or diminution of background growth.
[b] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17E Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物C

Report Title: *不純物C - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 1 **Study No.:** HIS2148

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-3

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	23.3 ± 1.5	90.3 ± 2.5	7.3 ± 3.8	6.7 ± 1.5	148.0 ± 7.0
	*不純物C	5	15.7 ± 5.9	87.7 ± 3.5	8.7 ± 2.5	7.3 ± 0.6	143.0 ± 13.1
		16	21.3 ± 3.2	82.7 ± 1.2	11.3 ± 4.0	7.0 ± 1.7	131.0 ± 6.2
		50	17.3 ± 3.5	86.7 ± 7.0	4.7 ± 3.8	7.0 ± 1.7	151.0 ± 14.2
		160	26.0 ± 7.0	97.3 ± 16.0	6.7 ± 2.3	7.0 ± 1.0	141.0 ± 14.7
		500	22.7 ± 2.3[a]	99.0 ± 5.3[a]	7.7 ± 6.4[a]	7.3 ± 3.5[a]	132.3 ± 7.6[a]
		1600	19.7 ± 1.5[a,b]	69.3 ± 16.8[a,b]	4.3 ± 2.5[a,b]	5.0 ± 2.6[a,b]	56.7 ± 8.5[a,b]
		5000	0.0 ± 0.0[a,b]	0.0 ± 0.0[a,b]	0.0 ± 0.0[a,b]	0.0 ± 0.0[a,b]	0.0 ± 0.0[a,b]
	Sodium azide	1.0	NA	NA	323.0 ± 7.2	NA	NA
		2.0	NA	498.3 ± 8.1	NA	NA	NA
	ICR191[c]	0.3	NA	NA	NA	183.3 ± 14.6	NA
	2-nitrofluorene	2.5	347.7 ± 19.4	NA	NA	NA	NA
	Mitocmycin C	0.3	NA	NA	NA	NA	737.3 ± 35.1

Table 2.6.7.17E Other Toxicity Studies - Genotoxicity Study on *不純物C **(Continued)** **Study No. HIS2148**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	DMSO	0	21.0 ± 3.6	102.3 ± 3.5	9.3 ± 3.2	7.7 ± 1.2	203.7 ± 11.9
	*不純物C	5	20.0 ± 7.2	86.7 ± 6.7	7.3 ± 1.5	6.3 ± 1.2	206.7 ± 18.1
		16	27.7 ± 7.1	87.3 ± 7.5	7.3 ± 2.9	7.7 ± 3.2	210.7 ± 8.7
		50	25.7 ± 5.5	96.3 ± 6.0	5.7 ± 1.2	5.7 ± 1.5	198.3 ± 13.5
		160	18.3 ± 2.1	91.7 ± 11.0	7.3 ± 1.2	6.7 ± 1.5	221.0 ± 7.8
		500	21.3 ± 0.6[a]	85.7 ± 17.1	10.3 ± 2.1	8.3 ± 1.5	195.7 ± 12.2
		1600	19.3 ± 3.5[a,b]	81.3 ± 11.1[a,b]	6.0 ± 2.6[a,b]	7.0 ± 1.7[a,b]	135.0 ± 14.0[a,b]
		5000	4.0 ± 1.0[a,b]	0.0 ± 0.0[a,b]	0.0 ± 0.0[a,b]	1.3 ± 1.5[a,b]	0.0 ± 0.0[a,b]
	2-aminoanthracene	1.5	1104.3 ± 31.3	1274.7 ± 88.8	179.7 ± 10.0	126.3 ± 16.8	NA
		8.0	NA	NA	NA	NA	900.7 ± 153.7

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] Toxicity indicated by clearing or diminution of background growth.
[b] Precipitate.
[c] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

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Table 2.6.7.17F Other Toxicity Studies - Genotoxicity Study on *不純物D **Test Article:** *不純物D

Report Title: *不純物D - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 1 **Study No.:** HIS2149

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-4

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: Water **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	Water	0	23.7 ± 4.0	89.7 ± 1.5	8.7 ± 3.5	5.7 ± 2.5	175.7 ± 10.3
	*不純物D	5	22.0 ± 6.0	98.0 ± 1.0	9.0 ± 0.0	5.7 ± 2.3	171.3 ± 4.5
		16	21.0 ± 1.7	91.3 ± 1.2	9.3 ± 2.5	7.0 ± 1.0	178.7 ± 3.2
		50	29.0 ± 5.3	108.0 ± 3.6	7.0 ± 1.0	4.7 ± 1.5	160.7 ± 12.0
		160	27.0 ± 6.0	106.3 ± 9.9	9.0 ± 2.6	5.7 ± 1.5	159.0 ± 13.0
		500	25.0 ± 1.7	88.0 ± 11.0	10.3 ± 1.5	6.0 ± 2.0	156.7 ± 13.0
		1600	23.3 ± 4.5	95.0 ± 16.5	10.0 ± 3.6	3.0 ± 1.7	162.7 ± 17.6
		5000	24.3 ± 2.5	99.0 ± 1.0	10.7 ± 2.1	5.7 ± 3.1	170.0 ± 22.6
	Sodium azide	1.0	NA	NA	353.3 ± 19.8	NA	NA
		2.0	NA	593.0 ± 34.8	NA	NA	NA
	ICR191[a]	0.3	NA	NA	NA	159.7 ± 11.7	NA
	2-nitrofluorene	2.5	413.7 ± 9.0	NA	NA	NA	NA
	Mitocmycin C	0.3	NA	NA	NA	NA	731.3 ± 68.9

Table 2.6.7.17F Other Toxicity Studies - Genotoxicity Study on *不純物D **(Continued)** **Study No. HIS2149**

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	Water	0	24.3 ± 5.1	97.3 ± 13.9	8.7 ± 0.6	5.0 ± 1.7	195.0 ± 1.7
	*不純物D	5	26.3 ± 6.4	91.7 ± 7.0	9.0 ± 2.6	6.7 ± 3.2	199.0 ± 2.6
		16	22.0 ± 3.0	89.3 ± 5.0	8.3 ± 3.5	8.0 ± 2.0	202.3 ± 9.0
		50	25.7 ± 2.1	88.3 ± 4.7	8.3 ± 3.1	7.3 ± 1.5	206.3 ± 16.5
		160	27.3 ± 0.6	89.0 ± 2.0	9.7 ± 3.1	8.0 ± 1.7	210.0 ± 14.0
		500	20.3 ± 4.7	98.3 ± 1.2	10.0 ± 3.5	7.0 ± 1.7	204.0 ± 7.0
		1600	31.0 ± 1.0	93.0 ± 4.4	9.3 ± 2.9	7.0 ± 1.0	216.3 ± 16.7
		5000	26.7 ± 3.5	80.3 ± 5.5	7.3 ± 3.8	7.7 ± 2.3	190.0 ± 2.6
	2-aminoanthracene	1.5	1081.3 ± 31.6	1250.0 ± 101.8	175.0 ± 15.1	122.7 ± 5.1	NA
		8.0	NA	NA	NA	NA	1028.0 ± 45.1

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

＊新薬承認情報提供時に置き換え

Table 2.6.7.17G Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物E

Report Title: *不純物E - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.:** HIS2154

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-5

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted] and [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	13.0 ± 5.0	87.7 ± 5.1	7.3 ± 1.5	5.3 ± 2.5	114.0 ± 12.3
	*不純物E	5	12.7 ± 3.5	88.3 ± 10.4	5.0 ± 0.0	5.3 ± 1.5	110.3 ± 24.0
		16	13.3 ± 2.3	79.7 ± 2.3	3.3 ± 0.6	5.0 ± 1.0	116.0 ± 1.0
		50	15.3 ± 3.8	92.7 ± 8.7	6.7 ± 3.8	5.7 ± 2.9	130.3 ± 16.7
		160	17.7 ± 3.5	84.0 ± 4.0	3.7 ± 2.3	4.7 ± 0.6	115.0 ± 12.8
		500	15.0 ± 4.6	86.0 ± 7.2	3.7 ± 2.1	7.7 ± 0.6	99.7 ± 2.1
		1600	17.3 ± 2.1[a]	67.7 ± 2.5[a]	4.7 ± 2.5[a]	4.3 ± 2.9[a]	69.0 ± 7.2[a]
		5000	15.0 ± 2.6[a,b]	21.7 ± 8.6[a,b]	2.0 ± 1.7[a,b]	6.3 ± 2.5[a,b]	5.3 ± 5.0[a,b]
	Sodium azide	1.0	NA	NA	278.7 ± 11.1	NA	NA
		2.0	NA	518.7 ± 44.8	NA	NA	NA
	ICR191[c]	0.3	NA	NA	NA	161.0 ± 12.2	NA
	2-nitrofluorene	2.5	313.0 ± 30.6	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	NA	NA	636.0 ± 30.0

Table 2.6.7.17G Other Toxicity Studies - Genotoxicity Study on *不純物E **(Continued)** **Study No. HIS2154**

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	DMSO	0	16.7 ± 3.2	86.0 ± 5.3	7.3 ± 2.3	9.3 ± 1.5	185.7 ± 4.9
	*不純物E	5	19.3 ± 3.5	78.7 ± 12.6	8.0 ± 1.0	5.3 ± 1.2	183.7 ± 9.7
		16	16.3 ± 6.8	93.0 ± 13.1	4.3 ± 2.1	6.7 ± 2.3	175.7 ± 12.5
		50	15.7 ± 4.0	85.7 ± 10.8	6.0 ± 2.6	11.7 ± 2.5	172.3 ± 14.0
		160	18.7 ± 3.5	91.7 ± 8.7	7.7 ± 1.2	9.7 ± 5.8	223.0 ± 9.0
		500	18.7 ± 4.9	96.7 ± 12.2	6.0 ± 2.6	7.0 ± 2.0	207.7 ± 29.7
		1600	22.0 ± 1.0	92.7 ± 10.5	4.7 ± 3.2	7.7 ± 3.2	178.7 ± 9.9
		5000	25.7 ± 5.7[b]	75.3 ± 9.1[b]	3.7 ± 1.5[b]	7.0 ± 3.0[b]	83.3 ± 11.6[b]
	2-aminoanthracene	1.5	1129.0 ± 50.2	1271.0 ± 45.7	169.0 ± 13.2	118.0 ± 10.0	NA
		8.0	NA	NA	NA	NA	1056.7 ± 145.2

Table 2.6.7.17G Other Toxicity Studies - Genotoxicity Study on *不純物E **(Continued)** **Study No. HIS2154**

First repeat of TA98, TA102 & TA1535

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	15.3 ± 1.5	NA	7.7 ± 3.8	NA	145.7 ± 12.5
	*不純物E	1.6	NA	NA	5.7 ± 1.5	NA	NA
		5	12.3 ± 3.1	NA	6.3 ± 2.1	NA	125.0 ± 8.9
		16	10.3 ± 1.5	NA	6.3 ± 2.9	NA	145.3 ± 12.1
		50	15.3 ± 3.5	NA	5.0 ± 5.2	NA	135.3 ± 6.1
		160	12.0 ± 1.7	NA	4.3 ± 1.5	NA	140.7 ± 6.4
		500	17.0 ± 4.4	NA	6.3 ± 4.0	NA	129.7 ± 6.0
		1600	16.0 ± 4.6[a]	NA	3.7 ± 0.6	NA	94.3 ± 5.5[a]
		5000	17.0 ± 6.0[a,b]	NA	2.7 ± 2.1[a,b]	NA	6.0 ± 1.0[a,b]
	2-nitrofluorene	2.5	382.7 ± 35.9	NA	NA	NA	NA
	Sodium azide	1.0	NA	NA	268.7 ± 25.7	NA	NA
	Mitocmycin C	0.3	NA	NA	NA	NA	834.7 ± 30.7

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] Toxicity indicated by clearing or diminution of background growth.
[b] Precipitate.
[c] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17H Other Toxicity Studies –Genotoxicity Study on *不純物F **Test Article:** *不純物F

Report Title: *不純物F - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 3 **Study No.:** HIS2155

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-6

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	14.7 ± 1.2	91.0 ± 7.0	5.0 ± 1.0	6.0 ± 2.0	144.0 ± 1.7
	*不純物F	5	14.0 ± 2.6	95.3 ± 7.6	8.0 ± 2.0	5.7 ± 1.2	145.0 ± 17.7
		16	17.0 ± 4.4	86.0 ± 8.7	4.3 ± 1.5	5.7 ± 5.0	142.0 ± 1.7
		50	15.3 ± 4.9	97.7 ± 6.7	6.3 ± 0.6	3.7 ± 1.2	143.0 ± 23.6
		160	16.0 ± 4.4	90.3 ± 13.1	4.3 ± 1.5	7.7 ± 4.0	130.7 ± 4.2
		500	14.3 ± 2.1	92.0 ± 5.6	3.3 ± 2.3	5.3 ± 0.6	143.0 ± 11.1
		1600	15.7 ± 4.2	93.0 ± 14.0	7.3 ± 2.1	5.0 ± 0.0	132.7 ± 5.0
		5000	12.3 ± 5.1	79.0 ± 4.6	6.0 ± 2.6	5.7 ± 0.6	73.0 ± 8.9
	Sodium azide	1.0	NA	NA	268.3 ± 5.0	NA	NA
		2.0	NA	507.3 ± 37.2	NA	NA	NA
	ICR191[a]	0.3	NA	NA	NA	164.3 ± 10.0	NA
	2-nitrofluorene	2.5	414.7 ± 14.8	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	NA	NA	707.7 ± 24.7

Table 2.6.7.17H Other Toxicity Studies - Genotoxicity Study on *不純物F **(Continued)** **Study No. HIS2155**

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	DMSO	0	17.7 ± 3.2	103.3 ± 2.5	5.7 ± 1.5	7.0 ± 3.6	186.0 ± 13.1
	*不純物F	5	16.0 ± 1.7	94.0 ± 8.2	6.3 ± 1.5	5.7 ± 2.1	211.7 ± 11.6
		16	19.0 ± 2.6	94.7 ± 10.1	6.3 ± 1.2	10.3 ± 2.5	203.0 ± 3.6
		50	20.0 ± 8.5	94.3 ± 9.9	4.7 ± 1.2	8.0 ± 4.0	220.3 ± 5.5
		160	18.3 ± 4.7	93.0 ± 7.8	6.0 ± 1.7	8.3 ± 2.1	210.3 ± 3.1
		500	21.3 ± 5.5	82.0 ± 13.9	8.0 ± 1.7	8.0 ± 2.6	207.3 ± 11.2
		1600	16.7 ± 3.1	92.3 ± 4.0	6.3 ± 1.5	4.3 ± 2.1	207.0 ± 6.1
		5000	25.3 ± 2.5	90.0 ± 13.5	6.3 ± 1.2	5.0 ± 0.0	139.3 ± 13.1
	2-aminoanthracene	1.5	1340.7 ± 99.7	1340.3 ± 70.5	178.7 ± 15.9	142.0 ± 17.5	NA
		8.0	NA	NA	NA	NA	1082.7 ± 11.9

Table 2.6.7.17H Other Toxicity Studies - Genotoxicity Study on *不純物F **(Continued)** **Study No. HIS2155**

First repeat of TA98 & TA1535

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	26.3 ± 1.2	NA	4.3 ± 2.1	NA	NA
	*不純物F	5	24.7 ± 9.0	NA	4.0 ± 2.0	NA	NA
		16	19.3 ± 2.1	NA	3.0 ± 1.7	NA	NA
		50	25.3 ± 6.4	NA	5.3 ± 1.5	NA	NA
		160	26.0 ± 7.0	NA	5.7 ± 1.2	NA	NA
		500	20.3 ± 2.9	NA	6.7 ± 1.5	NA	NA
		1600	25.0 ± 4.6	NA	6.0 ± 1.7	NA	NA
		5000	22.3 ± 1.5	NA	5.0 ± 2.0	NA	NA
	Sodium azide	1.0	NA	NA	270.0 ± 4.0	NA	NA
	2-nitrofluorene	2.5	367.7 ± 12.4	NA	NA	NA	NA
With Activation	DMSO	0	27.3 ± 5.5	NA	NA	NA	NA
	*不純物F	5	29.7 ± 2.1	NA	NA	NA	NA
		16	21.7 ± 4.0	NA	NA	NA	NA
		50	25.0 ± 2.6	NA	NA	NA	NA
		160	28.7 ± 2.1	NA	NA	NA	NA
		500	27.3 ± 5.7	NA	NA	NA	NA
		1600	28.0 ± 5.0	NA	NA	NA	NA
		5000	25.3 ± 3.1	NA	NA	NA	NA
	2-aminoanthracene	1.5	1143.0 ± 31.2	NA	NA	NA	NA

＊新薬承認情報提供時に置き換え

Table 2.6.7.17H Other Toxicity Studies - Genotoxicity Study on *不純物F **(Continued)** **Study No. HIS2155**

Second repeat of TA1535

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	NA	NA	5.7 ± 1.2	NA	NA
	*不純物F	5	NA	NA	5.0 ± 1.7	NA	NA
		16	NA	NA	6.3 ± 4.5	NA	NA
		50	NA	NA	6.0 ± 1.7	NA	NA
		160	NA	NA	5.0 ± 1.0	NA	NA
		500	NA	NA	6.0 ± 2.0	NA	NA
		1600	NA	NA	6.3 ± 3.5	NA	NA
		5000	NA	NA	4.7 ± 0.6	NA	NA
	Sodium azide	1.0	NA	NA	260.3 ± 4.2	NA	NA

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17I Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物I

Report Title: *不純物I - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 1 **Study No.:** HIS2161

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-7

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** No

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
Without Activation	DMSO	0	29.0 ± 6.2	100.7 ± 9.0	166.0 ± 7.0	6.7 ± 4.2	6.3 ± 4.0
	*不純物I	0.5	21.0 ± 4.6	86.0 ± 10.8	151.7 ± 11.5	6.7 ± 2.9	9.0 ± 3.5
		1.6	22.7 ± 7.2	86.3 ± 4.0	145.3 ± 11.1	5.7 ± 2.3	7.7 ± 3.1
		5	22.7 ± 3.1	92.3 ± 1.5	149.3 ± 10.8	5.3 ± 3.2	8.0 ± 1.0
		16	19.7 ± 4.5	90.7 ± 10.1	164.0 ± 7.2	6.7 ± 0.6	8.0 ± 3.6
		50	24.7 ± 2.1	97.7 ± 12.0	162.0 ± 14.1	4.3 ± 2.3	7.0 ± 0.0
		160	21.3 ± 6.0	96.7 ± 10.6	167.0 ± 15.6	4.0 ± 1.0	8.3 ± 1.5
		500	23.3 ± 3.8	91.7 ± 4.0	159.0 ± 12.2	7.3 ± 2.3	5.3 ± 1.5
	2-aminoanthracene	2.5	390.0 ± 13.5	NA	NA	NA	NA
	Sodium azide	1.0	NA	NA	NA	321.0 ± 6.2	NA
		2.0	NA	574.3 ± 53.6	NA	NA	NA
	Mitocmycin C	0.3	NA	NA	592.3 ± 29.5	NA	NA
	ICR191[a]	0.3	NA	NA	NA	NA	169.3 ± 15.0

Table 2.6.7.17I Other Toxicity Studies - Genotoxicity Study on *不純物I **(Continued)** **Study No. HIS2161**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
With Activation	DMSO	0	27.3 ± 0.6	107.3 ± 11.2	240.0 ± 14.4	6.7 ± 1.5	9.7 ± 2.5
	*不純物I	0.5	32.3 ± 3.8	99.7 ± 17.2	233.3 ± 18.9	6.3 ± 2.3	8.7 ± 2.1
		1.6	27.3 ± 2.9	102.0 ± 10.4	240.0 ± 11.1	9.3 ± 2.1	13.3 ± 5.8
		5	28.3 ± 4.2	100.7 ± 10.1	236.0 ± 13.9	10.3 ± 1.2	9.3 ± 3.2
		16	27.3 ± 2.9	122.3 ± 2.5	236.7 ± 2.3	6.3 ± 1.5	7.7 ± 3.2
		50	27.7 ± 3.8	90.3 ± 9.1	245.3 ± 2.1	6.0 ± 2.0	9.3 ± 2.1
		160	32.3 ± 6.5	101.3 ± 9.6	242.3 ± 9.3	6.7 ± 2.9	6.3 ± 0.6
		500	27.0 ± 4.4	106.7 ± 12.2	247.0 ± 11.3	10.7 ± 5.0	9.7 ± 4.9
	2-aminoanthracene	1.5	1318.0 ± 83.0	1559.0 ± 92.0	NA	187.3 ± 3.5	148.0 ± 4.6
		8.0	NA	NA	1027.0 ± 23.3	NA	NA

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17J Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物G

Report Title: *不純物G - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 1 **Study No.:** HIS2175

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-8

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: ethanol/water 80/20 (v/v) **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	Ethanol/water	0	21.0 ± 2.6	102.7 ± 6.1	7.3 ± 1.5	6.7 ± 0.6	157.7 ± 11.1
	*不純物G	0.25	22.0 ± 4.4	112.7 ± 4.7	8.7 ± 3.5	6.7 ± 1.5	169.0 ± 23.3
		0.8	27.7 ± 2.1	121.7 ± 15.3	10.7 ± 1.2	9.7 ± 2.1	173.3 ± 15.3
		2.5	31.7 ± 5.1	104.3 ± 0.6	8.7 ± 3.8	11.0 ± 1.0	167.3 ± 14.2
		8	20.0 ± 3.5	108.0 ± 20.0	7.7 ± 1.5	5.0 ± 1.7	169.0 ± 5.2
		25	23.3 ± 3.5	114.7 ± 9.6	6.7 ± 1.5	10.3 ± 2.5	166.0 ± 9.8
		80	24.3 ± 5.5	118.7 ± 8.1	6.3 ± 2.3	8.7 ± 2.5	169.3 ± 15.0
		250	19.0 ± 4.6	112.3 ± 11.2	10.3 ± 7.6	7.7 ± 3.2	170.0 ± 15.5
	Sodium azide	1.0	NA	NA	314.3 ± 23.0	NA	NA
		2.0	NA	562.7 ± 76.8	NA	NA	NA
	ICR191[a]	0.3	NA	NA	NA	142.7 ± 8.0	NA
	2-nitrofluorene	2.5	370.7 ± 8.1	NA	NA	NA	NA
	Mitocmycin C	0.3	NA	NA	NA	NA	610.0 ± 42.7

Table 2.6.7.17J Other Toxicity Studies - Genotoxicity Study on *不純物G **(Continued)** **Study No. HIS2175**

Metabolic Activation	Test Article	Dose Level (µg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
With Activation	Ethanol/water	0	26.0 ± 5.6	125.0 ± 2.0	9.3 ± 1.5	8.7 ± 1.5	203.7 ± 5.1
	*不純物G	0.25	29.7 ± 2.1	110.7 ± 1.2	9.3 ± 2.5	8.3 ± 1.2	198.0 ± 11.3
		0.8	22.3 ± 4.9	110.7 ± 22.7	10.3 ± 4.0	7.7 ± 1.5	211.3 ± 11.9
		2.5	27.0 ± 1.0	110.3 ± 7.8	9.0 ± 1.7	7.3 ± 1.2	196.7 ± 12.6
		8	30.0 ± 3.0	119.7 ± 2.9	11.0 ± 4.6	7.3 ± 1.5	185.3 ± 7.2
		25	20.3 ± 3.5	120.7 ± 6.7	12.7 ± 7.4	10.7 ± 2.9	195.3 ± 9.0
		80	28.7 ± 2.5	119.7 ± 4.2	13.0 ± 3.6	11.3 ± 3.5	200.7 ± 22.7
		250	26.0 ± 2.6	113.7 ± 16.7	9.7 ± 2.3	9.3 ± 3.2	201.3 ± 2.5
	2-aminoanthracene	1.5	1357.3 ± 107.2	1881.7 ± 91.2	181.3 ± 3.1	146.7 ± 13.3	NA
		8.0	NA	NA	NA	NA	1175.7 ± 184.6

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17K Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物H

Report Title: *不純物H - Bacterial Reverse Mutation Test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 3 **Study No.:** HIS2173

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-9

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: Test Article: DMSO **Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
Without Activation	DMSO	0	23.7 ± 4.0	94.7 ± 8.7	159.0 ± 14.7	9.7 ± 4.7	7.0 ± 1.7
	*不純物H	5	18.0 ± 6.1	101.7 ± 8.1	146.3 ± 12.7	5.3 ± 2.3	6.3 ± 2.5
		16	18.3 ± 1.5	94.3 ± 11.0	157.7 ± 23.8	8.0 ± 1.0	5.3 ± 3.2
		50	21.3 ± 4.5	93.7 ± 9.1	145.3 ± 4.5	6.7 ± 2.1	4.0 ± 1.0
		160	14.0 ± 4.4	86.0 ± 9.5	142.0 ± 11.3	7.0 ± 0.0	7.3 ± 2.5
		500	25.0 ± 2.6	91.0 ± 12.5	96.7 ± 20.1	4.0 ± 1.0	10.3 ± 2.5
		1600	25.0 ± 8.9	57.3 ± 24.1[a]	8.0 ± 3.6[a]	2.3 ± 0.6	3.7 ± 1.5
		5000	1.7 ± 1.5[a]	0 ± 0[a]	0 ± 0[a]	1.3 ± 2.3[a]	0 ± 0[a]
	Sodium azide	1.0	NA	NA	NA	289.7 ± 9.1	NA
		2.0	NA	557.0 ± 19.0	NA	NA	NA
	ICR191[b]	0.3	NA	NA	NA	NA	154.0 ± 17.3
	2-nitrofluorene	2.5	378.7 ± 25.7	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	688.7 ± 26.6	NA	NA

Table 2.6.7.17K Other Toxicity Studies - Genotoxicity Study on *不純物H **(Continued)** **Study No. HIS2173**

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
With Activation	DMSO	0	22.0 ± 3.6	107.3 ± 3.8	211.0 ± 12.8	12.0 ± 4.6	8.7 ± 1.5
	*不純物H	5	19.7 ± 3.1	106.0 ± 9.5	208.7 ± 12.7	8.3 ± 1.2	6.0 ± 0.0
		16	22.0 ± 4.6	108.3 ± 5.9	234.3 ± 18.9	6.0 ± 1.0	5.0 ± 2.0
		50	25.3 ± 5.9	107.3 ± 9.6	226.0 ± 11.0	5.3 ± 1.2	7.7 ± 2.5
		160	27.7 ± 3.8	105.7 ± 7.0	228.7 ± 18.0	7.0 ± 1.0	6.0 ± 1.0
		500	23.7 ± 5.5	97.7 ± 8.5	207.3 ± 17.0	2.0 ± 0.0	7.7 ± 2.5
		1600	21.3 ± 3.2	71.0 ± 8.7	31.0 ± 6.6[a]	4.0 ± 2.6	5.3 ± 1.5
		5000	0.3 ± 0.6[a]	0.3 ± 0.6[a]	1.3 ± 2.3[a]	0.0 ± 0.0[a]	0.3 ± 0.6[a]
	2-aminoanthracene	1.5	1337.3 ± 57.3	1551.7 ± 79.7	NA	170.0 ± 2.6	122.3 ± 6.8
		8.0	NA	NA	1132.7 ± 27.6	NA	NA

Table 2.6.7.17K Other Toxicity Studies - Genotoxicity Study on *不純物H **(Continued)** **Study No. HIS2173**

First repeat of TA1535

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	NA	NA	4.7 ± 1.2	NA	NA
	*不純物H	5	NA	NA	5.3 ± 0.6	NA	NA
		16	NA	NA	6.3 ± 5.1	NA	NA
		50	NA	NA	5.7 ± 3.8	NA	NA
		160	NA	NA	6.3 ± 0.6	NA	NA
		500	NA	NA	7.3 ± 0.6	NA	NA
		1600	NA	NA	4.3 ± 1.2	NA	NA
		5000	NA	NA	0.0 ± 0.0[a]	NA	NA
	Sodium azide	1.0	NA	NA	275.0 ± 14.4	NA	NA
With Activation	DMSO	0	NA	NA	8.7 ± 1.5	NA	NA
	*不純物H	0.16	NA	NA	7.3 ± 2.5	NA	NA
		0.5	NA	NA	2.7 ± 1.5	NA	NA
		1.6	NA	NA	5.7 ± 2.5	NA	NA
		5	NA	NA	5.0 ± 1.0	NA	NA
		16	NA	NA	4.3 ± 2.1	NA	NA
		50	NA	NA	7.0 ± 3.6	NA	NA
		160	NA	NA	6.3 ± 3.8	NA	NA
		500	NA	NA	8.0 ± 4.4	NA	NA
		1600	NA	NA	4.3 ± 1.5	NA	NA
	2-aminoanthracene	1.5	NA	NA	168.7 ± 25.5	NA	NA

Table 2.6.7.17K Other Toxicity Studies - Genotoxicity Study on *不純物H (Continued) **Study No. HIS2173**

Second repeat of TA1535

Metabolic Activation	Test Article	Dose Level (μg/plate)	Initial Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	TA102
Without Activation	DMSO	0	NA	NA	7.0 ± 1.0	NA	NA
	*不純物H	5	NA	NA	7.7 ± 1.2	NA	NA
		16	NA	NA	3.7 ± 1.5	NA	NA
		50	NA	NA	5.3 ± 2.5	NA	NA
		160	NA	NA	4.0 ± 2.6	NA	NA
		500	NA	NA	5.7 ± 2.1	NA	NA
		1600	NA	NA	1.3 ± 0.6[a]	NA	NA
		5000	NA	NA	1.3 ± 2.3[a]	NA	NA
	Sodium azide	1.0	NA	NA	301.7 ± 18.6	NA	NA

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] Toxicity indicated by clearing or diminution of background growth.
[b] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17L Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物A

Report Title: *不純物A - Bacterial reverse mutation test (Ames test)

Test for Induction of: Reverse mutation in bacterial cells **No. of Independent Assays:** 2 **Study No.:** HIS1952

Test System: *Salmonella typhimurium* **No. of Independent Cultures:** 3 **Location in Dossier:** 4.2.3.7.6-10

Metabolizing System: Aroclor 1254-induced rat liver S9 **No. of Cells Analyzed/Culture:** Not given

Vehicle: for Test Article: DMSO **for Positive Controls:** DMSO or water **GLP Compliance:** Yes

Treatment: 48 hours **Dates of Treatment:** [redacted], 20[redacted]

Genotoxic Effects: None

Plate incorporation method

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
Without Activation	DMSO	0	18.0 ± 3.5	118.7 ± 9.5	231.7 ± 10.3	10.0 ± 1.7	6.7 ± 3.1
	*不純物A	5	15.0 ± 2.6	105.0 ± 9.6	228.0 ± 10.5	11.0 ± 1.7	5.0 ± 2.6
		16	17.3 ± 2.3	127.3 ± 3.2	245.3 ± 20.2	8.0 ± 1.0	5.0 ± 2.6
		50	16.3 ± 4.0	126.7 ± 15.0	245.3 ± 5.5	10.7 ± 1.5	7.0 ± 2.6
		160	13.0 ± 3.6	128.0 ± 6.2	229.7 ± 20.6	7.7 ± 1.2	4.7 ± 0.6
		500	17.3 ± 3.5	117.0 ± 15.9	238.3 ± 12.7	8.3 ± 2.1	6.3 ± 0.6
		1600	14.7 ± 0.6	119.7 ± 15.2	229.7 ± 21.5	9.7 ± 3.1	3.7 ± 3.1
		5000	21.0 ± 6.1	134.3 ± 13.5	246.3 ± 13.2	9.3 ± 4.0	6.0 ± 2.6[a]
	Sodium azide	1.0	NA	NA	NA	348.7 ± 25.9	NA
		2.0	NA	662.7 ± 16.1	NA	NA	NA
	ICR191[b]	0.3	NA	NA	NA	NA	209.0 ± 12.0
	2-nitrofluorene	2.5	402.3 ± 10.4	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	838.7 ± 28.3	NA	NA

Table 2.6.7.17L Other Toxicity Studies - Genotoxicity Study on *不純物A **(Continued)** **Study No. HIS1952**

Plate incorporation method

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
With Activation	DMSO	0	24.7 ± 7.5	122.0 ± 11.5	230.3 ± 18.9	6.7 ± 2.5	10.3 ± 0.6
	*不純物A	5	23.3 ± 5.7	114.7 ± 12.1	229.3 ± 4.7	9.3 ± 0.6	4.7 ± 1.2
		16	21.3 ± 0.6	116.0 ±10.1	236.0 ± 8.2	14.7 ± 4.5	10.3 ± 4.0
		50	24.3 ± 3.1	120.0 ± 10.6	240.3 ± 3.5	8.0 ± 4.4	6.7 ± 1.2
		160	19.0 ± 4.4	128.7 ± 10.7	251.7 ± 24.7	8.7 ± 2.1	7.0 ± 4.6
		500	21.3 ± 5.1	125.3 ± 14.6	241.0 ± 9.8	11.7 ± 2.5	10.7 ± 4.5
		1600	24.3 ± 3.2	112.7 ± 6.4	251.3 ± 24.7	7.7 ± 7.4	8.0 ± 3.6
		5000	23.3 ± 2.9	121.3 ± 10.8	242.3 ± 10.0	5.7 ± 0.6	6.7 ± 2.1
	2-aminoanthracene	1.5	814.0 ± 10.6	1087.3 ± 97.4	NA	164.7 ± 29.8	87.3 ± 3.5
		8.0	NA	NA	703.7 ± 12.5	NA	NA

Table 2.6.7.17L Other Toxicity Studies - Genotoxicity Study on *不純物A **(Continued)** **Study No. HIS1952**

Preincubation method

Metabolic Activation	Test Article	Dose Level (μg/plate)	Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
Without Activation	DMSO	0	13.7 ± 2.1	141.0 ± 7.8	257.3 ± 10.2	8.3 ± 3.2	5.3 ± 2.5
	*不純物A	5	13.3 ± 1.5	133.7 ± 13.4	248.0 ± 22.3	8.0 ± 1.0	4.0 ± 2.6
		16	16.7 ± 4.0	131.0 ± 6.1	258.7 ± 26.6	8.7 ± 2.1	5.7 ± 2.5
		50	16.7 ± 5.7	141.7 ± 16.5	254.7 ± 25.8	10.7 ± 2.9	7.0 ± 2.0
		160	17.3 ± 8.1	153.0 ± 4.4	251.7 ± 7.6	7.0 ± 1.7	6.3 ± 3.2
		500	11.3 ± 2.3	163.3 ± 20.6	263.0 ± 16.6	8.0 ± 2.0	4.7 ± 4.7
		1600	17.0 ± 8.7	152.7 ± 11.5	231.3 ± 16.4	11.0 ± 2.6	7.7 ± 2.3
		5000	14.3 ± 1.2	169.7 ± 26.3	203.0 ± 6.2[a]	9.3 ± 4.2	8.0 ± 4.0
	Sodium azide	1.0	NA	NA	NA	403.3 ± 27.0	NA
		2.0	NA	682.3 ± 12.1	NA	NA	NA
	ICR191[b]	0.1	NA	NA	NA	NA	91.7 ± 5.9
	2-nitrofluorene	2.5	673.3 ± 27.3	NA	NA	NA	NA
	Mitomycin C	0.3	NA	NA	1016.0 ± 52.4	NA	NA

Table 2.6.7.17L Other Toxicity Studies - Genotoxicity Study on *不純物A **(Continued)** **Study No. HIS1952**

Preincubation method

Metabolic Activation	Test Article	Dose Level (μg/plate)	Initial Mutation assay: Number of Revertant colonies/plate (Mean ± SD)				
			TA98	TA100	TA102	TA1535	TA1537
With Activation	DMSO	0	22.7 ± 3.1	155.3 ± 12.1	246.3 ± 7.4	8.0 ± 2.6	8.7 ± 2.5
	*不純物A	5	21.0 ± 1.0	157.0 ± 17.8	250.7 ± 6.4	10.7 ± 0.6	8.7 ± 2.1
		16	22.3 ± 3.2	145.3 ± 8.7	279.3 ± 17.2	7.7 ± 3.1	5.7 ± 1.2
		50	24.3 ± 4.2	162.0 ± 2.6	275.7 ± 16.6	9.0 ± 3.0	7.3 ± 1.5
		160	23.3 ± 6.1	155.7 ± 3.1	273.3 ± 21.0	7.3 ± 1.5	5.3 ± 2.1
		500	20.0 ± 2.6	154.0 ± 11.5	277.3 ± 13.5	10.3 ± 3.2	7.3 ± 2.5
		1600	29.3 ± 3.5	155.3 ± 6.0	268.3 ± 18.6	8.7 ± 3.1	7.3 ± 1.2
		5000	26.3 ± 7.0	160.7 ± 12.4	227.3 ± 7.2[a]	11.0 ± 4.6	5.3 ± 4.2
	2-aminoanthracene	1.5	794.0 ± 27.6	1022.7 ± 65.4	NA	NA	63.3 ± 9.0
		2.5	NA	NA	NA	128.3 ± 7.5	NA
		10.0	NA	NA	759.7 ± 46.0	NA	NA

DMSO = dimethylsulfoxide; NA = not applicable; SD = standard deviation.
[a] Toxicity indicated by clearing or diminution of background growth.
[b] 6-Chloro-9-(3-[2-chloroethylamino]propylamino)-2-methoxyacridine dihydrochloride.

Table 2.6.7.17M Other Toxicity Studies - Genotoxicity Study on Impurity **Test Article:** *不純物A

Report Title: *不純物A - In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Test for Induction of: Chromosomal aberrations **No. of Independent Assays:** 3 **Study No.:** MAF0133

Test System: Cultured human peripheral blood lymphocytes **No. of Independent Cultures:** 2 **Location in Dossier:** 4.2.3.7.6-11

Metabolizing System: Aroclor S9 mix **No. of Cells Analyzed/Culture:** 200

Vehicle: Test Article: DMSO **Positive Controls:** water **GLP Compliance:** No

Treatment: 3 or 20 hours **Dates of Treatment:** [redacted], 20[redacted]

Cytotoxic Effects: At 1.25 mM in 20 hours treatment.

Genotoxic Effects: None

Treatment Metabolic Activation	Test Article	Concentration (mM)	Mitotic Index (%)	Cells with Structural Aberrations (%)		
				Including gaps[a]	Excluding gaps[b]	Exchanges[a]
20-hour treatment Without S9	DMSO	0	100	2.0	0.5	0.0
	*不純物A [c]	0.23	93.5	2.5	1.5	0.0
		0.63	76.3	2.5	1.0	0.0
		1.25	48.4	4.0	0.0	0.0
	Mitomycin C	0.2 µg/mL	74.2	26.5	24.0*	9.0
3-hour treatment Without S9	DMSO	0	100.0	2.5	2.5	0.0
	*不純物A [d]	2.5	100.0	1.0	0.0	0.0
		5.0	98.1	4.0	3.0	0.0
		10.0	79.0	1.5	1.5	0.0
	Mitomycin C	0.3 µg/mL	80.0	24.5	23.5*	4.0

Table 2.6.7.17M Other Toxicity Studies - Genotoxicity Study on *不純物A **(Continued)** **Study No. MAF0133**

Treatment Metabolic Activation	Test Article	Concentration (mM)	Mitotic Index (%)	Cells with Structural Aberrations (%)		
				Including gaps[a]	Excluding gaps[b]	Exchanges[a]
3-hour treatment With S9	DMSO	0	100.0	1.0	0.5	0.0
	*不純物A [c]	2.5	98.1	3.0	0.5	0.0
		5.0	96.1	2.0	0.5	0.0
		10.0	85.4	1.0	1.0	0.0
	Cyclophosphamide	7.5 µg/mL	67.0	18.0	16.0*	2.5

DMSO = dimethylsulfoxide; * = Statistically significant at $p \leq 0.05$ (Fisher's Exact test).
[a] No statistics performed.
[b] Inclusive of exchanges.
[c] Concentrations of 0.12 to 10 mM were tested; 10 mM corresponds to 2950 µg/mL.
[d] Concentrations of 0.23 to 10 mM were tested; 10 mM corresponds to 2950 µg/mL.

18 参考文献

[1] Nambiar PR, Turnquist SE, Morton D. Spontaneous tumor incidence in rasH2 mice: review of internal data and published literature. Toxicol Pathol. 2012; 40:614-23.

[2] Takaoka M, Sehata S, Maejima T, et al. Interlaboratory comparison of short-term carcinogenicity studies using CB6F1-rasH2 transgenic mice. Toxicol Pathol. 2003; 31:191-99.