ヨンデリス点滴静注用 0.25 mg

ヨンデリス点滴静注用 1 mg

第 2 部（モジュール 2）：CTD の概要（サマリー）

2.6.6　毒性試験の概要文

大鵬薬品工業株式会社

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略号一覧表

略号	内容
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 concentration-time curve：血漿中濃度－時間曲線下面積
$AUC_{0-\infty}$ AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity：投与 0 時間から無限大時間まで外挿した血漿中濃度－時間曲線下面積
AUC_{0-t}	area under the concentration-time curve from time zero up to the time at the last observable concentration：投与 0 時間から最終測定可能な濃度の時間までの血漿中濃度－時間曲線下面積
BUN	blood urea nitrogen：尿素窒素
CFU-Meg	megakaryocytic colony-forming units：巨核球コロニー形成細胞
CL	total body clearance：全身クリアランス
C_{max}	maximum plasma concentration：最高血漿中薬物濃度
CPK	creatine phosphokinase：クレアチンホスホキナーゼ
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
ICH	International Conference on Harmonization：日米 EU 医薬品規制調和国際会議
LLOQ	lower limit of quantification：定量下限
MNPCE	micronucleated polychromatic erythrocyte：小核を有する多染性赤血球
MTD	maximum tolerated dose：最大耐量
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
OECD	Organization for Economic Co-operation and Development：経済協力開発機構
PCE	polychromatic erythrocyte：多染性赤血球
$t_{1/2}$	terminal elimination half-life：最終相の消失半減期
Vd_{ss}	volume of distribution at steady state：定常状態分布容積

※　ラット及びサルの投与用量「μg/kg」から「$\mu g/m^2$」への変換：「μg/kg」で示した用量にラットでは 6 倍，サルでは 12 倍を乗じた.

2.6.6 毒性試験の概要文

2.6.6.1 まとめ

トラベクテジンの毒性を検討するために，単回投与及び反復投与毒性試験（薬物を 3 週間ごとにサイクル 8 まで投与），遺伝毒性試験，生殖発生毒性試験及び局所刺激性試験を行った．*In vitro* 及び *in vivo* では，毒性機序に関する試験を実施し，特に肝毒性の発生機序を評価した．更に，代謝物，不純物及び分解産物の毒性，トラベクテジンの[redacted]原薬及び[redacted]原薬の毒性の差並びに[redacted]を用いた製剤及び[redacted]を用いた製剤の毒性の差について評価した．

主要な毒性試験は経済協力開発機構（OECD）の「医薬品の安全性に関する非臨床試験の実施の基準（GLP）」に従って実施した．その他の試験は非 GLP 下で実施した．試験の概要を第 2.6.7.1 項に示した．

トラベクテジンの毒性は，マウス，ラット，イヌ及びサルで評価した．サルはヒトの代謝及び毒性プロファイルと類似性を示すことから，ヒトの毒性を予測するのに適切な動物モデルであると考えられた．

単回急速静脈内投与後の最大耐量（MTD）は雄性ラットでは 75 µg/kg/day，雌性ラットでは 50 µg/kg/day であった．3 週間ごとの 3 時間持続静脈内投与を 3 サイクル反復したラットの MTD は雌雄のいずれも 25 µg/kg/day であったが，全身毒性は雌性ラットで顕著であった．

トラベクテジンの主要な毒性作用は，骨髄抑制，肝毒性，腸粘膜上皮の萎縮及び潰瘍並びに投与部位の局所刺激性であった．骨髄抑制の特徴は，好中球数減少，骨髄細胞減少，リンパ系組織の萎縮又は細胞減少であった．肝毒性の特徴は，トランスアミナーゼの増加，肝細胞壊死並びに胆管の炎症，線維化及び増殖であった．この肝毒性はラットでは不可逆的で，蓄積的であり，雌性ラットで顕著であった．

カニクイザルでの MTD は，雌雄のいずれも 3 週間ごとの反復投与後では 25 µg/kg/day であった．ほとんどの全身毒性はラットの毒性に類似していた．しかし，サルでみられた肝毒性はそれほど顕著なものではなく，可逆的で非蓄積的であり，その特徴はトランスアミナーゼの増加，肝細胞肥大，肝細胞変性及び限局性壊死であった．カニクイザルの 3 週間ごとの 3 時間又は 24 時間持続静脈内投与による反復投与試験では，投与時間による毒性の発生に顕著な差を認めなかった．この反復投与試験の用量制限毒性は，好中球数減少及び投与部位の局所刺激性であった．その他に，腸管の壊死性潰瘍及び上皮の扁平化を伴う尿細管拡張を認めた．

トラベクテジンの肝毒性の種差及びラットでの性差は，代謝，肝胆道系の排泄，薬物及び（又は）代謝物の肝臓での蓄積の差又はこれらの要因が複合している可能性が考えられた．

トラベクテジンは *in vitro* 及び *in vivo* 試験系で遺伝毒性を示した．

トラベクテジンはラット及びウサギの生殖発生毒性試験で胚胎児毒性及び催奇形性を示さなかった．しかし，試験に用いた投与量は母体の用量制限毒性のためにヒトの予定臨床用量よりかなり低かったことから，これらの試験の結果はヒトへの外挿性が乏しいと考えられる．

ウサギの局所刺激性試験では，低濃度である 2.5 µg/mL のトラベクテジンの静脈内投与及び静脈傍（皮下及び筋肉内）投与により顕著な局所刺激性が生じることが示され，静脈傍では特に刺激性が強く壊死及び潰瘍を認めた．

[redacted]原薬，[redacted]原薬，[redacted]を用いた及び[redacted]を用いた製剤又は不純物を添加したトラベクテジン製剤で認めたトラベクテジンの毒性又はトキシコキネティクス特性は類似していた．

動物の MTD とヒトの投与量を比較した場合，トラベクテジンの曝露はヒトよりも動物の方が低かったが，これは抗悪性腫瘍剤ではまれな所見ではないと考えられる．

2.6.6.2　単回投与毒性試験

トラベクテジンの単回投与毒性試験では MF1 マウス，Fischer 344 ラット及びビーグル犬に急速静脈内投与し，SD 系ラットに持続静脈内投与した．詳細は第 2.6.7.5 項に示した．

2.6.6.2.1　マウス

2.6.6.2.1.1　単回急速投与毒性試験（試験番号 [redacted]）

GLP 試験として，成熟した雄性 MF1 マウス 15 匹/群（200 μg/kg/day 投与群では 30 匹/群）に，0，100，150 及び 200 μg/kg/day の用量で[redacted]トラベクテジンを単回急速静脈内投与した（第 4.2.3.1.1 項）．投与後 14 日，42 日及び 56 日の観察期間を設定した．

150 μg/kg/day 投与群では，瀕死状態のため 2 匹を安楽死させた（投与後 22 日及び 30 日）． 200 μg/kg/day 投与群では，投与翌日に 2 匹が死亡し，8 匹は一般状態悪化により投与後 1～10 日に安楽死させた．多くのマウスで立毛及び尾の病変を認め，投与後 7 日までは体重減少を認めた．投与後 14 日の剖検時には，赤血球数及び一部の関連する検査値が対照群より低値を示した．これは 200 μg/kg/day 投与群で死亡又は瀕死による安楽死例でみられた骨髄細胞の減少と関連していた．更に，200 μg/kg/day 投与群の胸腺重量が減少した．死亡又は安楽死させたマウスでは，うっ血や重度の凝固壊死を含む肝毒性の徴候とともに，消化管の様々な部位に壊死を認めた．投与後 14 日の剖検では，損傷の修復を示す有糸分裂像の増加を認めた．投与後 42 日及び 56 日では，投与に関連した影響は認めなかった．投与後 14 日又はそれ以前に剖検した 200 μg/kg/day 投与群では，心筋壊死を示す所見も認めたが，投与後 56 日までにいずれのマウスの心臓にも病変を示す所見は認めなくなった．200 μg/kg 投与群のマウスで投与後 14 日に髄外造血の著しい亢進を認めたが，投与後 42 日には回復性を示し，投与後 56 日までに完全に回復した．

以上より，マウスでのトラベクテジンの単回静脈内投与では，肝胆道系の毒性，骨髄抑制，投与部位の局所刺激性などを認め，MTD は 100 μg/kg/day，概略の致死量は 100～150 μg/kg/day であった．これらの毒性の大部分は少なくとも部分的に回復性を示すことが考えられた．

2.6.6.2.2　ラット

2.6.6.2.2.1　単回急速投与毒性試験［試験番号 [redacted]］

GLP 試験として，雌雄の Fischer 344 ラット 10 匹/性に 9，75 又は 90 μg/kg/day の用量で[redacted]トラベクテジンを単回急速静脈内投与した（第 4.2.3.1.2 項）．単回投与後，29 日間の回復期間を設定した．また投与後 8 日に中間検査用として一部を安楽死させた（5 匹/性/群）．

75 及び 90 μg/kg/day 投与群の各群雌 5 匹（両群の雌合計 10 匹）は，投与後 26 日以内に死亡又は瀕死により安楽死させた．一般状態の変化は雄より雌で顕著であり，動物の全身状態の悪化を反映していた．75 μg/kg/day 以上の投与群の雌雄の体重は，対照群より統計学的に有意な低値を示し投与後 29 日までに回復しなかった．75 μg/kg/day 以上の投与群の雌雄でいくつかの血液学的変化を認め，これらには好中球数減少，白血球数減少，リンパ球数減少，貧血，血小板数減少，ヘモグロビン量及びヘマトクリット値の減少，さらに平均赤血球容積及び有核赤血球の増加が含まれていた．75 μg/kg/day 以上の投与群の雌雄で，アスパラギン酸アミノトランスフェラーゼ（AST）値，アラニン・アミノトランスフェラーゼ（ALT）値，総ビリルビン値及び直接ビリルビン値の増加を認めた．75 μg/kg/day 以上の投与群の雌雄で認めた病理組織学的変化は，骨髄細胞の減少，

結腸の炎症，腺拡張及び上皮過形成，肝臓の胆管炎，壊死及び炎症，腸間膜リンパ節及び脾臓の細胞減少並びに胸腺の萎縮などであった．

以上より，Fischer 344 ラットにトラベクテジンを単回急速静脈内投与した際の主要な標的器官は肝臓，骨髄，リンパ系組織及び結腸であり，MTD は，雄では 90 μg/kg/day，雌では 9 μg/kg/day，概略の致死量は雄では 90 μg/kg/day を超え，雌では 9～75 μg/kg/day であった．

2.6.6.2.2.2　単回 3 時間持続投与毒性試験（試験番号 [redacted]）

非 GLP 試験として，SD 系ラット 3 匹/性/群に雌では 50 及び 100 μg/kg/day，雄では 75 及び 100 μg/kg/day の[redacted]トラベクテジン（[redacted]を用いた水溶液製剤）を 3 時間持続静脈内投与した（第 4.2.3.1.3 項）．投与後に 14 日間の観察期間を設定した．

投与後 1 週に全ての投与群の雌雄のラットで体重及び摂餌量のわずかな減少を認めた．

75 μg/kg/day 投与群の雄では，投与後 4 日に網状赤血球数，単球数及び好酸球数の減少を認めた．観察期間終了時には，血液学的変化として，網状赤血球，平均赤血球容積及び平均赤血球ヘモグロビン量の増加並びにヘマトクリット値，赤血球数，好酸球数，ヘモグロビン量及び血小板数の減少を認めた．更に，投与後 4 日に，総蛋白値及びクレアチニン値のわずかな減少，アルブミン値の中等度の減少及びアルカリホスファターゼ（ALP）値のわずかな増加を認めた．観察期間終了時には生化学的変化として，トリグリセライド値，AST 値及び ALT 値の顕著な増加，血中尿素窒素（BUN）値のわずかな減少，総ビリルビン値及び ALP 値の増加などを認めた．

50 μg/kg/day 投与群の雌では，投与後 4 日に白血球数及び好酸球数の中等度の減少，網状赤血球数及び単球数の顕著な減少，リンパ球数及び好中球数のわずかな減少を認めた．投与後に総ビリルビン値，トリグリセライド値，ALP 値，AST 値，ALT 値及びコレステロール値の増加を認め，観察期間終了後にも増加した状態であった．2 週間の観察期間終了時の血液学的変化は 75 μg/kg/day 投与群の雄のものに類似していたが，雄より顕著であった．肝臓の限局性壊死を雌雄のラットで認めた．

100 μg/kg/day 投与群のラットはすべて 4～7 日目に死亡又は安楽死させた．血液学的及び生化学的変化は雄の 75 μg/kg/day 又は雌の 50 μg/kg/day 投与群で認めたものと類似していた．剖検所見では大部分のラットに悪液質，脱水，肝臓及び副腎の腫脹，大腸の血様内容物，小腸壁の菲薄化，胃の変化及び黄色皮下組織などを認めた．組織学的には，骨髄細胞の減少，肝臓の類洞細胞の腫脹，類洞細胞の赤血球貪食，多巣性の肝細胞変性並びに腸管上皮の萎縮及び潰瘍を認めた．死亡の主要原因は消化管障害と考えられた．

SD 系ラットに 3 時間静脈内単回投与したトラベクテジンの MTD は，雄では 75 μg/kg/day，雌では 50 μg/kg/day で，概略の致死量は雄では 75～100 μg/kg/day，雌では 50～100 μg/kg/day あった．

2.6.6.2.2.3　単回 3 時間又は 24 時間持続投与毒性試験（試験番号 [redacted]）

GLP 試験として，SD 系ラット（10 匹/性/群）に 50 μg/kg/day の用量で[redacted]トラベクテジン（[redacted]を用いた製剤）を 3 時間又は 24 時間持続静脈内投与した．投与後，3 日間及び 3 週間の観察期間を設け投与時間による毒性を比較した（第 4.2.3.1.4 項及び第 4.2.3.1.5 項）．

また，この試験では同定されたトラベクテジン原薬中の不純物（不純物 B*）と併用したトラベクテジンの毒性についても評価した．このデータは第 2.6.6.8.4.1 項に示した．

雌雄のいずれも，毒性の主要な標的器官は造血器系臓器であり，その特徴は可逆的な白血球数減少，血小板数減少及び貧血などであった．骨髄細胞の顕著な減少は，特に 3 時間静脈内投与で認めたが，観察期間終了時までにほぼ完全な回復性を示した．雌では，ALT 値，AST 値及び ALP

値の増加と関連して，肝細胞壊死，急性胆管炎及び胆管過形成を認めた．この肝毒性の特徴は，肝細胞の腫脹，肝細胞壊死，胆管の増殖/炎症，クッパー細胞の増殖などであった．観察期間終了時の所見として，中等度の比較的びまん性の慢性炎症，類洞細胞の色素沈着，胆管上皮の増殖性変化及び肝細胞壊死を認めた．雌雄のラットでは，トラベクテジンの単回 3 時間又は 24 時間持続静脈内投与により投与部位の局所刺激性を認め，血管壁の壊死を伴っていた．雄ではごく軽微な膵腺房細胞の壊死を認め，雌では投与後 3 日に膵臓の腫脹を認めた．観察期間終了後にトラベクテジンを投与したすべての雌に腎皮質尿細管の細胞質内色素沈着を伴った明澄な空胞化を認め，膵腺房細胞の細胞質内チモーゲン顆粒のわずかな増加及び脾臓の過形成変化を伴っていた．

肝毒性の程度は雄より雌で明らかに強く認めた．3 時間持続静脈内投与群では（主に骨髄への影響に関連した）毒性が 24 時間持続静脈内投与群よりわずかに強く認められた．

サテライト動物で得られたトキシコキネティクスデータでは，それぞれの静脈内投与の開始時及び終了時に得られた血漿中濃度は，雄と雌で類似していることが示された（第 4.2.3.1.5 項）．投与後，トラベクテジンは血漿中より速やかに消失した．3 時間又は 24 時間持続静脈内投与では，血漿中濃度－時間曲線下面積（AUC_{0-t}）で比較した場合，雄と雌の曝露量は同程度であった（表 2.6.6.2-1）．

表 2.6.6.2-1　雌雄 SD 系ラットにおけるトラベクテジン 50 µg/kg 単回 3 時間又は 24 時間持続静脈内投与時の C_{max} 及び AUC

Duration of infusion (h)	Sex	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)
3	Male	0.804	1.72
	Female	0.994	2.94
24	Male	0.131	2.76
	Female	0.188	3.74

Pharmacokinetic parameters were calculated on the mean plasma levels (n = 2 or 4/sampling point/sex)
第 4.2.3.1.5 項 試験報告書 No.[redacted] Table 5-2 改変

以上より，ラットでのトラベクテジンの単回静脈内投与では，肝胆道系の毒性，骨髄抑制，消化管壊死及び投与部位の局所刺激性を認め，雌雄の MTD は 50 µg/kg/day で，概略の致死量は 50 µg/kg/day を超えた．また，毒性の発生率及び程度は雌性ラットで顕著であった．血液毒性は，肝臓の変化とは対照的に可逆的であると考えられた．

2.6.6.2.3　イヌ

2.6.6.2.3.1　単回急速投与毒性試験［試験番号[redacted]］

GLP 試験として，ビーグル犬（2 匹/性）に 0，10，27 又は 35 µg/kg/day の用量で[redacted]トラベクテジンを単回急速静脈内投与した（第 4.2.3.1.6 項）．イヌの半数は投与後 8 日目に剖検し，残りは投与後 29 日目に剖検した．

27 又は 35 µg/kg/day 投与群では死亡を認めず，一般状態の変化は投与後 24 時間までの嘔吐のみであった．主として雌の 27 µg/kg/day 以上の投与群で用量依存的な体重減少又は体重増加抑制を認め（投与後 8 日又は 11 日に最も大きな影響），摂餌量の減少と関連していた．主として 27 又は 35 µg/kg/day 投与群で白血球数，赤血球数，ヘモグロビン量，ヘマトクリット値，網状赤血球数，血小板数及び分葉核好中球数の減少を認めた．ALP 値，ALT 値及び AST 値の増加をそれぞれ 27 µg/kg/day 以上の投与群で認めたが，可逆的な変化であった．27 µg/kg/day 以上の投与群で，投

与後 29 日まで急性胆管炎を認め，炎症性細胞浸潤，軽微から中等度の胆管過形成，持続的な生化学的変化を伴うものもあれば，伴わないものもあった．27 μg/kg/day 以上の投与群で認めた胆嚢の慢性胆嚢炎及び骨髄や膵臓の軽度の細胞毒性（アポトーシス及び膵腺房細胞萎縮の増加）は可逆的で，投与後 29 日までに回復傾向を認めた．

以上より，トラベクテジンをビーグル犬に単回急速投与した場合，軽度の血液学的変化及び急性の肝胆道系障害がみられた．肝胆道系の障害は回復性が乏しかった．雌雄のビーグル犬におけるトラベクテジン（単回急速静脈内投与後）の MTD は 27 μg/kg/day で概略の致死量は 35 μg/kg/day を超えた．

2.6.6.3 反復投与毒性試験（トキシコキネティクス評価を含む）

反復静脈内（急速又は持続）投与毒性試験は，マウス，ラット，イヌ及びサルで行った．投与は 5 日間連続投与又は臨床と同様に回復期間を含んだ投与スケジュールで反復投与した．詳細は第 2.6.7.7 項に示した．

2.6.6.3.1 マウス

2.6.6.3.1.1 5 日間反復投与毒性試験［試験番号 [redacted]］

GLP 試験として，CD_2F_1 マウス（10 匹/性/群）に[redacted]トラベクテジンを 0，40，60，又は 80 μg/kg/day の用量で 5 日間急速反復投与後，17 日間の回復期間を設けた（第 4.2.3.2.1 項）．5 日間投与の累積用量は 0，200，300 又は 400 μg/kg であった．各群 4 又は 5 匹/群を投与後 8 日に，生存動物は投与後 22 日に剖検した．

投与後 2～4 日に 5 匹が死亡した（40 μg/kg/day の 1 匹，60 μg/kg/day の 2 匹及び 80 μg/kg/day の 2 匹）. 死亡したマウス 5 匹中 3 匹では, 骨髄の中等度から重度の細胞減少を認めた. 80 μg/kg/day 投与群の雄及び雌で平均体重が減少した．すべての投与群で投与直後に投与に関連した主な一般状態の変化として，呼吸困難，運動失調，衰弱，痙攣などを認めた．

血液学的検査項目の減少は投与後 8 日に認め，これらには 40 μg/kg/day 以上の投与群での赤血球数，ヘモグロビン量及びヘマトクリット値の用量依存的な減少，40 μg/kg/day 以上の投与群の雄及び 60 μg/kg/day 以上の投与群の雌の網状赤血球数及び絶対好酸球数の減少，更に 60 μg/kg/day 投与群の雄及び 80 μg/kg/day 投与群の雌の絶対分葉核好中球数の減少が含まれていた．

組織学的には，投与後 8 日に 80 μg/kg/day 投与群で骨髄の赤芽球系，骨髄球系細胞及び巨核球数の顕著な減少並びに脾臓及び肝臓の髄外造血細胞数の減少を認めた．投与後 22 日までに，血液学的検査項目は正常又は対照より高くなった．投与後 22 日には 80 μg/kg/day 投与群のすべての動物に，骨髄の過形成又は脾臓の髄外造血細胞の過形成を認めた．

雌雄の CD_2F_1 マウスに 5 日間急速静脈内投与したトラベクテジンの MTD は，この試験結果に基づいて決定することができなかった．毒性の主要な標的器官は骨髄であった．この影響は可逆的であり，投与後 22 日までに回復した．脾臓及び肝臓の髄外造血はトラベクテジン投与によって減少したが，投与後 22 日までに回復した．

2.6.6.3.2　ラット

2.6.6.3.2.1　3 時間持続反復投与毒性試験（3 週間ごと 1 回投与，3 サイクル）（試験番号 [redacted]）

GLP 試験として, 雌雄の SD 系ラットに[redacted]トラベクテジン（[redacted]を用いた製剤）の 3 時間静脈内投与を 3 サイクル実施した（第 4.2.3.2.2 項及び第 4.2.3.2.3 項）．各サイクルは，単回 3 時間持続静脈内投与とこれに続く 3 週間の回復期間とした（表 2.6.6.3.2.1-1）．

表 2.6.6.3.2.1-1　試験デザイン

	3-Hour Infusion Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3)					
Group	**1**	**2**	**3**	**4**	**5**	**6**
No. of Animals/sex	10	10 (females)	10	10	10	10 (males)
No. of Doses Administered	3	3	3	3	3	3
Days of Treatment	0, 21, 42	0, 21, 42	0, 21, 42	0, 21, 42	0, 21, 42	0, 21, 42
No. of Days of Recovery Following Last Treatment	3 (5/sex) 21 (5/sex)	3 (5 females) 21 (5 females)	3 (5/sex) 21 (5/sex)	3 (5/sex) 21 (5/sex)	3 (5/sex) 21 (5/sex)	3 (5 males) 21 (5 males)
Dose/infusion (µg/kg)	0 (0.9% Saline)	2.5	10	25	50	75
Dose/infusion (µg/m^2)	0	15	60	150	300	450

第 4.2.3.2.2 項 試験報告書 No.[redacted]

50 µg/kg/day 以上の投与群の雌雄で反復投与後に死亡又は安楽死させた. 50 µg/kg/day 投与群の雌では，サイクル 2～3 の期間に 6 匹が死亡又は安楽死させた．雌 2 匹及び雄 1 匹は回復期間中に安楽死させた．75 µg/kg/day 投与群の雄では，6 匹がサイクル 2 の前に死亡又は安楽死させ，1 匹は回復期間中に死亡した．毒性は主として，体重減少，用量依存性の明らかな肝毒性［トランスアミナーゼ（ALP，AST，ALT）値の増加，総ビリルビン値の増加，肝細胞壊死，胆管の炎症及び増殖，胆管炎］であった．肝毒性は蓄積的で，雌性ラットで顕著であった．また，骨髄抑制（貧血，白血球数減少，骨髄細胞の減少，リンパ系組織のび漫性萎縮）並びに，投与部位の炎症及び壊死，消化管の単細胞壊死，潰瘍及び上皮萎縮を認めた．毒性は蓄積的で，雌性ラットで顕著であった．血液学的変化では部分的な回復性を示したが，雌の肝臓の変化はごくわずかな回復性しか示さなかった.

同様の所見を，低用量（2.5，10 及び 25 µg/kg/day）でも認めた．これらの用量での所見は，それほど顕著でなく用量反応性を示した．最低用量（2.5 µg/kg/day）での所見には，サイクル 3 後のアルブミン値のわずかな低下並びに脾臓，肝臓及び内側腸骨リンパ節の重量の増加を認めた（肝臓重量は完全に回復した）．肉眼的及び病理組織学的変化として，投与部位の壊死性炎症，線維血管腫様組織の著明な増殖, 投与部位の炎症に関連した可能性が高い骨髄細胞の増加, 更に胆管炎，胆管増殖，限局性の肝細胞壊死などを含む肝臓の変化を認めた.

50 µg/kg/day 以上の投与群で死亡又は安楽死した雄性ラットにおいて，精巣の精上皮の変性，精子巨細胞の出現及び精巣上体に細胞残屑を認めた. 75 µg/kg/day 投与群の雄性ラットの生存例でも精巣上体に細胞残屑を認めたが，3 週間の回復期間後には回復性を示した.

50 µg/kg/day 投与群で死亡又は安楽死した雌性ラットにおいて性周期の若干の遅延（周期性のわずかな低下）を認めた.

単回 3 時間持続静脈内投与（サイクル 1）後の MTD は，死亡率に基づくと雌雄ラットのいずれでも 50 µg/kg/day であった．サイクル 3 の後の雌雄の MTD は 25 µg/kg/day であった.

トラベクテジンの最高血漿中薬物濃度（C_{max}）は，通常静脈内投与終了時に認め，血漿中濃度は投与中止後に急速に低下した（第 4.2.3.2.3 項）．50 µg/kg/day 投与群では，曝露量は雌雄で類似

しており性差はなかった．また，個体変動を考慮に入れると初回と 3 回目投与との間で顕著な差を認めず，トラベクテジンの薬物動態は時間依存性でないこと（定常キネティクス）を示唆している．

トラベクテジンの曝露量は，検討した用量範囲では，十分に用量比例的に増加した．トキシコキネティクスデータを表 2.6.6.3.2.1-2 に示した．

表 2.6.6.3.2.1-2　3 時間持続静脈内投与時の初回及びサイクル 3 の C_{max} 及び AUC

Cycle[a)]	Sex	Dose (μg/kg)	C_{max} (ng/mL)	AUC[b)] (ng•h/mL)
1	Male[c)]	10	0.947	0.910
		25	0.814	2.15
		50	1.63	4.76
		75	2.00	5.97
1	Female[c)]	2.5	0.154	NC
		10	0.483	0.634
		25	0.481	1.23
		50	1.30	3.30
3	Male[c)]	10	0.351	0.635
		25	1.25	2.21
		50	1.92	7.43
		75	NA	NA
3	Female[c)]	2.5	NC	NC
		10	0.302	0.740
		25	1.01	2.15
		50	1.29	8.55

a) Single 3-hour i.v. infusions of trabectedin were given every 3 weeks (=a cycle)
b) AUC values noted are expressed as AUC_{0-t}
c) N = 2
NA = not available (all animals died before the third dose administration); NC = not calculated (all measured plasma concentrations were below the LLOQ [0.05 ng/mL])
第 4.2.3.2.3 項 試験報告書 No.[redacted] Table 5-2 及び 5-3 改変

以上より，ラットにトラベクテジンを単回投与及び 3 週間ごとの反復投与後では同様の毒性標的器官（骨髄，肝胆道系，消化管及び投与部位）が確認された．MTD は雌雄のいずれも 25 μg/kg/day であると判定されたが，毒性の強さは雌で顕著であった．肝胆道系の毒性は，雌性ラットではその程度は強く蓄積的であり不可逆的であったが，血液毒性は投与後 21 日以内に部分的に回復した．ラットでも分割投与の忍容性は良好であった．

2.6.6.3.3　イヌ

2.6.6.3.3.1　5 日間反復投与毒性試験（試験番号[redacted]）

非 GLP 試験として，ビーグル犬（2 匹/性）に[redacted]トラベクテジンを 0, 5, 8 又は 11 μg/kg/day の用量で 1 日 1 回 5 日間急速反復静脈内投与した（第 4.2.3.2.4 項）．初回投与から合計 11 日間又は 36 日間観察した（6 日間又は 31 日間回復期間）．

毒性は 8 及び 11 μg/kg/day 投与群で，骨髄，肝臓，胆嚢，胸腺及びリンパ節に毒性を認めた．11 μg/kg/day 投与群で投与後に体重減少及び摂餌量減少を認め，その傾向は 8 μg/kg/day 投与群でも認めた．初回投与後 11 日に中間検査のために安楽死させた 8 及び 11 μg/kg/day 投与群では，白血球数減少（成熟した好中球数及びリンパ球数の減少）を認め，骨髄細胞の減少並びに胸腺及びリンパ節のリンパ球減少を伴っていた．また，11 μg/kg/day 投与群で，血小板数減少を認め，それより程度は弱いが，8 μg/kg/day 投与群でも認めた．8 及び 11 μg/kg/day 投与群で認めた肝臓の病理組織学的変化（グリコーゲン減少，門脈周囲の亜急性炎症，門脈周囲の浮腫及び胆管過形成）及

び生化学的変化（ALP 値，ALT 値，AST 値，γ グルタミルトランスフェラーゼ値及びコレステロール値の増加，総蛋白値及び/又はアルブミン値の減少）から，トラベクテジンは肝細胞及び肝胆道系の障害を引き起こすことが示された．また，中間剖検では 8 及び 11 µg/kg/day 投与群で胆嚢の変化（浮腫形成及び亜急性炎症）を認めた．初回投与後 11 日には，病理組織学的変化を 5 µg/kg/day 投与群の雄の骨髄（細胞減少）及び肝臓（グリコーゲン減少及び胆管過形成）で認めたが，臨床病理学的検査項目の対応する変化を伴っていなかった．初回投与後 36 日の最終剖検までに回復性を示したが，8 及び 11 µg/kg/day 投与群ではごく軽微な肝臓病変が残存し，11 µg/kg/day 投与群では肝臓の生化学的検査項目にまだ増加がみられた．初回投与後 36 日まで投与部位の肉眼的及び病理組織学的変化をすべての用量（5，8 及び 11 µg/kg/day）で認めた．5 µg/kg/day 投与群においても，骨髄，肝臓，投与部位に変化を認めたことから，無毒性量は 5 µg/kg/day 以下と判断した．

以上より，イヌにトラベクテジンを 5 日間投与すると，げっ歯類と同様の器官に影響を認め（骨髄，肝臓及び胆管であるが，投与部位の反応は弱い），肝臓の変化の一部は回復性を認めない又は限定的であった．

2.6.6.3.4　サル

2.6.6.3.4.1　3 時間又は 24 時間持続反復投与毒性試験（3 週間ごと 1 回投与，4 サイクル）（試験番号 [redacted]）

GLP 試験として，カニクイザル（2 匹/性/群）に[redacted]トラベクテジン（[redacted]を用いた製剤）の静脈内投与（3 又は 24 時間持続）を 4 サイクル実施する用量設定試験を行った（第 4.2.3.2.5 項及び第 4.2.3.2.6 項）．各サイクルは，1 回 3 時間（第 1～4 群）又は 24 時間（第 5 群）持続静脈内投与とこれに続く 3 週間の回復期間とした（表 2.6.6.3.4.1-1）．各群 1 例の動物をサイクル 4 投与後 5 日～7 日（1 週間回復期間）に剖検し，残りの動物は 3 週間の回復期間後に剖検した．

表 2.6.6.3.4.1-1　試験デザイン

Group	**1**	**2**	**3**	**4**	**5**
No. of Animals/Sex	2	2	2	2	2
	Each treatment followed by a 3-week treatment-free period/cycle (Cycles 1, 2, 3)				
No. of Doses Administered[a)]	3	3	3	3	3
Duration of Infusion	3 hours	3 hours	3 hours	3 hours	24 hours
Day of Treatment	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43
Dose/infusion (µg/kg)	0	25	50	75	75
Dose/infusion (µg/m^2)	0	300	600	900	900
	Treatment followed by 1 and 3-week treatment-free periods (Cycle 4)				
No. of Doses Administered[a)]	1	1	1	1	1
Duration of Administration	3 hours	3 hours	3 hours	3 hours	24 hours
Day of Treatment	62	62	62	62	62
No. of Weeks Following Last Dose Administration	1 and 3	1 and 3	1 and 3	1 and 3	1 and 3
Dose/infusion (µg/kg)	0	120	75	100	100
	0.9% saline				
Dose/infusion (µg/m^2)	0	1440	900	1200	1200

a) Groups 1-4 were infused (3-hour infusion) via a peripheral vein. The group 5 animals (24-hour i.v. infusion group) were fitted with a vascular access port.
Note: 1/sex/group held for 1 week recovery period prior to sacrifice; 1/sex/group held for 3 week recovery period prior to sacrifice.

第 4.2.3.2.5 項 試験報告書 No.[redacted]

25 μg/kg/day（サイクル 1～3）/120 μg/kg/day（サイクル 4）を 3 時間持続静脈内投与した群の両雄サルは，初回投与後 62 日に第 4 投与サイクルとして 120 μg/kg/day を投与した後に死亡し（初回投与後 66～67 日），死亡前に一般状態の変化を伴っていなかった．同群の雌 1 匹はサイクル 4 の投与から約 2 週間後に瀕死により安楽死させた．

50 μg/kg/day（サイクル 1～3）/75 μg/kg/day（サイクル 4）を 3 時間持続静脈内投与した群（50/75 μg/kg/day 投与群）の雄 1 匹は，75 μg/kg/day のサイクル 4 の投与（初回投与後 62 日）から 18 日後（初回投与後 80 日）に瀕死状態で発見され採血後に死亡した．

75 μg/kg/day（サイクル 1～3）を 3 時間持続静脈内投与した雄 1 匹及び雌 1 匹は，それぞれ初回投与後 61 日及び 59 日（75 μg/kg/day の 3 回目投与から約 3 週間後）に，一般状態の悪化により安楽死させた．

75 μg/kg/day（サイクル 1～3）/100 μg/kg/day（サイクル 4）（75/100 μg/kg/day 投与群）を 24 時間持続静脈内投与した雌 1 匹は，100 μg/kg/day のサイクル 4 の投与から 2 週間後に死亡した．

これらの動物の剖検では，主として肝臓の腫大又は硬化，脾臓及び（又は）胸腺の縮小化，骨髄の顕著な低形成，中等度の肝細胞肥大/壊死などを認めた．死亡の正確な原因は確認することができなかった．

一般状態の変化は，前述の死亡例のもの以外では，初回投与後 72 日から 24 時間持続静脈内投与として 75 μg/kg/day（サイクル 1～3）/100 μg/kg/day（サイクル 4）を投与した雄 1 匹の自発運動の低下に限定されていた．体重，摂餌量，眼科学的検査及び心電図検査のデータでは，すべての群で著変を認めなかった．3 時間持続静脈内投与による 25 及び 50 μg/kg/day のサイクル 2 の直後並びに 3 時間及び 24 時間持続静脈内投与による 75 μg/kg/day のサイクル 1 の後から，すべての投与動物で軽度から中等度の貧血を認めた．回復期間中の回復性は明らかでなかった．

75/100 μg/kg/day（3 及び 24 時間持続静脈内投与）では，試験期間中に貧血が増加する傾向にあった．白血球数の減少（主として一過性）は，25/120，50/75 及び 75/100 μg/kg/day を 3 時間持続静脈内投与を行った群の各サイクル後に雌雄のほとんどでみられた．75/100 μg/kg/day（24 時間持続静脈内）投与群では，試験期間を通して白血球数が高く，一部のサイクル後（回復期間中）に一過性の低下を伴うものもあった．75/100 μg/kg/day（24 時間持続静脈内）投与群の雌雄及び 75/100 μg/kg/day（3 時間持続静脈内）投与群の雌 1 匹で，フィブリノーゲンの増加が高い頻度でみられた．網状赤血球数の増加は，サイクル 3 及び（又は）サイクル 4 の 50/75，75/100 μg/kg/day（3 時間持続静脈内）投与群及び 75/100 μg/kg/day（24 時間持続静脈内投与）投与群でみられた．75/100 μg/kg/day（24 時間持続静脈内投与）投与群以外の投与群では骨髄性及び赤芽球系成分の著しい減少を認めた．

トラベクテジンを投与したすべての群の約半数のサル（及び対照の雄）では，最初の投与サイクル後に AST 値，ALT 値及び（又は）クレアチンホスホキナーゼ（CPK）値が投与前値から一過性に増加した．その後，CPK の高値が AST 及び ALT の高値を伴った場合もあり，特にサイクル 4 の後に高い頻度で認めた．

75/100 μg/kg/day（24 時間持続静脈内投与）投与群では，試験終了時に尿中に蛋白及び（又は）血液を認める傾向にあった．

すべてのトラベクテジン投与群で腎臓及び（又は）肝臓重量の増加と胸腺重量の減少を認め，これらは時間とともに回復した．

75/100 µg/kg/day（24 時間持続静脈内）投与群でのみ，サイクル 4 投与後に腎臓の腫大及び蒼白化を認めた．投与部位の血腫，硬結及び肥厚を（死亡例及び対照を含む）一部の動物で認め，これらは時間とともに改善する所見を示した．

用量又は時間と関係なくすべての群で，1 週間の回復期間終了時（サイクル 4）に，ごく軽微から中等度の肝細胞肥大，顕著な肝細胞変性/壊死，軽度から中等度の類洞及び門脈域の混合性の炎症性細胞などを認めたが，胆管の障害は認めなかった．75/100 µg/kg/day を 24 時間持続静脈内投与した群の雄のごく軽微な肝細胞肥大を例外として，3 週間回復後の生存動物では肝臓の変化を認めなかった．中等度から顕著な骨髄細胞の減少と脾臓及び胸腺のリンパ球減少をすべての群で認めた．75/100 µg/kg/day を 24 時間持続静脈内投与した群で，1 週間の回復期間終了時に，骨髄性成分の顕著な増加及び赤芽球系成分の減少を認めた．同群の動物の 3 週間の回復期間終了時には，十分な細胞充実性を認めた．トラベクテジンを投与したすべての群で静脈炎，血栓性静脈炎，静脈壁の壊死及びコラーゲン分解，静脈周囲の出血，炎症性細胞，皮下組織筋肉の変性/壊死性ミオパシーを認めた．75/100 µg/kg/day 投与群の一部で，上皮の扁平化及び軽度の上皮変性/壊死を伴う，ごく軽微から顕著な腎尿細管拡張を認め，24 時間持続静脈内投与した群では顕著であった．これらの結果が得られたが，最初の 3 回の投与と 4 回目の投与では用量を変更しているため，毒性変化に対する用量反応性を詳細に評価することは難しいと考えた．

骨髄及び腎臓の変化を除き，75/100 µg/kg/day の用量を 3 時間持続静脈内投与した動物と 24 時間持続静脈内投与した動物との間で差は認めなかった．

トキシコキネティクス分析では，投与終了時にトラベクテジンの血漿中濃度は急速に低下した後，極めて徐々に減少していくことが示された（第 4.2.3.2.6 項）．トラベクテジンの全身クリアランス（CL）は肝血流量の半分程度から高い値を示し，また見かけ上の分布容積（Vd_{ss}）は体内総水分量より明らかに大きく，トラベクテジンは広範囲に組織内に分布することを示している．最終相の消失半減期（$t_{1/2}$）の推定値は，約 2～10 日の範囲であり，血漿中濃度の定量下限の影響で $t_{1/2}$ の算出に用いることができる測定時点数が個体ごとで異なったため幅広い値になったと考えた．

全体として，トラベクテジンの血漿中濃度はサイクル 1 とサイクル 3 との間でかなり類似し，明らかな性差も認めなかった．曝露量（$AUC_{0-\infty}$）は，検討した用量範囲では投与用量に比例して増加していた（表 2.6.6.3.4.1-2）．

表 2.6.6.3.4.1-2　3 時間又は 24 時間持続静脈内投与時の初回及び反復投与時の薬物動態学的パラメータ

Cycle[a)]	Sex	Dose (μg/kg)	C_{max} (ng/mL)		$AUC_{0-\infty}$ (ng•h/mL)[b)]		$t_{1/2}$ (h)		CL (L/h/kg)		Vd_{ss} (L/kg)	
			3h	24h	3h	24h	3h	24h	3h	24h	3h	24h
1	M[c)]	25	0.783	-	7.79	-	41	-	3.21	-	142	-
		50	2.80	-	22.7	-	77	-	2.20	-	161	-
		75	3.24	-	30.3	-	74	-	2.47	-	176	-
		75	-	1.76	-	51.6	-	109	-	1.45	-	106
1	F[c)]	25	0.824	-	10.9	-	81	-	2.28	-	197	-
		50	6.80	-	28.2	-	77	-	1.78	-	80.7	-
		75	2.58	-	26.9	-	96	-	2.79	-	287	-
		75	-	1.04	-	-	-	-	-	-	-	-
3	M[c)]	25	0.792	-	6.80	-	48	-	3.68	-	193	-
		50	5.29	-	-	-	173	-	-	-	-	-
		75	1.66	-	24.3	-	63	-	3.09	-	230	-
		75	-	1.75	-	-	-	-	-	-	-	-
3	F[c)]	25	0.987	-	11.3	-	83	-	2.21	-	200	-
		50	2.86	-	-	-	229	-	-	-	-	-
		75	1.38	-	27.1	-	231	-	2.77	-	534	-
		75	-	1.66	-	-	-	-	-	-	-	-
4	M[c)]	120	4.27	-	-	-	-	-	-	-	-	-
		75	3.66	-	34.9	-	92	-	2.15	-	212	-
		100	-	-	-	-	62	-	-	-	-	-
		100	-	0.835	-	30.5	-	81	-	3.28	-	292
4	F[c)]	120	5.68	-	84.0	-	137	-	1.43	-	219	-
		75	5.08	-	33.5	-	99	-	2.24	-	171	-
		100	5.62	-	-	-	-	-	-	-	-	-
		100	-	1.21	-	49.7	-	74	-	2.01	-	167

a) Dose cycles gives on Days 1, 23, 43 and 64; no toxicokinetic sampling was performed during the 2nd cycle (Day 23)
b) AUC_{0-7d} after repeated dose administration (Week 11) in the groups receiving weekly infusion
c) N = 1 or mean of N = 2
- = Sample not available, parameter not calculated or analysis not performed; M = male; F = female
第 4.2.3.2.6 項 試験報告書 No.[redacted] Table 5-1～5.3 抜粋

2.6.6.3.4.2　3 時間持続反復投与毒性試験（1 週間ごと 1 回投与又は 3 週間ごと 1 回投与，3～4 サイクル）（試験番号 [redacted]）

GLP 試験として，カニクイザルに[redacted]トラベクテジン（[redacted]を用いた製剤）の静脈内投与を 3 サイクル又は 4 サイクル実施する用量設定毒性試験を行った（第 4.2.3.2.7 項及び第 4.2.3.2.8 項）．1 週間ごと 1 回投与群では，3 時間持続静脈内投与を週 1 回 3 週間行った後 1 週間休薬を 1 サイクルとし，計 3 サイクル投与した．3 週間ごと 1 回の投与群では，3 週間ごとに 1 回を 1 サイクルとし，計 4 サイクル投与した．投与終了時に，所定の動物には 1 週間又は 3 週間の回復期間を設けた（表 2.6.6.3.4.2-1）．

表 2.6.6.3.4.2-1　試験デザイン

Group	**1**	**2**	**3**	**4**	**5**
No. of Animals/Sex	2	2	2	2	2[a)]
No. of Treatment Cycles	3	3	3	3	4
No. of Treatments/Cycle	3	3	3	3	1
Total No. of Treatments	9	9	9	9	4
Duration of Infusion	3 hours	3 hours	3 hours	3 hours	3 hours
Frequency of Administration[b)]	Once/week for 3 weeks, followed by a 1-week treatment-free period				Once/3 weeks
Dose/infusion (µg/kg)	0 0.9% saline	10	20	30	70
Dose/infusion (µg/m^2)	0	120	240	360	840
Dose/cycle (µg/m^2)	0	360	720	1080	840
No. of Recovery Weeks Following Last Cycle[c)]	1 and 3	1 and 3	1 and 3	1 and 3	1 and 3

a) One Group 5 female died post dosing on test Day 1. This animal was immediately replaced.
b) Groups 1-4 treated on Days 1, 8, 15, 29, 36, 43, 57, 64, and 71; Group 5 treated on Days 1, 22, 43, and 64.
c) 1/sex/group held for 1 week recovery period prior to sacrifice; 1/sex/group held for 3 week recovery period prior to sacrifice.
第 4.2.3.2.7 項 試験報告書 No.[redacted]

70 µg/kg/day を 3 週間ごとに 1 回投与した投与群の 3 匹（雌 2 匹，雄 1 匹）が予定剖検前に死亡した．

雌 1 匹は，横臥位，自発運動の低下，凝視及び体温上昇（40°C 以上）がみられた後，初回投与終了後 1～2 時間に死亡し，関連した病理組織学的変化はみられなかった．

雄 1 匹は，急激な一般状態の悪化によりサイクル 2 の投与から約 2 週間後の早期（初回投与後 38 日）に安楽死させた．死亡前の臨床病理学的データでは，白血球のほぼ完全な消失，重度の貧血及びフィブリノーゲン値の増加がみられた．病理組織学的検査による主要な所見は，結腸/直腸の限局性の壊死性潰瘍及び上皮の扁平化を伴う尿細管拡張であった．

別の雌 1 匹は，急激な一般状態の悪化により，初回投与後 61 日のサイクル 4 から 5 日後（初回投与後 66 日）に早期に安楽死させた．死亡前の生化学的データでは，主として電解質障害と AST 値及び ALT 値の増加がみられた．剖検での主要な所見は，十二指腸と他の腸管の癒着及び外壁の肥厚及び粘膜の壊死/出血を伴った盲腸の拡張であった．病理組織学的検査での主要な所見は，腸及び腹腔の病変であった（投与に関連した腸の壊死性/壊疽性盲腸炎及び腸病変の二次的な変化である腹膜炎）．

瀕死により安楽死させた 70 µg/kg/day 投与群の動物では，死亡の 1 日前又は 2 日前に体温上昇（40°C 以上）がみられた．週 1 回の投与群ではいずれにも早期の死亡を認めなかった．

死亡前に認めた変化を除き，一般状態の変化はほとんどのトラベクテジン投与例で認めた投与部位の肥厚/創傷/壊死のみであった．

体重，摂餌量，眼科学的検査及び心電図検査のデータ並びに尿検査及び器官重量のデータでは，すべての群で著変を認めなかった．

すべてのトラベクテジン投与群で軽度から重度の貧血を認めた（程度及び発現時間は用量依存的であった）．回復期間中の検査項目の回復性は明らかでなかった．70 µg/kg/day 投与群では，試験期間中に貧血の程度が悪化する傾向にあった．30 及び 70 µg/kg/day 投与群での所見は類似していた．更に，試験の中間から試験終了時にかけて網状赤血球数の増加を 20，30 及び 70 µg/kg/day 投与群で用量に関係なく認めた．

トラベクテジンを投与した群で，対照と比較して，用量依存的に骨髄性成分の低下（成熟指数の低下と関連したもの）及び赤芽球系成分の増加（正赤芽球数の増加と関連したもの）を認め，

骨髄性細胞/赤芽球の比の低下をもたらしていた．これらの所見は，最終投与後 3 週で比較的顕著であった．

対照群を含めたほぼすべての投与動物で，最初の投与サイクル後に一過性に AST 値，ALT 値，CPK 値及び（又は）乳酸脱水素酵素値の増加を認めた．しかし，それぞれの対照と比較すると，これらの増加は 20，30 又は 70 µg/kg/day 投与群の雄で比較的顕著であった．その後，これらの検査項目は基準範囲内に回復した．

剖検では，トラベクテジン投与群の投与部位の変化の発生率が最終投与後 1 週及び 3 週に高かった．

3 週間ごとに 1 回投与した 70 µg/kg/day 投与群では，主要な病理組織学的所見は胸骨の骨髄細胞減少と胸腺及びリンパ節のリンパ球減少であり，サイクル 2 の投与 2 週間後に安楽死させた雄及びサイクル 4 の投与後 5 日に安楽死させた雌で認めた．これらの所見は，最終投与後 21 日に安楽死させた同投与群の生存した雌では認めなかった．

更に，週 1 回投与の 20 及び 30 µg/kg/kg 投与群では，胸腺のリンパ球減少を 1 週間の回復期間終了後の雌雄と 3 週間の回復期間終了後の雌で認めた．

高用量群の毒性の程度及び死亡率に基づくと，週 1 回投与（30 µg/kg/day）は，3 週間ごとの投与スケジュール（70 µg/kg/day）より良好な忍容性であった．しかし，総累積用量はいずれの投与サイクルでも類似していた[週 1 回（30 µg/kg/day）及び 3 週間ごと（70 µg/kg/day）の投与レジメンでそれぞれ 270 及び 280 µg/kg].

トキシコキネティクス分析の結果では，カニクイザルにおける既知の所見（第 4.2.3.2.8 項），すなわち肝血流量と比較して半分から高い値の CL，大きな見かけ上の Vd_{ss}，長い $t_{1/2}$，明らかな性差はないこと，反復投与により影響を受けない血漿中薬物動態，検討した用量範囲内では投与用量に比例した曝露量の増加がみられることが確認された（表 2.6.6.3.4.2-2）.

表 2.6.6.3.4.2-2　3 時間持続静脈内投与時の初回及び反復投与時の薬物動態学的パラメータ

Cycle	Sex	Dose (µg/kg)[b)]	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•h/mL)[a)]	$t_{1/2}$ (h)	CL (L/h/kg)	Vd_{ss} (L/kg)
Three cycles, each cycle: 3-hour infusion weekly for 3 weeks followed by 1 week of recovery (=a cycle)							
1	Male[c)]	10	0.40	-	-	-	-
		20	0.95	8.64	60	2.32	137
		30	1.48	-	149	-	-
	Female[c)]	10	0.40	-	-	-	-
		20	0.59	-	73	-	-
		30	1.83	12.9	-	2.32	125
3	Male[c)]	10	0.40	3.49	63	2.87	-
		20	1.10	10.5	49	1.90	-
		30	1.85	-	-	-	-
	Female[c)]	10	0.67	4.18	85	2.39	-
		20	1.17	11.2	74	1.79	-
		30	3.41	15.9	138	1.89	-
Four cycles, each cycle: 3-hour infusion every 3 weeks (=a cycle)							
1	Male[c)]	70	2.63	29.6	61	2.37	160
	Female[c)]	70	5.29	31.6	42	2.21	121
4	Male[c)]	70	3.95	36.2	64	1.94	132
	Female[c)]	70	6.19	40.0	45	1.75	94.4

a) AUC_{0-7d} after repeated dose administration (Week 11) in the groups receiving weekly infusion
b) cumulative doses per cycle were 360, 720, and 1080 µg/m^2, respectively
c) N = 1 or mean of N = 2
- = parameter not calculated

第 4.2.3.2.8 項 試験報告書 No. [redacted] Table 5-2～5-5 抜粋

2.6.6.3.4.3　24 時間持続反復投与毒性試験（3 週間ごと 1 回投与，4 サイクル）（[redacted]）

非 GLP 試験として，カニクイザルに[redacted]トラベクテジン（[redacted]を用いた製剤）を血管アクセスポートを用い，3 週間ごとに 1 回の 24 時間持続静脈内投与を 8 サイクル実施する計画とした（表 2.6.6.3.4.3-1）（第 4.2.3.2.9 項）．しかし，早期に判明した所見に基づいて，この試験はサイクル 4 の投与後に終了した．

表 2.6.6.3.4.3-1　試験デザイン

Group	**1**	**2**	**3**	**4**
No. of Animals/Sex	5	3	3	5
No. of Treatment Cycles	4	4	4	4
No. of Treatments/Cycle	1	1	1	1
Total Number of Treatments	4	4	4	4
Duration of Administration	24 hours	24 hours	24 hours	24 hours
Frequency of Administration	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks
Dose/infusion (µg/kg)	0 (0.9% saline)	25	50	70
Dose/infusion (µg/m^2)	0	300	600	840
Dose/cycle (µg/m^2)	0	300	600	840
Cumulative Dose (µg/m^2)	0	1200	2400	3360

Note: Study design reflects early study termination.
第 4.2.3.2.9 項 試験報告書 No.[redacted]

サイクル 3 の投与後に，数匹のサル（25 µg/kg/day 投与群の雌 3 匹中 2 匹及び雄 3 匹中 3 匹，50 µg/kg/day 投与群の雌 3 匹中 3 匹及び雄 3 匹中 1 匹，70 µg/kg/day 投与群の雌 5 匹中 4 匹及び雄ではなし）に，投与部位の腫脹，発赤，硬結などを認め，これらは一部の動物では最終的に有痛性の壊死性変化になった．投与部位の重篤な壊死性変化のため，70 µg/kg/day 投与群の雌 1 匹はサイクル 3 投与後に安楽死させた．4 回目の投与後に，50 µg/kg/day 投与群の他の雄 2 匹，70 µg/kg/day 投与群の雌 1 匹及び雄 2 匹も投与部位の重篤な壊死性変化により安楽死させた．70 µg/kg/day 投与群の最後の雄 1 匹は，主として一般状態の悪化により安楽死させた．科学的観点からみて，残りの動物数は極めて少なく，適切な毒性学的及びトキシコキネティクス評価を行うことが不可能であった．また，局所反応（壊死，疼痛）が臨床的，血液学的（白血球増多症），生化学的（CPK 値増加），トキシコキネティクスなどの所見及び病理組織学的所見の解釈に影響を及ぼした可能性がある．これまでのサルの試験と比較して著しい有痛性の局所反応が生じているこれらのサルを使用して試験を続行することは，倫理的にできないと判断した．

したがって，サイクル 4 の 3 週間後に試験を終了した．最終評価は，血液学的，生化学的検査，既知の標的器官（投与部位，肝臓，骨髄，腎臓，リンパ器官，遠隔の筋肉）及び肉眼的病変を有する器官の病理組織学的検査に限定した．同時に計画していたトキシコキネティクス分析は実施しなかった．

体重，摂餌量，心電図，眼科学的検査又は尿検査のデータでは，投与に関連した影響を認めなかった．

血管アクセスポート部位に重篤な刺激性変化がみられたサルでは，概してその前に体温のわずかな上昇を認めた．

50 及び 70 µg/kg/day 投与群での軽度な貧血傾向は，試験期間中に悪化し，70 µg/kg/day 投与群では総白血球数のわずかな低下を認めた．すべての群でサイクル 2 又は 3 以降にフィブリノーゲ

ン値及び血小板数の増加を認めた. 更に, すべての群で試験期間を通して無機リンの低値を認め, 70 µg/kg/day 投与群で，試験終了時に BUN 値及びクレアチニン値の増加を認めた.

50 又は 70 µg/kg/day 投与群で尿管拡張を伴った腎臓の蒼白化及び（又は）腫大を認め，70 µg/kg/day 投与群で胸腺の縮小化を認めた.

安楽死した 70 µg/kg/day 投与群の雄 2 匹に未熟精巣を認めた.

投与部位の用量依存的な肥厚，硬結，炎症及び変性を認め，その発現頻度及び程度はトラベクテジンを投与した動物で高かった．投与した静脈壁（用量依存的な変化），静脈周囲の組織及び皮下組織筋肉の炎症，変性，壊死などの変化をすべての用量で認めた．用量依存的な腎症（主として片側性であることから，おそらくカニューレを挿入した静脈で認めた重度の血栓性静脈炎による二次的なものと考えられた）及び胸腺のリンパ球減少を 50 又は 70 µg/kg/day 投与群で認めた. 更に，脾臓のリンパ球減少を 70 µg/kg/day 投与群の雄 1 匹でも認め，また用量依存的な骨髄の細胞減少を 25，50 及び 70 µg/kg/day 投与群の胸骨骨髄で認めた.

検討したいずれの投与群でも投与に関連した肝臓の所見はみられなかった.

以上より，この試験の条件下では，被験物質の投与はすべての用量でみられた投与部位の用量依存的な肥厚，硬結，変性及び炎症性の変化と関連しており，このため 50 µg/kg/day 投与群及び 70 µg/kg/day 投与群の数匹を早期に安楽死させざるを得なかった．全身的には，トラベクテジンの 25 µg/kg/day によるサイクル 4 の投与後では，概ね良好な忍容性であり，この用量では軽度の骨髄細胞減少を除いて，臨床，臨床検査又は全身の病理検査に顕著な所見はみられなかった.

2.6.6.3.4.4　3 時間持続反復投与毒性試験（3 週間ごと 1 回投与，4～8 サイクル）（[redacted]）

GLP 試験として，投与部位の局所刺激性を軽減するために変更した試験デザインを用い，サルの反復投与毒性試験を行った（第 4.2.3.2.10 項）.

大静脈の中心静脈カテーテル（カテーテル留置部: 大腿静脈から腎臓近辺の下大静脈）を用い，更に投与容量を減量し，[redacted]トラベクテジン（[redacted]を用いた製剤）を 3 時間持続静脈内投与した. カテーテルは 3 時間の投与終了後に生理食塩液で連続的にフラッシングした. 0, 25, 50 及び 65 µg/kg/day の各投与後に 3 週間の回復期間を設けた．各用量雌雄それぞれ 3 匹とし，また 8 週間の回復期間に供するために雌雄各 2 匹を溶媒群及び 65 µg/kg/day 投与群に追加した.

中間用量及び高用量群の投与は，多数の動物が死亡したために投与を中止した．これらの群の生存例はサイクル 4 終了の翌日から 8 週間の回復期間に変更した．加えて同じ入荷動物の（カテーテル挿入及び生理食塩液投与を受けた）被験物質を投与していない予備の雌 2 匹も同様の投与スケジュールに変更した．対照群の 3 匹/性の再割付けはサイクル 6 の投与前に行った．これらの動物は中ー低用量群（35 µg/kg/day）とし，6 サイクルの投与を行った後，サイクル 6 の終了から 144 時間後に剖検を行った．対照群の残り 2 匹/性はサイクル 6，7 及び 8 の投与を受け，低用量群の動物（25 µg/kg/day）と同時に剖検を行った（表 2.6.6.3.4.4-1）.

表 2.6.6.3.4.4-1　試験デザイン

Treatment: No. of Animals	5(2)[a]/sex	2f[b]	3/sex	3/sex	5/sex	3/sex[a]
Recovery: No. of Animals	-	2f	-	1m and 2f	2f	-
No. of Treatment Cycles	8	4	8	4	4	6
No. of Treatments/Cycle	1	1	1	1	1	1
Total Number of Treatments	8	4	8	4	4	6
Duration of Administration	3 hours	3 hours	3 hours	3 hours	3 hours	3 hours
Frequency of Administration	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks	Once every 3 weeks
Recovery	N/A	2 months	N/A	2 months	2 months	N/A
Dose/infusion (μg/kg)	0	0	25	50	65	35
Dose/infusion (μg/m^2)	0	0	300	600	780	420
Dose/cycle (μg/m^2)	0	0	300	600	780	420

a) Three/sex animals from the control group were re-allocated to 35μg/kg group
b) Two spare female animals were assigned to control group and underwent an 8-week recovery period.
第 4.2.3.2.10 項 試験報告書 No.[redacted]

カニクイザルに 3 週間ごとに 3 時間かけて 1 回トラベクテジンを静脈内投与したところ，死亡例が生じたが，生存動物では 50 及び 65 μg/kg/day で 4 サイクルが投与可能で，35 μg/kg/day の投与量では 6 サイクルが投与可能であった．25 及び 0 μg/kg/day の投与量では予定した 8 サイクルが投与可能であった．

50 μg/kg/day 投与群の雄 2 匹及び 65 μg/kg/day 投与群の雄 1 匹の一般状態は，初回又は 2 回目の投与後に悪化した．これらの早期死亡例は重度の白血球数減少（好中球，単球又はリンパ球を含む）及び免疫抑制（リンパ節及び骨髄の萎縮）とこれに起因した細菌媒介性の病変（消化管，肺，肝臓又は心臓の炎症，壊死，出血巣又は細菌巣）に起因したものと推察した．

その後，50 μg/kg/day 投与群の雌 1 匹並びに 65 μg/kg/day 投与群の雄 4 匹及び雌 3 匹の 4 回目投与時又は投与後，35 μg/kg/day 投与群の雌 1 匹の 5 回目投与後に認めた一般状態の悪化及び死亡の原因は，初期の所見とは異なっており，ほとんどが白血球増多症並びにこれに伴った投与部位（カテーテル留置部：大腿静脈から腎臓近辺の下大静脈）の広範性の炎症性，線維性及び壊死性の変化から成り，尿管，腎臓，肝臓，腹筋，横隔膜，神経や血管などを含む周囲組織に影響が及んでいた．

これらのサルでは，50 及び 65 μg/kg/day 投与群の生存動物と同様に，四肢，指，尿生殖器側の腰部，腹部及び（又は）胸部領域の軽度から重度の腫脹を認め，8 週間の回復期間中にも継続して認めた．これらの観察所見は発現と持続時間に変動があり，またその程度は用量依存的でなかった．すべての雄と 25 μg/kg/day 投与群の雌 1 匹及び 35 μg/kg/day 投与群の雌は，類似した変化を示した．多くの場合，これらの動物は腫脹の発現期間中及び発現後に四肢の活動制限，筋緊張の低下及び（又は）異常歩行を示したが自発運動は可能であった．対照群の動物ではこれらの変化を認めなかった．

トラベクテジンを投与した群の大部分で，最初のサイクルの投与から約 1 週間後に一過性に摂餌量が減少したが，一般状態の変化を認めた場合には剖検まで継続して認めた．50 及び 65 μg/kg/day 投与群で体温上昇又は体温低下を認め，状態悪化を示す他の症状と関連していた．体重，心電図データ，尿検査及び器官重量のデータでは，投与した動物の肝臓及び腎臓重量の増加を除き，すべての群で著変を認めなかった．

50 及び 65 μg/kg/day 投与群で，サイクル 1 から 3 の終了後に，白血球数及び好中球数が減少した．サイクル 4 終了後に安楽死させた 50 及び 65 μg/kg/day 投与群の動物では，白血球数及び好中球数の増加を認め，これは四肢，尿生殖器領域及び（又は）腹部の著しい腫脹並びに投与部位の重度の炎症と関連していた．50 及び 65 μg/kg/day 投与群の生存動物の白血球系検査値は 8 週間の回復期間中に正常値に戻った．50 及び 65 μg/kg/day 投与群の動物で，投与期間中に貧血を認め，回復期間終了時までに投与前の水準に回復する傾向にあった．25 及び 35 μg/kg/day 投与群の動物で，白血球数及び赤血球系検査項目が一過性且つわずかに減少した．

65 μg/kg/day 投与群の雌雄各 1 匹で，ALP 値の増加を認めたが，肝胆道系の病理組織学的変化を伴っていなかった．他の肝機能検査は変化なく，肝臓の病理組織学的変化もみられなかった．

35，50 及び 65 μg/kg/day 投与群の動物で，サイクル 2 以降に様々な程度のアルブミン値減少を認め，四肢，尿生殖器領域の著しい腫脹症状の発現と関連していることが多かった．同様に，50 μg/kg/day 投与群の雌 1 匹, 65 μg/kg/day 投与群の雄数匹及び 35 μg/kg/day 投与群の雌 1 匹では，早期の安楽死前に BUN 値及び（又は）クレアチニン値の中等度から重度な増加がみられ，四肢，尿生殖器領域及び（又は）腹部の著しい腫脹と関連していた．

トラベクテジンに関連した病理学的変化として，初期の免疫抑制（重度の好中球数減少を伴った胸腺及び骨髄の萎縮）が，細菌に関連した腸病変を発症後に死亡した高用量又は中間用量の 3 匹で認めた．これらの変化は，この試験の他の動物ではみられなかった．

すべての動物の投与部位（カテーテル留置部：大腿静脈から腎臓近辺の下大静脈）では，カテーテルの先端部，上方及び下方に，顕著な血栓による血管腔の閉塞を認め，著しく広範性の血管周囲炎及び線維化，広範性の血管及び血管周囲性の壊死及び炎症を伴い，尿管，腎臓，肝臓，腹筋，横隔膜，神経及び血管を含む領域組織から成る大きな腫瘤を形成していた．外部の手術部位では，カテーテルに隣接した炎症性病変及び線維化を認め，一部の動物では，壊死部，皮下の炎症や浮腫部位も認めた．

腎臓では，片側性又は両側性で線維化を伴った間質の顕著な炎症とともに，尿細管の好塩基性化及び拡張，腎盂拡張などを認めた．これらの病変は，隣接した投与部位の病変による二次的なものである可能性が高い．皮下組織でみられた真皮及び皮下の顕著な浮腫は，腎臓の変化と関連していた．

肝臓では，類洞の貪食細胞及び炎症性細胞を認めた．これらの変化は投与部位の広範な病変による二次的なものであると考えられた. 65 μg/kg/day 投与群のほとんどの動物では最も広範囲の病変を認めたが，65 μg/kg/day 投与群に限らず，25 μg/kg/day 投与群の動物にも重度の病変を認めることがあった．

65 μg/kg/day 投与群の雌雄の全例と 25 及び 50 μg/kg/day 投与群の一部の動物の膵臓では，回復性ある軽度な膵腺房の脱顆粒を認めた．

最終のサイクル 8 の後に，25 μg/kg/day 投与群の雄の左眼に，限局性の網膜浮腫を認めた．当該動物の追加の評価は行わなかったことから，回復性を評価できなかった．また，サイクル 4 の後に 35 μg/kg/day 投与群の雌の左眼に限局性の網膜浮腫を認め，更に同様の病変を最終のサイクル 6 の後に当該動物の右眼に認めた．これらの病変の意義は検討されていないが，これらはトラベクテジンを投与後の網膜毒性の徴候を示している可能性もある．

回復期間の終了時まで生存した動物（中間用量及び高用量群のみの生存動物）では，投与終了時と同程度の腎臓及び投与部位の病変がみられた．腎臓及び投与部位の病変は対照群でもみられたが，その程度はかなり弱かった．

トキシコキネティクス分析の結果は，これまでのカニクイザルにおける試験のデータとおおむね一致していた（表 2.6.6.3.4.1-2 及び表 2.6.6.3.4.2-2）．トラベクテジンは肝血流量と比較して半分から高い値の CL，大きい見かけ上の Vd_{ss}，長い $t_{1/2}$ を示し，雌雄間の明らかな差はみられなかった．初回投与後では，全身曝露量の増加は投与量に比例していた（表 2.6.6.3.4.4-2）．トラベクテジンを最高サイクル 4 まで投与したこれまでの反復投与試験とは対照的に，この試験の数匹は 6～8 回の投与サイクル後に全身曝露量の減少を示した．

表 2.6.6.3.4.4-2　3 時間持続静脈内投与時の初回及び反復投与時の薬物動態学的パラメータ

Cycle	Sex	Dose (μg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	Vd_{ss} (L/kg)
Cycle: 3-h infusion every 3 weeks							
1	Male	25	1.70	12.3	45.1	2.08	82.9
1		35	2.50	--	--	--	--
1		50	2.96	23.3	63.7	2.21	131
1		65	3.71	28.8	53.0	2.27	116
1	Female	25	2.09	12.9	60.1	1.96	92.5
1		35	1.99	13.1	36.7	3.10	116
1		50	3.76	25.0	84.1	2.04	147
1		65	5.23	31.5	70.9	2.10	121
8	Male	25	0.09	--	--	--	--
6		35	1.94	--	--	--	--
8	Female	25	0.99	--	--	--	--
6		35	1.85	--	--	--	--

n = 3/sex/group for 25, 35 and 50 μg/kg; n = 5/sex/group for 65 μg/kg
-- = parameter could not be estimated accurately
第 4.2.3.2.10 項 試験報告書 No. [redacted] Table TK-1.1～1.6 抜粋

本試験では毒性の標的器官（骨髄，肝臓，腎髄質及び筋肉）中のトラベクテジン濃度を測定した．これらの組織を数回の投与サイクル後及び最終投与後の各時点で採取したが，組織中のトラベクテジンはほぼ定量できなかった．血漿中及び（又は）筋肉以外の組織中濃度を測定できた場合でも，対応する筋肉中濃度は常に定量限界以下であった．組織及び血漿中のトラベクテジンを定量可能であった少数の場合では，組織中濃度は血漿中濃度より著しく高かった．

以上より，カニクイザルの用量制限毒性は，重度ではあるが回復性がある白血球数減少（好中球数減少を含む）及び投与部位の局所刺激性であり，MTD は 25 μg/kg/day であると判断された．

2.6.6.4　遺伝毒性試験

トラベクテジンの遺伝毒性試験として，復帰突然変異試験，染色体異常試験及びマウス骨髄の小核試験を実施した．抗悪性腫瘍剤で予想されるように，これらの試験の結果は陽性であり，詳細をそれぞれ第 2.6.7.8 項及び第 2.6.7.9 項に示した．

2.6.6.4.1　非哺乳動物細胞系での*in vitro*試験

2.6.6.4.1.1　復帰突然変異試験（試験番号 [redacted]）

GLP 試験として，[redacted] トラベクテジン（溶媒：エタノール）について，Aroclor で誘導したラット肝 S9 の代謝活性化存在下及び非存在下でネズミチフス菌株 TA98，TA100，TA1535 及び TA1537 並びに大腸菌株 WP2*uvrA* を用いた復帰突然変異試験を行った（第 4.2.3.3.1.1 項）．予備試験では，最高用量を 10 μg/plate として試験した．被験物質の沈殿は認めなかったが，代謝活性化の存在下及び非存在下のネズミチフス菌ではそれぞれ 1.0 μg/plate 以上及び 0.67 μg/plate 以上で細胞毒性を認めた．最高用量は，代謝活性化の存在下及び非存在下のネズミチフス菌ではそれぞれ

3.3 µg/plate 及び 1.0 µg/plate とした．大腸菌で細胞毒性を確認するために，代謝活性化の存在下及び非存在下の菌株 WP2*uvrA* を用いた試験では最高用量を 20 µg/plate として試験した．

主試験では，ネズミチフス菌株 TA100 の代謝活性化存在下で陽性反応を認めた．0.33 µg/plate で復帰変異コロニー数が対照群の 2.4 倍増加（陽性の結果とするには対照群の 2 倍の増加が必要である）したためトラベクテジンは復帰突然変異誘発能は陽性であると判断した．

2.6.6.4.2 哺乳動物細胞系での*in vitro*試験

2.6.6.4.2.1 染色体異常試験（試験番号 [redacted]）

GLP 試験として，[redacted]トラベクテジン（溶媒：ジメチルスルホキシド）について，Aroclor で誘導したラット肝 S9 を用いた代謝活性化の存在下及び非存在下でチャイニーズハムスター卵巣（CHO）細胞を用いた染色体異常試験を行った（第 4.2.3.3.1.2 項）．

予備試験の結果に基づいて，染色体異常試験に選択した濃度は，代謝活性化の 4 時間処理群では 0.001～2 µmol/L，非代謝活性化の 4 時間及び 20 時間連続処理群では 0.001～1 µmol/L の範囲であった．

細胞増殖抑制は試験した最高用量（非代謝活性化及び代謝活性化の 4 時間処理群ではそれぞれ 0.05 µmol/L 及び 0.125 µmol/L）で 52%及び 29%であった．分裂抑制は非代謝活性化の 20 時間処理群で評価した最高用量である 0.01 µmol/L で 56%であった．

非代謝活性化の 4 時間処理群では評価したすべての用量で溶媒対照群と比較して統計学的に有意で用量依存的な染色体構造異常細胞数の増加を認めた．染色体数的異常細胞数の統計学的に有意な増加も 0.05 µmol/L（評価した最高用量）で認めた．しかし，数的異常細胞出現率（%）は蓄積した溶媒対照データの 0%～8%の範囲内にあることから，生物学的に意義はないと考えられた．

代謝活性化の 4 時間処理群の 0.0625 及び 0.125 µmol/L で染色体構造異常細胞数が統計学的に有意に増加し用量依存性も認めた．代謝活性化の 4 時間処理群では溶媒対照群と比べて統計学的に有意な染色体数的異常細胞数の増加を認めなかった．

非代謝活性化の 20 時間連続処理群では，評価したすべての用量で溶媒対照群に比べて統計学的に有意で用量依存的な染色体構造異常細胞数の増加を認めた．非代謝活性化の 20 時間連続処理群では，溶媒対照群と比べて統計学的に有意な染色体数的異常細胞数の増加を認めなかった．

CHO 細胞を用いた代謝活性化及び非代謝活性化によるトラベクテジンの試験では，染色体構造異常の誘発能は陽性で，染色体数的異常の誘発能は陰性であると判断した．

2.6.6.4.3 哺乳動物系での*in vivo*試験

2.6.6.4.3.1 マウスの小核試験（試験番号 [redacted]）

GLP 試験として，雌雄の ICR マウスに[redacted]トラベクテジンを急速静脈内投与して小核試験を行い，骨髄における小核を有する多染性赤血球（MNPCE）の出現率を評価した（第 4.2.3.3.2.1 項）．

パイロット毒性試験では，雄性マウスに 10，50，100 又は 200 µg/kg/day を投与し，雌雄のマウスに 400 µg/kg/day を投与した．400 µg/kg/day 投与群の雄性マウス 5 匹中 3 匹が死亡したため，小核試験の高用量は，最大投与可能量であると考えられる 300 µg/kg/day に設定した．

最初の試験では，雌雄のマウスに 75，150 及び 300 µg/kg/day を投与した．75 µg/kg/day を投与した雄性マウス 10 匹中 1 匹及び 300 µg/kg/day の雌性マウス 15 匹中 1 匹が死亡した．

骨髄細胞を投与後 24 時間及び 48 時間に採取し，MNPCE の有無を顕微鏡下で検査した．

多染性赤血球（PCE）/総赤血球比では，溶媒対照に比べてトラベクテジン群の投与後 24 時間では軽度の低下（14%以下），投与後 48 時間で顕著な低下（99%以下）を認めた．これらの低下は，トラベクテジンが骨髄毒性を誘発することを示唆した．

150 及び 300 µg/kg/day 投与群の投与後 24 時間の雌雄のマウスでは，それぞれの対照と比べて MNPCE の統計的に有意な増加を認めた．75 µg/kg/day 投与群の投与後 24 時間の雌雄のマウスでは，MNPCE の増加を認めた．投与後 24 時間群の雌雄では MNPCE 数が用量依存的に増加した．投与後 48 時間では，PCE 数が過度に低下（82%～99%）したことから，雌雄の 75，150 及び 300 µg/kg/day 投与群では PCE 2000 個/匹の小核数を評価しなかった．

最初の試験の結果から，トラベクテジンは 75，150 及び 300 µg/kg/day の用量で，骨髄細胞に対する顕著な細胞毒性作用を有しており，マウスの小核試験では陽性であることが示された．

無毒性量を確認するために，1.5，5，15，又は 50 µg/kg/day の用量で雌雄のマウスの小核試験を繰り返した．いずれの用量でも死亡は認めなかった．

骨髄細胞を投与後 48 時間に採取し，MNPCE の有無を顕微鏡下で検査した．被験物質投与群では，それぞれの溶媒対照と比べて PCE/総赤血球比の軽度の低下（12%以下）を認めた．これらの低下から，トラベクテジンは赤血球生成を阻害しなかったことを示唆している．投与後 48 時間の雌雄のマウスでは MNPCE の増加は認めなかった．

2.6.6.5 がん原性試験

トラベクテジンは，臨床で抗悪性腫瘍剤として使用されることから，日米 EU 医薬品規制調和国際会議（ICH）ガイドライン S1A「医薬品におけるがん原性試験の必要性に関するガイダンス」及び ICH S9 ガイドライン「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，トラベクテジンの長期がん原性試験を実施しなかった．当該ガイドラインでは「対象患者群で長期の延命が望めないような場合（すなわち 2～3 年以下）では，がん原性試験を必要としない」と明記されている．また ICH S9 ガイドラインでは進行がんの患者の治療を目的とした医薬品の製造販売承認申請には，がん原性試験は必要とされないとされている．

2.6.6.6 生殖発生毒性試験

トラベクテジンが発生に影響を及ぼす可能性を，CD ラット及びニュージーランドホワイトウサギの用量設定試験及び本試験で検討した．詳細は第 2.6.7.11 項及び第 2.6.7.13 項に示した．

2.6.6.6.1 受胎能及び着床までの初期胚発生に関する試験

トラベクテジンは，臨床で抗悪性腫瘍剤として使用されることから，ICH ガイドライン S9「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，トラベクテジンの受胎能及び着床までの初期胚発生に関する試験は実施しなかった．

2.6.6.6.2 胚及び胎児発生に関する試験

2.6.6.6.2.1 ラットにおける静脈内投与の用量設定生殖発生毒性試験（試験番号 [redacted]）

非 GLP 試験として，雌性 CD ラット（5 匹/群）でのトラベクテジンの発生毒性試験の用量設定のために用量設定試験を実施した（第 4.2.3.5.2.1 項）．一定期間中に交尾した雌性 CD ラットの妊娠 6 日～17 日に，[redacted] トラベクテジンを 0，0.3，1，3，10 及び 30 µg/kg/day の用量で急速静

脈内投与した．妊娠 20 日に帝王切開によって胎児を分娩させ，生存胎児の外表，内臓又は骨格異常について評価した．

10 及び 30 μg/kg/day 投与群の動物はすべて死亡した，又は瀕死により安楽死させた．一般状態の変化はこれらの投与群のみでみられ，軽度の脱水，脱毛，自発運動の低下，運動失調，眼及び鼻周囲の暗色物質，円背姿勢，黄疸，努力性呼吸，立毛，被毛粗剛，削痩及び橙色尿などを認めた．

母体の体重及び体重増加量は，すべての投与群で用量依存的に減少し，3 μg/kg/day では（対照群と比較して）－11%及び－43%に達した．3 及び 10 μg/kg/day 投与群では，体重減少と一致して摂餌量が統計的に有意な減少を認めた．帝王切開時の検査項目では，生存した投与群のすべての動物で影響を認めなかった．これらの群では胎児毒性を認めなかった．この試験の結果に基づいて，生殖発生毒性の主試験の用量は 0.1，0.5 及び 2.5 μg/kg/day を選択した．

2.6.6.6.2.2　ラットにおける静脈内投与の生殖発生毒性試験（試験番号 [redacted]）

非GLP試験として，トラベクテジンの生殖発生毒性をCDラットで評価した（第4.2.3.5.2.2項）．一定期間中に交尾した雌性 CD ラット（25 匹/群）の妊娠 6～17 日に，[redacted]トラベクテジンを 0，0.1，0.5 又は 2.5 μg/kg/day の用量で 1 日 1 回急速静脈内投与した．妊娠 20 日に帝王切開によって胎児を分娩させ，生存胎児の外表，内臓又は骨格異常について評価した．

母体毒性として投与期間の後半に 2.5 μg/kg/day 投与群に統計的に有意な体重減少を認めた．また，2.5 μg/kg/day 投与群では体重の総重量（－7%）と増加量（－25%）及び摂餌量（－12%）も統計的に有意に減少した．0.1 及び 0.5 μg/kg/day 投与群では，母体の投与に関連した所見は認めなかった．胎児体重は 0.5 μg/kg/day 投与群の雌及び 2.5 μg/kg/day 投与群の雌雄で軽度であったが，統計学的に有意な低値を示した．0.1 μg/kg/day 投与群では，トラベクテジンに関連した胎児毒性作用を認めなかった．トラベクテジンに関連した胚毒性又は胎児発生毒性はいずれの用量でも認めなかった．

2.6.6.6.2.3　ウサギにおける静脈内投与の用量設定生殖発生毒性試験（試験番号 [redacted]）

非 GLP 試験として，ニュージーランドホワイトウサギ（5 匹/群）におけるトラベクテジンの発生毒性試験の用量選択ために用量設定試験を実施した（第 4.2.3.5.2.3 項）．一定期間中に交尾したニュージーランドホワイトウサギの妊娠 7～20 日に，[redacted]トラベクテジンを 0.3，1，3，10 又は 25 μg/kg/day の用量で急速静脈内投与した．妊娠 29 日に帝王切開によって胎児を分娩させ，肉眼的異常を評価した．

10 μg/kg/day 投与群（妊娠 14 日及び 15 日）及び 25 μg/kg/day 投与群（妊娠 11 日及び 12 日）の雌性ウサギはすべて死亡又は瀕死により安楽死させた．更に，3 μg/kg/day 投与群の雌性ウサギ 1 匹は妊娠 28 日に死亡した．25 及び 10 μg/kg/day 投与群の動物では，それぞれ妊娠 10 日及び妊娠 11 日から体重増加量の統計的に有意な減少と，投与開始又は妊娠 12 日から死亡まで摂餌量の減少を認めた．3 μg/kg/day 投与群では，胎児 1 匹の腎臓には褪色及び斑点，別の胎児では臍ヘルニアを認めた．これらの所見が投与に関連しているか否かは不明である．3 μg/kg/day 以上の投与群雌性ウサギすべてで，被験物質の局所作用として耳介の腫脹，炎症及び（又は）壊死を認めた．0.3 及び 1 μg/kg/day 投与群では，母体毒性，胚毒性，胎児毒性又は投与に関連した胎児の肉眼的

異常を示す所見を認めなかった. この試験の結果に基づいて, 生殖発生毒性の主試験の用量は 0.3, 0.75 及び 2 μg/kg/day を選択した.

2.6.6.6.2.4　　ウサギにおける静脈内投与の生殖発生毒性試験（試験番号 [redacted]）

非 GLP 試験として, トラベクテジンの発生毒性をニュージーランドホワイトウサギ(20 匹/群)で評価した（第 4.2.3.5.2.4 項）. 一定期間中に交尾したウサギの妊娠 7～20 日に, [redacted]トラベクテジンを 0.3，0.75 又は 2 μg/kg/day の用量で 1 日 1 回急速静脈内投与した. 妊娠 29 日に帝王切開によって胎児を分娩させ，胎児の外表，骨格及び内臓異常について評価した.

トラベクテジンの投与により，2 μg/kg/day 投与群では母体の摂餌量の減少（最高で対照と比較して妊娠 21 日で－23%），また 0.75 μg/kg/day 以上の投与群では投与部位の刺激性がみられた. 被験物質による胚毒性，胎児毒性又は胎児発生毒性はいずれの用量でも認めなかった.

2.6.6.6.3　　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

トラベクテジンは，臨床で抗悪性腫瘍剤として使用されることから，ICH ガイドライン S9「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，トラベクテジンの出生前及び出生後の発達に関する試験を実施しなかった.

2.6.6.6.4　　新生児を用いた試験

トラベクテジンを新生児に投与する毒性試験は行っていない.

2.6.6.7　　局所刺激性試験

これらの試験の詳細は第 2.6.7.16 項に示した.

2.6.6.7.1　　ウサギにおける静脈内及び静脈傍投与試験(試験番号 [redacted])

GLP 試験として, 雄のニュージーランドホワイトウサギの右後耳介に[redacted]トラベクテジン（[redacted]を用いた製剤）を 2.5 及び 25 μg/mL の濃度で静脈内（1.0 mL）又は静脈傍組織内（0.3 mL）投与した. すなわち，トラベクテジンが約 1 及び 10 μg/kg/day の用量で刺激性を有するか否かについて評価した（第 4.2.3.6.1 項）. 対側の左耳介静脈には生理食塩液を投与し対照とした.

静脈傍投与（2.5 及び 25 μg/mL）後 72 時間以内の刺激性を示す臨床所見として，投与部位の腫脹，軽度から重度の紅斑，血腫及び血管拡張を認めた. 病理組織学的変化として，潰瘍，限局性の類線維素壊死，上皮壊死，亜急性炎症，浮腫などを認めた.

静脈内投与では刺激性（投与部位の腫脹及び紅斑）を示す臨床所見を認め，2.5 μg/mL 投与では 25 μg/mL 投与の場合よりその程度は弱かった. 25 μg/mL の静脈内投与では，限局性の類線維素壊死，上皮壊死，亜急性炎症，浮腫などを認めた. 静脈内投与群では潰瘍は認めなかった. 2.5 μg/mL の静脈内投与では，潰瘍に進行する可能性は低いが，不快感をもたらす可能性が高い病変がみられた. これら 2.5 μg/mL 投与で認めた変化が臨床使用に対して外挿性があるかは不明であった.

以上より, トラベクテジンの 2.5 及び 25 μg/mL を投与したところ, 静脈傍投与後では 2.5 μg/mL の低濃度から顕著な刺激を認めた. トラベクテジンの静脈内投与では 25 μg/mL で顕著な刺激を認め（しかし潰瘍は伴わない），2.5 μg/mL ではそれより程度が弱かった.

2.6.6.7.2　ウサギにおける局所刺激性/組織反応性試験（試験番号[redacted]）

GLP 試験として，雌のニュージーランドホワイトウサギの周縁耳介静脈に[redacted]トラベクテジン（[redacted]を用いた製剤）及び[redacted]トラベクテジン（[redacted]を用いた製剤）を臨床濃度と同じ 7 µg/mL（投与容量 0.3 mL/kg 体重）で単回及び反復（週 1 回 4 週間）投与（2.1 µg/kg/day）投与し，両者の局所刺激性/組織反応を比較した（第 4.2.3.6.2 項）．剖検を単回投与後 3 日及び 4 回反復投与後 3 日に行った．

[redacted]又は[redacted]トラベクテジンを 4 回反復静脈内投与後に一部のウサギの投与部位では刺激性を示す臨床所見（周縁耳介静脈領域の軽度な紅斑）を認めた．これらの変化は剖検時にみられた投与部位の限局性の軽微な変色と相応していた．病理組織学的所見として，[redacted]及び[redacted]トラベクテジンを 4 回静脈内投与後に軽微から軽度の刺激性（血管障害）を認めた．[redacted]を用いた製剤と[redacted]を用いた製剤の間で刺激性の差は認めなかった．

2.6.6.8　その他の毒性試験

これらの試験の詳細は第 2.6.7.17 項に示した．

2.6.6.8.1　抗原性

トラベクテジンの抗原性試験は実施していない．

2.6.6.8.2　免疫毒性

トラベクテジンの免疫毒性試験は実施していない．

2.6.6.8.3　機序に関する試験

2.6.6.8.3.1　ヒト及びマウスの血液前駆細胞に及ぼす影響に関する*in vitro*評価

In vitro 試験により，ヒト及びマウスの骨髄細胞に及ぼすトラベクテジンの毒性を評価した（第 2.6.2.3 項）．マウス前駆細胞及びヒト前駆細胞で増殖阻害を認め，1～3 時間の処理後で有意に増殖が阻害された CFU-Meg は他の前駆細胞よりトラベクテジンへの感受性が高かった．これは，トラベクテジンが投与された癌患者で血小板数減少が発現する可能性があることを示唆している．

2.6.6.8.3.2　肝毒性に関連した機序に関する研究

2.6.6.8.3.2.1　4 種の動物の肝細胞を用いたトラベクテジンの細胞毒性に関する比較試験（試験番号[redacted]）

非 GLP 試験として，マウス，ラット，サル及びヒトから分離した肝細胞の初代培養に対する[redacted]トラベクテジンの細胞毒性を評価した（第 4.2.3.7.3.1 項）．肝細胞を分離，培養し，0.03 nmol/L，0.3 nmol/L，1 nmol/L，3 nmol/L，10 nmol/L，30 nmol/L，100 nmol/L，300 nmol/L 及び 2 µmol/L の ^{14}C 標識トラベクテジンを添加し，8 又は 24 時間インキュベーションした．細胞毒性はミトコンドリアのコハク酸デヒドロゲナーゼが 3-(4,5-di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide（MTT）基質（テトラゾリウム塩）を不溶性の青色ホリマザンに変換する活性によって評価した．

トラベクテジンの 10 nmol/L 濃度で，24 時間インキュベーション後にマウス及びヒトの肝細胞に細胞毒性を示した．これに対して，ラット及びサルの肝細胞では 100 nmol/L 以上の濃度のトラベクテジンを加えて 24 時間培養した場合にのみ細胞毒性を認めた．

2.6.6.8.3.2.2　肝細胞，肝癌及び肝癌以外の細胞株におけるトラベクテジンとその代謝物ET-729 の細胞毒性試験（試験番号 [redacted]）

非 GLP 試験として，前述の試験と同じ濃度範囲及び評価項目を用いて（第 2.6.6.8.3.2.1 項），マウス，ラット，サル及びヒトから分離した肝細胞の初代培養における[redacted]トラベクテジンとその N-脱メチル化代謝物 ET-729 の細胞毒性を評価した（第 4.2.3.7.3.2 項）.

HepG2 を両化合物の 1 nmol/L～2 µmol/L 濃度の範囲でインキュベーションした．24 時間インキュベーション後の細胞生存率を MTT アッセイによって分析した．また，ウォッシュアウトから 48 時間後にトラベクテジン及び ET-729 の細胞毒性を評価した.

マウスの肝細胞及び雌性ラットの肝細胞は，トラベクテジン及び ET-729 に対して最も感受性の高い細胞であった．ET-729 の毒性はトラベクテジンのものと明らかな差はなかった．いずれの場合も，細胞毒性はわずかに遅延し 24 時間インキュベーションの 48 時間後に顕著であった．雌性ラットの肝細胞は両化合物に対して雄性ラットよりやや感受性が高かった.

2.6.6.8.3.2.3　ラットの肝毒性に対する高用量デキサメタゾンによる軽減作用

非 GLP 試験として，トラベクテジンによる雌の Wistar ラットの肝毒性の発現をデキサメタゾンによって軽減することができるか否かについて検討した[1]．肝毒性は，血漿中 ALP，AST 及びビリルビン値の測定と，肝臓の病理組織学的検査によって評価した.

[redacted]トラベクテジン単独（240 µg/m^2，急速投与）（40 µg/kg）投与により，血漿中 ALP，AST 及びビリルビン値の劇的な増加と，胆管上皮細胞の変性及び斑状の限局性壊死がみられた．トラベクテジン投与の 24 時間前にデキサメタゾン（5～20 mg/kg，経口）をラットに前投与した場合では，肝毒性の生化学的及び病理組織学的変化が軽減又は消失した.

これに対して，デキサメタゾンとトラベクテジンを同時に投与した場合では，トラベクテジンの毒性は軽減しなかった.

また，トラベクテジン投与の 24 時間前にデキサメタゾン（10 mg/kg，経口）を前投与した場合では，トラベクテジンによって誘導されたラット肝臓の遺伝子発現の変化も逆転した．このようなデキサメタゾン投与では，肝臓の組織中トラベクテジン濃度がトラベクテジン単独投与と比較して減少した．1 時間の時点の肝臓中トラベクテジン濃度は 37 pmol/g 組織と高かったが，デキサメタゾンを前投与した動物では 5 pmol/g 組織を超えなかった．しかし，デキサメタゾンを併用後の血漿中トラベクテジン濃度はトラベクテジン単独投与したラットのものと顕著な差がなかった．なお，13762 乳癌を移植したラット及びマウスモデルでは，デキサメタゾンの前投与によってトラベクテジンの抗腫瘍効果が抑制されなかった.

これらの結果は，高用量デキサメタゾン（20 mg/kg）の前投与が，トラベクテジンによるラットの肝障害を軽減することを示唆している．このようなデキサメタゾンによる保護作用では，肝臓中トラベクテジン濃度の顕著な減少を伴った．しかし，全身のトラベクテジン濃度は影響を受けなかった.

2.6.6.8.3.3　代謝物に関する試験

2.6.6.8.3.3.1　マウスでのトラベクテジン及び代謝物（ET-729）単回静脈内投与によるMTD比較試験（試験番号 [redacted]）

非 GLP 試験として，雌雄の CD-1 マウス 5 匹/性に[redacted]トラベクテジン（[redacted]を用いた製剤）とその代謝物 ET-729 を単回静脈内投与し MTD を比較した（第 4.2.3.7.5.1 項）．単回

静脈内投与後，一般状態及び死亡について投与後 14 日間観察した．[redacted]トラベクテジンは 200，225，250 及び 300 μg/kg/day の用量を，ET-729 は 75，100，125 及び 150 μg/kg/day の用量を急速静脈内投与した．

ET-729 を投与した動物では，投与後 3 日から一般状態の変化を認めた．投与後 3 から 8 日に ET-729 の 125 μg/kg/day 投与群の 10 匹中 5 匹及び 150 μg/kg/day 投与群の 10 匹中 9 匹が死亡した．ET-729 の 75 又は 100 μg/kg/day 投与群では，死亡は認めなかった．

トラベクテジンの 300 μg/kg/day 投与群の雄性マウスでは投与後 2 週目に一般状態の変化を認めた．これらのマウス 5 匹中 4 匹は投与後 10 から 13 日に死亡した．300 μg/kg/day 投与群の雌性マウスでは，投与後 8 日に 1 匹のみが死亡した．トラベクテジンの 250 μg/kg/day 投与群の雄性マウス 1 匹は，投与後 13 日に死亡した．雌雄のいずれもトラベクテジンの 225 又は 200 μg/kg/day 投与群では死亡は認めなかった．

以上より，マウスは代謝物（ET-729）に対してわずかに高い感受性を示した．MTD は，ET-729 では雌雄のいずれも 100 μg/kg/day，トラベクテジンは雄で 225 μg/kg/day，雌で 250 μg/kg/day であった．

2.6.6.8.4　不純物に関する試験

トラベクテジンに存在する可能性のある不純物（第 2.3.S.3.2 項）である不純物 B*，不純物 C*，不純物 F*，不純物 A*，不純物 D*及び不純物 E*の毒性評価を行った．

2.6.6.8.4.1　単回投与毒性試験（試験番号[redacted]）

GLP 試験として，SD 系ラット（10 匹/性/群）にトラベクテジン原薬中で同定された不純物（不純物 B*，[redacted]%）を[redacted]トラベクテジン（[redacted]を用いた製剤）48.5 μg/kg/day と併用投与した．この併用投与ではラットに 3 時間持続静脈内投与として 1 回投与した後，3 日間及び 3 週間の回復期間を設けた（第 4.2.3.1.4 項及び第 4.2.3.1.5 項）．また，この試験では 3 時間又は 24 時間持続静脈内投与として 1 回投与した後，3 日間及び 3 週間の回復期間を設けた場合のトラベクテジン単独の毒性についても評価した．この試験部分の要約は第 2.6.6.2.2.3 項に示した．

トラベクテジンとトラベクテジン不純物不純物 B*（[redacted]%）の併用による毒性プロファイルは，トラベクテジン単独による毒性と類似していた（第 2.6.6.2.2.3 項）．トラベクテジンと不純物の併用で特有と考えられる毒性所見は認めなかった．

2.6.6.8.4.2　単回投与毒性試験（試験番号[redacted]）

GLP 試験として，SD 系ラット（10 匹/性/群）にトラベクテジン原薬中で同定された不純物不純物 C*（[redacted]%）及び不純物 F*（[redacted]%）を[redacted]トラベクテジン（[redacted]を用いた製剤）48.3 μg/kg/day と併用投与した．この併用投与では 3 時間持続静脈内投与した（第 4.2.3.7.6.1 項）．

[redacted]トラベクテジンとトラベクテジン不純物不純物 C*（[redacted]%）及び不純物 F*（[redacted]%）の併用による毒性プロファイルは，[redacted]トラベクテジン単独による毒性と類似していた．[redacted]トラベクテジンとこれらの不純物の併用に特有と考えられる毒性所見を認めなかった．

また，この GLP 試験では SD 系ラット（10 匹/性/群）に 50 μg/kg/day を 3 時間持続静脈内投与として 1 回投与した後，3 日間及び 3 週間回復期間を設けた場合の[redacted]及び[redacted]トラベクテジン（[redacted]を用いた製剤）の毒性及びトキシコキネティクスを比較した．

[redacted]又は[redacted]トラベクテジンの 50 μg/kg/day を 3 時間持続静脈内投与しても両投与群で明らかな毒性プロファイルの差は認めなかった.

すべての動物で，血漿中トラベクテジン濃度は投与終了後に急速に低下し，3 時間持続静脈内投与開始後 24 時間では LLOQ（0.05 ng/mL）未満であった．トキシコキネティクスデータでは，[redacted]又は[redacted]原薬を含む製剤間でトラベクテジンを投与後の薬物動態に明らかな差はなく（C_{max} 及び AUC 値は類似し），性差はみられないことが示された．トキシコキネティクスデータを表 2.6.6.8.4.2-1 にまとめた.

表 2.6.6.8.4.2-1　雌雄 SD 系ラットにおける[redacted]又は[redacted]トラベクテジン 50 μg/kg/day 単回 3 時間持続静脈内投与時の C_{max} 及び AUC

Drug Substance Source	Sex	C_{max} (ng/mL)	$AUC_{0\text{-}5h}$ (ng·h/mL)
[redacted]	Male	1.35	2.24
	Female	0.924	1.90
[redacted]	Male	1.07	2.35
	Female	1.14	2.16

N = 2
第 4.2.3.7.6 1 項 試験報告書 No.[redacted] Table TK1 抜粋

2.6.6.8.4.3　単回投与毒性試験（試験番号：[redacted]）

GLP 試験として，SD 系ラット（10 匹/性/群）に 50 μg/kg/day（MTD）の用量の[redacted]トラベクテジン又は不純物である不純物 D*（[redacted]%）及び不純物 E*（[redacted]%）若しくは不純物 A*（[redacted]%）をスパイクした同用量の[redacted]トラベクテジンを 3 時間持続静脈内投与し，投与後 3 日間又は 3 週間観察した（第 4.2.3.7.6.2 項）.

トラベクテジンの主要な毒性は投与部位の局所刺激性（これは 3 週間の観察期間終了までに進行し線維化に至った），細胞増殖が盛んな組織及び器官に対する早期の細胞毒性（骨髄，リンパ器官及び消化管を含む，3 週間の観察期間終了までに部分的に回復した）及び肝細胞及び胆管に対する早期の肝毒性（肝毒性は 3 週間の観察期間終了時にも認めた）であった.

[redacted]トラベクテジン単独群の雌では死亡例は認めなかったが，[redacted]トラベクテジン/不純物 A*群で，雌の 1 匹で骨髄抑制の程度が強く，局所刺激性に関連した肉眼的変化の発生率及び（又は）重症度が高かったために死亡した．さらに同群の雄 1 例及び雌全例でよろめき歩行を認めた．このことは[redacted]トラベクテジン/不純物 A*投与群の毒性がわずかに強いことを示唆している可能性もあった.[redacted]トラベクテジン群と[redacted]トラベクテジン/不純物 D*及び不純物 E*投与群との間では，毒性の大きな差は認めなかった.

2.6.6.8.5　[redacted]及び[redacted]を用いた製剤の比較

2.6.6.8.5.1　単回投与毒性試験（試験番号[redacted]）

非 GLP 試験として，SD 系ラット（10 匹/性/群）に[redacted]トラベクテジン・[redacted]を用いた製剤，[redacted]トラベクテジン・[redacted]を用いた製剤及び投与前に強制劣化した[redacted]トラベクテジン・[redacted]を用いた製剤を 50 μg/kg/day の用量で単回 3 時間持続静脈内投与し，3 バッチのトラベクテジンについて毒性を評価した（第 4.2.3.7.6.3 項）．強制劣化[redacted]トラベクテジン・[redacted]を用いた製剤は[redacted]%の不純物 G*を含んでいた．投与後の動物に 3 日間又は 3 週間の回復期間を設けた.

一般状態の変化は雌で顕著であり，3 つの製剤のいずれも発生率は類似していた．体重及び摂餌量の減少を試験の最初の数日間に 3 つの製剤のすべてで認めた．これらの変化は部分的に回復性を示した．

血液学的変化（軽度の貧血，リンパ球数及び単球数の減少），生化学的変化（電解質の変化，ビリルビン値，コレステロール値及びトリグリセライド値の増加，肝酵素活性の増加）及び尿の変化（潜血及び尿中ビリルビン）を，3 つの製剤のすべてで認めた．これらの所見のほとんどは部分的に回復性を示した．

肝臓及びリンパ節重量の増加と胸腺及び脾臓重量の減少をすべての製剤で認めた．

肉眼的検査ではリンパ節の腫大を伴った投与部位の刺激性を認めた．投与部位の病理組織学的検査では，各製剤で刺激性を認め 3 週間の回復期間後に回復性を認めなかった．3 つの製剤間では投与部位の変化に明らかな差は認めなかった．

以上より，検討した 3 つのトラベクテジン製剤（[redacted]トラベクテジン・[redacted]を用いた製剤，[redacted]トラベクテジン・[redacted]を用いた製剤及び強制劣化[redacted]トラベクテジン・[redacted]を用いた製剤）の間では毒性の大きな差は認めなかった．

2.6.6.8.6　　光毒性試験

ICH ガイドライン S10「医薬品の光安全性評価ガイドライン」では，290 nm～700 nm の間の波長で光を吸収しないものは直接的光毒性を引き起こすほどの光反応性がないとされている．トラベクテジンの吸収スペクトルでは，290 nm～700 nm の波長に吸収極大はなく，大部分の光吸収は 290 nm 以下で認められた（第 3.2.P.5.6 項 図 3.2.P.5.6.2.3-2）．したがって，光毒性試験の実施は必要ないと判断した．

国内臨床試験（10045020 試験，10045030 試験，10045040 試験）の結果，投与量 1.2 mg/m^2 を 3 週間ごとに 24 時間投与した患者（73 名）に光過敏症や光アレルギーなど光毒性に起因すると治験責任医師が判断した有害事象はなかった（第 5.3.5.3.1 項）．また，本剤は 2007 年 9 月に欧州で悪性軟部腫瘍を対象とした効能・効果で承認を受けており，承認後，2014 年 9 月までの 7 年間で本剤を投与した患者は約[redacted]名（累積推定患者数）であったが，海外の市販後で報告された有害事象には，光線過敏症性反応といった光アレルギーを示唆する基本語は含まれていなかった（第 2.7.4.7 項）．

以上のことより臨床でトラベクテジンによる光毒性が発症する可能性は低いと考えた．

2.6.6.9　　考察及び結論

非臨床毒性試験では，毒性の標的器官を明らかにすること，認められた毒性作用の可逆性を評価すること，トラベクテジンによる遺伝毒性の誘発能を確認すること，生殖発生の評価項目に影響を及ぼす可能性を評価すること，更に認められた毒性の機序を検討することなどを目的とした．これらの目的は，上記に概要を示した一連の試験によって達成されている．

トラベクテジンの単回急速静脈内投与試験をマウス，ラット及びイヌで行い，急性毒性を検討し，MTD を決定した．

単回急速静脈内投与での MTD は，雄性マウスでは 100 µg/kg/day，雌雄のラットではそれぞれ 50 及び 75 µg/kg/day であった．これらの試験に加えて，トラベクテジンの 50 µg/kg/day を単回 3 時間及び 24 時間持続静脈内投与として SD 系ラットに投与し，評価した肝毒性の重症度は雄より雌で顕著であったが，3 時間と 24 時間持続静脈内投与の間で投与時間の違いには，有意な毒性の差はみられなかった．ビーグル犬では，単回急速静脈内投与での MTD は 27 µg/kg/day であった．

ラットの単回投与試験では，MTD でのトラベクテジンの毒性及びトキシコキネティクスプロファイルは[redacted]及び[redacted]のトラベクテジンの間で大きな差は無かった．代謝物 ET-729 の毒性をマウスを用いて評価し，不純物（不純物 B*，不純物 C*，不純物 F*，不純物 D*及び不純物 E*）を含むトラベクテジン製剤の毒性をラットを用いて評価した．いずれについてもトラベクテジン単独投与時と類似した毒性を示した．

ラットの反復投与試験では（3 サイクル以下，各サイクルは 3 週間ごとに単回 3 時間持続静脈内投与とした），MTD は雌雄のいずれも 25 μg/kg/day であったが，全身毒性は雌性ラットで顕著であった．ラットで確認された主な毒性の標的は蓄積性の肝毒性であり，その特徴はトランスアミナーゼ値の増加，ビリルビン値の増加，肝臓の限局性壊死及び胆管炎とこれに伴った胆管過形成であった．ラットで確認された別の標的器官には，投与部位の炎症及び壊死，更に骨髄抑制とこれに伴った白血球数減少，骨髄細胞減少及びリンパ系組織のび漫性萎縮が含まれていた．血液学的変化では部分的な回復を認めたが，雌性ラットの肝臓の変化についてはごく限られた回復を認めた．

In vitro の代謝プロファイル及び *in vivo* の毒性プロファイル（ヒトの治療用量に近い MTD，骨髄抑制及び可逆的な肝臓の変化）がヒトとサルで類似していることに基づくと，サルはトラベクテジンの毒性を評価するのにマウス，ラット又はイヌより適切で，予測可能な動物種であると考えられる．そこで，反復投与試験はサルで行い，8 回以下の投与サイクルとし，3 週間ごとに 3 時間又は 24 時間の持続静脈内投与を行った．サルでは，連続した投与サイクル後の MTD は 25 μg/kg/day であった（第 2.6.6.3.4.4 項）．40 μg/kg/day 以上でみられた所見には，腸の変化とともに骨髄抑制（重度の白血球数減少，貧血，リンパ球又は髄の細胞減少）に関連した早期の死亡が含まれていた．3 回以上の投与サイクル後には，重度の局所刺激性とこれに伴った血栓性静脈炎，壊死，線維化及び潰瘍を認め，周囲の組織にも影響が及んでいた．末梢血管アクセスポートを用いた場合では，皮膚の壊死性病変がみられたため，倫理的な理由により安楽死させた．中心静脈カテーテルによってトラベクテジンを投与した場合では，腎臓及び肝臓の炎症性変化を伴った大静脈及びその周囲の顕著な炎症性，血栓性，線維性及び壊死性病変に伴って，腎臓及び肝臓の不可逆的な変化がみられ，死亡に至った．肝毒性がみられた場合では，その特徴は特に初回投与サイクル後のトランスアミナーゼ値の一過性の増加，肝細胞肥大，中等度から顕著な肝細胞の変性，壊死，更に類洞及び門脈域の軽度の炎症性細胞浸潤であった．数頭のサルで ALP 値の増加を認めたが，関連する肝胆道系の病理組織学的変化を伴っていなかった．更に，結腸及び直腸の壊死性潰瘍，軽微な膵腺房細胞の脱顆粒及び（トラベクテジンを末梢性に投与した場合では）上皮の扁平化を伴う尿細管拡張を認めた．用量反応関係は血液毒性でみられ，また局所反応及び肝毒性でもある程度認めた．生存動物では，大部分の造血系の変化は 3 週間の回復期間内に回復性を示した（貧血を除く）．腸管への影響は回復期間後にはみられなかった．同様に，肝臓及び腎臓の変化についても深部血栓性静脈炎に関連していない場合には，ほぼ完全な回復性を示した．反復サイクルとして 3 時間又は 24 時間持続静脈内投与によってトラベクテジンを投与したサルでは，投与時間による顕著な毒性の差を認めなかった．

トラベクテジンの肝毒性作用における種差及びラットでの性差は，肝臓の代謝，肝胆道系の排泄か，薬物及び（又は）代謝物の蓄積の差又はこれらの要因が複合している可能性が考えられた．

デキサメタゾンを前投与すると，トラベクテジンによるラットの肝障害が軽減されることが示唆された[1]．デキサメタゾンの事前投与は嘔吐予防のために臨床でも一般的に使用するレジメンで

あり，非臨床試験の結果からデキサメタゾンの事前投与は臨床においてトラベクテジンの肝毒性を軽減する可能性もある．

トラベクテジンは *in vitro* 及び *in vivo* 試験系で遺伝毒性を示した．しかし，遺伝毒性の陽性結果は DNA に作用する細胞障害性抗悪性腫瘍剤に共通した予測されるものであり，また進行癌の治療を意図した薬剤では一般に許容範囲内の特徴であると考えられる．

ラット及びウサギの生殖発生毒性試験（胚及び胎児発生に関する試験）を行った．トラベクテジンの投与では，いずれの用量においても胚毒性の徴候を認めず，また外表，内臓及び骨格異常の検査でも催奇形性を示す所見はみられなかった．しかし，胚及び胎児発生に関する試験で用いた投与量は母体の用量制限毒性のためにヒトの臨床用量よりかなり低かった．ラットの生殖毒性試験の最高用量は 15 μg/m^2（2.5 μg/kg/day）であったが，ラットの反復投与毒性試験の同用量のトキシコキネティクス結果より C_{max} は 0.154 ng/mL，AUC はほとんどの計測時点で検出限界以下であったため計算できなかった（表 2.6.6.3.2.1-2）．一方，国内の臨床用量（1.2 mg/m^2）の曝露量（C_{max}：1.66 ng/mL，AUC：66.0 ng·h/mL）（表 2.6.6.9-1）と比較すると，ラットの胚・胎児発生に関する試験でのトラベクテジン曝露量は，臨床曝露量と比較してはるかに低かった．一方，ウサギの血漿中濃度は測定していないが，3 週間ごと 1 回投与である臨床用量（1.2 mg/m^2）と比較して器官形成期（妊娠 7 日～20 日）の連日投与したウサギの投与量は 24 μg/m^2（2 μg/kg/day）と著しい低値であった．したがって，これらの試験の結果はトラベクテジンのヒトの妊娠に対する危険性を適切に評価できていない可能性が高い．

ICH ガイドライン S9「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，生殖機能に及ぼすトラベクテジンの影響を検討するためのその他の特別な試験は実施しなかった．

反復静脈内投与したラット及びサルの MTD は 25 μg/kg/day であった．第 II 相臨床試験の投与用量である 1.2 mg/m^2 投与時のトラベクテジンの曝露とラット及びサルの MTD でのトラベクテジンの曝露を比較した（表 2.6.6.9-1）．

血漿タンパク結合には種差がみられることから，遊離未変化体の曝露量でも比較した．動物の MTD での曝露量と臨床用量の曝露量を比較した場合，トラベクテジンの曝露はヒトよりも動物の方が低かった．ラットとサルの遊離未変化体の曝露を比較するとサルの曝露の方が高かった．動物の曝露がヒトの曝露より低いことは抗悪性腫瘍剤ではまれな所見ではない[2]ものの，動物で認められた毒性はヒトでも生じるリスクはあると考えられる．

表 2.6.6.9-1　トラベクテジンのヒトと動物での曝露比較

Species	No. of Cycles[a)]	Dose[b)] (μg/m^2)	Dose[b)] (μg/kg)	C_{max} (ng/mL)	AUC (ng•h/mL)	% of Free Drug	AUC for Free Drug (ng•h/mL)
SD rats[c)] （表 2.6.6.3.2.1-2）	1 3	150	25	0.89	1.94	4.72%	0.09
Cynomolgus Monkeys[c)] (表 2.6.6.3.4.1-2)	1 3	300	25	0.85	9.20	5.60%	0.52
Patients （表 2.7.2.2.1.2-1）	—	1.2 mg/m^2	—	1.66	66.0	2.73%	1.80

a) A cycle (rat, monkey) was defined as a single 3-hour i.v. infusion of trabectedin administered once every 3 weeks.
b) Animal data were shown in MTD.
c) N = 2 (rat, monkey); mean data (combined from both sexes and cycles) are presented.

2.6.6.10 図表

試験結果を補足する表を本文中に記載した．試験の概要を第 2.6.7 項に示した．

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ヨンデリス点滴静注用 0.25 mg

ヨンデリス点滴静注用 1 mg

第 2 部（モジュール 2）：CTD の概要（サマリー）

2.6.7　毒性試験の概要表

大鵬薬品工業株式会社

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※　概要表中の「ET-743」,「R279741」,「Trabectedin」はいずれも「トラベクテジン」を示す.

※　投与用量「μg/kg」から「$\mu g/m^2$」への変換：「μg/kg」で示した用量にマウスでは 3 倍，ラットでは 6 倍，ウサギでは 12 倍，イヌでは 20 倍，サルでは 12 倍を乗じた.

2.6.7　毒性試験の概要表

2.6.7.1　毒性試験：一覧表

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ ($\mu g/kg$)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Single-Dose Toxicity	MF1 Mice (Male)	i.v. bolus (0.05 mol/L phosphate buffer, pH 4, control = 0.9% saline)	Single	0 300 (100) 450 (150) 600 (200)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.1.1
	Fischer 344 Rats (Male/Female)	i.v. bolus (0.05 mol/L potassium phosphate buffer, pH 4.0)	Single	0 45 (9) 450 (75) 540 (90)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.1.2
	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile aqueous solution)	Single (3 hr)	M: 450 (75) 600 (100) F: 300 (50) 600 (100)	[redacted][b]	No	No	[redacted]	[redacted]	4.2.3.1.3
	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection, control = 0.9% saline)	Single (3 or 24 hr)	0, 300 (50) or 291 $\mu g/m^2$ (48.5 $\mu g/kg$)[b]/ 9 $\mu g/m^2$ (1.5 $\mu g/kg$)[c]	[redacted][b] [redacted][c]	Yes	Yes	[redacted]	[redacted]	4.2.3.1.4

[a] [redacted] R279741 (unformulated)
[b] [redacted] R279741 ([redacted] formulation)
[c] Impurity (不純物 B*)

Note: Dose conversion to $\mu g/m^2$: multiply $\mu g/kg$ by 3 for mice, 6 for rats, 20 for dogs, or 12 for monkeys

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Single-Dose Toxicity (cont.)	Beagle Dogs (Male/Female)	i.v. bolus (0.05 mol/L potassium phosphate buffer, pH 4.0)	Single	0 200 (10) 540 (27) 700 (35)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.1.6

[a] [redacted] R279741 (unformulated)

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ ($\mu g/kg$)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Repeat-Dose Toxicity	CD_2F_1 Mice(Male/Female)	i.v. bolus (0.05 mol/L potassium phosphate buffer, pH 4.0)	5 days	0 120 (40) 180 (60) 240 (80)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.2.1
	Sprague Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection; control = 0.9% saline)	3 (3 hr) cycles (every 3 weeks)	DRF - M 0 150 (25) 300 (50) 600 (100) DRF – M&F 0 54 (9) 450 (75) 540 (90) Main Study – 15 (2.5) F only 60 (10) 150 (25) 300 (50) 450 (75) M only	[redacted][b]	Yes	Yes	[redacted]	[redacted]	4.2.3.2.2

[a] [redacted] R279741 (unformulated)
[b] [redacted] R279741 ([redacted] formulation)

DRF = dose range finding
F = female; M = male

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses μg/m^2 (μg/kg)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Repeat-Dose Toxicity (cont.)	Beagle Dogs (Male/Female)	i.v. bolus (potassium phosphate buffer, pH 4.0)	5 days	0 100 (5) 160 (8) 220 (11)	[redacted][a]	Yes[b]	No	[redacted]	[redacted]	4.2.3.2.4
	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection; control = 0.9% saline)	4 (3 hr) cycles[d] or 4 (24 hr) cycles[e]	Cycles 1, 2, 3 Gp 1: 0 Gp 2: 300 (25)[d] Gp 3: 600 (50)[d] Gp 4: 900 (75)[d] Gp 5: 900 (75)[e] Cycle 4 Gp. 1: 0 Gp 2: 1440 (120)[d] Gp 3: 900 (75)[d] Gp 4: 1200 (100)[d] Gp 5: 1200 (100)[e]	[redacted][c]	Yes	Yes	[redacted]	[redacted]	4.2.3.2.5

[a] [redacted] R279741 (unformulated)
[b] Most samples were below the lower limit of quantification (<1 ng/mL); analytical method not sensitive enough to quantify drug in sample
[c] [redacted] R279741 ([redacted] formulation)
[d] 4 cycles: 3 cycles (3-hour infusion) every 3 weeks, followed by a higher dose on Week 9
[e] 4 cycles: 3 cycles (24-hour infusion) every 3 weeks, followed by a higher dose on Week 9

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses μg/m^2 (μg/kg)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Repeat-Dose Toxicity (cont.)	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection; control = 0.9% saline)	3 (3 hr) cycles[b] 4 (3 hr) cycles[c]	0 120 (10)[b] 240 (20)[b] 360 (30)[b] 840 (70)[c]	[redacted][a]	Yes	Yes	[redacted]	[redacted]	4.2.3.2.7
	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection; control = 0.9% saline)	4 (24 hr) cycles[d]	0 300 (25) 600 (50) 840 (70)	[redacted][e]	No	No	[redacted]	[redacted]	4.2.3.2.9
	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection; control = 0.9% saline	4-8 (3 hr) cycles[f]	0 300 (25) 420 (35) 600 (50) 780 (65)	[redacted][e]	Yes	Yes	[redacted]	[redacted]	4.2.3.2.10

[a] [redacted] R279741 ([redacted] formulation)
[b] Once weekly (3-hour infusion) for 3 weeks (3 infusions/cycle; dose/cycle = 0, 360, 720, 960 μg/m^2) followed by 1 week recovery (cycle repeated 3 times).
[c] Single 3-hour infusion every 3 weeks (1 infusion/cycle) followed by 3 weeks recovery (cycle repeated 4 times)
[d] Single 24-hour infusions every 3 weeks. The study duration was 8 cycles per protocol; however, due to severe local irritation, the study was discontinued after 4 cycles
[e] [redacted] R279741 ([redacted] formulation)
[f] Single 3-hour infusions every 3 weeks

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (µg/kg)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Genotoxicity	*S. Typhimurium* (TA98, TA100, TA1535, TA1537) and *E. Coli* (WP2*uvrA*)	*In vitro* (ETOH)	NA	*S. Typhimurium*: Up to 1 µg/plate (-S9) and 3.3 µg/plate (+S9) *E. Coli:* Up to 20 µg/plate (-S9 or +S9)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.3.1.1
	CHO cells	*In vitro* (DMSO)	4 hr, 20 hr[b]	up to 1 µmol/L (-S9) and 2 µmol/L (+ S9)	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.3.1.2
	ICR Mice (Male/Female)	i.v. bolus (sterile distilled water; control = 0.9% saline)	Single	0 225 (75) 450 (150) 900 (300) 0 4.5 (1.5) 15 (5) 45 (15) 150 (50)	[redacted][c]	No	Yes	[redacted]	[redacted]	4.2.3.3.2.1

[a] [redacted] R279741 (unformulated)
[b] Non-activated (-S9) 4 and 20 hr exposure; activated (S9) 4 hr exposure
[c] [redacted] R279741 ([redacted] formulation)

NA = not applicable

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses μg/m^2 (μg/kg)	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Carcinogenicity[a]										
Reproductive and Developmental Toxicity	CD® Rats (Female)	i.v. bolus (sterile distilled deionized water; control = 0.9% saline[b])	GD 6 - 17	DRF 0 1.8 (0.3) 6 (1) 18 (3) 60 (10) 180 (30)	[redacted]	No	No	[redacted]	[redacted]	4.2.3.5.2.1
	CD® Rats (Female)	i.v. bolus (sterile water for injection; control = 0.9% saline)	GD 6 - 17	0 0.6 (0.1) 3 (0.5) 15 (2.5)	[redacted][c]	No	No	[redacted]	[redacted]	4.2.3.5.2.2
	NZW Rabbits (Female)	i.v. bolus (sterile water for injection; control = 0.9% saline)	GD 7 – 20	DRF 0 3.6 (0.3) 12 (1) 36 (3) 120 (10) 300 (25)	[redacted][c]	No	No	[redacted]	[redacted]	4.2.3.5.2.3
	NZW Rabbits (Female)	i.v. bolus (sterile water for injection; control = 0.9% saline)	GD 7 - 20	0 3.6 (0.3) 9 (0.75) 24 (2.0)	[redacted][c]	No	No	[redacted]	[redacted]	4.2.3.5.2.4

[a] No studies conducted
[b] Vehicle on Day 1 of dosing (GD6) = sterile distilled deionized water; due to irritation at the injection site, the vehicle was changed to 0.9% saline
[c] [redacted] R279741 ([redacted] formulation)

DRF = dose range finding; GD = gestation day; NZW = New Zealand White

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Local Tolerance	NZW Rabbits (Male)	i.v./p.v. bolus (sterile water for injection; control = 0.9% saline)	Single	2.5 and 25 µg/ml	[redacted][a]	No	Yes	[redacted]	[redacted]	4.2.3.6.1
	NZW Rabbits (Female)	i.v. bolus (pyrogen free water for injection; control = 0.9% saline)	Once/week for 4 weeks	7 µg/ml	[redacted][a] [redacted][b]	No	Yes	[redacted]	[redacted]	4.2.3.6.2

[a] [redacted] R279741 ([redacted] formulation)
[b] [redacted] R279741 ([redacted] formulation)

NZW = New Zealand White; p.v. = paravenous

2.6.7.1 毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Other Toxicity Studies	Hepatocytes	*In Vitro*	8 hr, 24 hr	0.03 nmol/L – 2 μmol/L	[redacted]	No	No	[redacted]	[redacted]	4.2.3.7.3.1
	Hepatocytes	*In Vitro*	24 hr, 48 hr	0.03 nmol/L - 2 μmol/L	[redacted]	No	No	[redacted]	[redacted]	4.2.3.7.3.2
	Wistar Rats (Female)	i.v. bolus (water for injection)	Single	240 μg/m^2 (40 μg/kg)	[redacted]	No	No	[redacted]	NS	4.3.44

NS = not specified

2.6.7.1　毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Other Toxicity Studies (cont.)	CD-1 Mice (Male/Female)	i.v. bolus (sterile water for injection; control = 0.9% saline)	Single	600, 675, 750, 900 μg/m^2 (200, 225, 250, 300 μg/kg)	[redacted][a]	No	No	[redacted]	[redacted]	4.2.3.7.5.1
	Sprague-Dawley Rats (Male/Female)	i.v. infusion (water for injection, control = 0.9% saline)	Single (3 or 24 hr)	0 300 μg/m^2 (50 μg/kg)[a] 291 μg/m^2 (48.5 μg/kg)[a]/ 9 μg/m^2 (1.5 μg/kg)[b]	[redacted][a][b]	No	Yes	[redacted]	[redacted]	4.2.3.1.4
	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection; control = 0.9% saline)	Single (3 hr)	0 300 μg/m^2 (50 μg/kg)[a,c] 290 μg/m^2 (48.3 μg/kg)[c]/ 6.6 μg/m^2 (1.1 μg/kg)[d]/ 3.6 μg/m^2 (0.6 μg/kg)[e]	[redacted][a][c][d][e]	Yes	Yes	[redacted]	[redacted]	4.2.3.7.6.1

[a] [redacted] R279741 ([redacted] formulation)
[b] Impurity (不純物 B*)
[c] [redacted] R279741 ([redacted] formulation)
[d] [redacted] R279741 containing [redacted]% 不純物 C* (impurity of [redacted] R279741; Lot No. [redacted], [redacted] formulation)
[e] 不純物 F*

2.6.7.1　毒性試験：一覧表（続き）

Test Article: R279741（Trabectedin）

Type of Study	Species and Strain	Route (Vehicle/Formulation)	Duration of Dosing	Doses	Batch No.	Toxicokinetics	GLP Compliance	Testing Facility	Study No.	Location in CTD
Other Toxicity Studies (cont)	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection, control = 0.9% saline)	Single (3 hr)	0 300 μg/m^2 (50 ug/kg)	[redacted][b,d]	No	Yes	[redacted]	[redacted]	4.2.3.7.6.2
	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection, control = 0.9% saline)	Single (3 hr)	0 300 μg/m^2 (50 ug/kg)	[redacted][a] [redacted][b]	No	No	[redacted]	[redacted]	4.2.3.7.6.3

[a] [redacted] R279741 ([redacted] formulation)
[b] [redacted] R279741 ([redacted] formulation)
[c] [redacted] R279741 (stressed [redacted] formulation; [redacted])
[d] Administered as three groups: 1) "pure" [redacted] batch [redacted]; 2) [redacted] spiked with [redacted]% 不純物 D* and [redacted]% 不純物 E*; 3) [redacted] spiked with [redacted]% 不純物 A*.

2.6.7.2 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

Test Article: R279741（Trabectedin）

Type of Study	Test System	Route (Vehicle/Formulation)	Doses μg/m^2 (μg/kg)	GLP Compliance	Study No.	Location in CTD
Single Dose Toxicity	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection)	300 (50)	Yes	[redacted][a]	4.2.3.1.5
Other Toxicity	Sprague-Dawley Rats (Male/Female)	i.v. infusion (sterile water for injection)	300 (50)	Yes	[redacted][b]	4.2.3.7.6.1
Repeat Dose Toxicity	Sprague-Dawley Rats (Male/Female)	i.v. infusion (water for injection)	15 (2.5) females only 60 (10) 150 (25) 300 (50) 450 (75) males only	Yes	[redacted][c]	4.2.3.2.3

[a] Companion toxicokinetics report for data from Study No. [redacted] ([redacted] R279741, [redacted] formulation). Single infusion administered for 3 or 24 hours.
[b] Single infusion administered for 3 hours. Study conducted with [redacted] and [redacted] R279741, [redacted] formulation.
[c] Companion toxicokinetics report for data from Study No. [redacted] ([redacted] R279741 [redacted] formulation). Single infusion administered for 3 hours once every 3 weeks for total of 3 infusions. Samples collected after 1st and 3rd infusion.

Note: Dose conversion to μg/m^2: multiply μg/kg by 6 for rats, 20 for dogs, or 12 for monkeys

2.6.7.2 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（続き）

Test Article: R279741（Trabectedin）

Type of Study	Test System	Route (Vehicle/Formulation)	Doses μg/m^2 (μg/kg)	GLP Compliance	Study No.	Location in CTD
Repeat Dose Toxicity	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection)	Cycles 1, 2, 3 Gp 2: 300 (25)[a] Gp 3: 600 (50)[a] Gp 4: 900 (75)[a] Gp 5: 900 (75)[b] Cycle 4 Gp 2: 1440 (120)[a] Gp 3: 900 (75)[a] Gp 4: 1200 (100)[a] Gp 5: 1200 (100)[b]	No	[redacted][c,d]	4.2.3.2.6
Repeat Dose Toxicity	Cynomolgus Monkeys (Male/Female)	i.v. infusion (water for injection)	120 (10)[e] 240 (20)[e] 360 (30)[e] 840 (70)[f]	Yes	[redacted][d,g]	4.2.3.2.8

[a] 4 cycles: 3 cycles (3-hour infusion) every 3 weeks, followed by a higher dose on Week 9
[b] 4 cycles: 3 cycles (24-hour infusion) every 3 weeks, followed by a higher dose on Week 9
[c] Companion toxicokinetics report for data from Study No. [redacted] ([redacted] R279741, [redacted] formulation). Single infusion administered for 3 or 24 hours once every 3 weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.
[d] Samples collected after the first administration of cycle 1 or after last administration of cycles 3 and 4.
[e] Once weekly (3-hour infusion) for 3 weeks (3 infusions/cycle; dose/cycle = 0, 360, 720, 1080 μg/m^2) followed by 1 week recovery (cycle repeated 3 times).
[f] Single 3-hour infusion every 3 weeks (1 infusion/cycle) followed by 3 weeks recovery (cycle repeated 4 times)
[g] Companion toxicokinetics report for data from Study No. [redacted] ([redacted] R279741 [redacted] formulation). Single infusion administered continuously for 3 hours once every week for 3 weeks followed by a 1-week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m^2) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of cycle 1 or after last administration of cycles 3 and 4.

2.6.7.2 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（続き）

Test Article: R279741（Trabectedin）

Type of Study	Test System	Route (Vehicle/Formulation)	Doses μg/m^2 (μg/kg)	GLP Compliance	Study No.	Location in CTD
Repeat Dose Toxicity	Cynomolgus Monkeys	i.v. infusion (water for injection)	300 (25) 600 (50) 780 (65) 420 (35)	Yes	[redacted][a]	4.2.3.2.10

[a] Study conducted with [redacted] R279741, [redacted] formulation. Single 3-hour infusions every 3 weeks

2.6.7.3 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

Test Article: R279741（Trabectedin）

Dose/infusion (μg/m²)[b]	Dose/cycle (μg/m²)[b]	Dose No./Dose Cycle	AUC[a] (ng•h/mL) Sprague-Dawley Rat Male 3h[i]	Male 24h[i]	Female 3h	Female 24h	Cynomolgus Monkey Male 3h	Male 24h	Female 3h	Female 24h
60	60	1/Cycle 1[c]	0.910	-	0.634	-				
60	60	3/Cycle 3[c]	0.635	-	0.740	-				
150	150	1/Cycle 1[c]	2.15	-	1.23	-				
150	150	3/Cycle 3[c]	2.21	-	2.15	-				
300	300	1/Cycle 1[c]	4.76	-	3.30	-				
300	300	3/Cycle 3[c]	7.43	-	8.55	-				
300	300	1/[d]	1.72	2.76	2.94	3.74				
300	300	1/[e]	2.24	-	1.90	-				
300	300	1/[e]	2.82	-	--	-				
300 ([redacted])	300 ([redacted])	1/[e]	2.35	-	2.16	-				
300 ([redacted])	300 ([redacted])	1/[e]	2.69	-	--	-				
300	300	1/Cycle 1[f]					7.79	-	10.9	-
300	300	3/Cycle 3[f]					6.80	-	11.3	-
300	300	1/Cycle 1[g]					12.3 (11.2)	-	12.9 (11.5)	-
300	300	8/Cycle 8[g]					-- (2.99)		-- (7.34)	
120	360	9/Cycle 3[h]					3.49	-	4.18	-
420	420	1/Cycle 1[g]					-- (12.5)	-	13.1 (12.1)	-
420	420	6/Cycle 6[g]					-- (12.5)		-- (8.41)	
450	450	1/Cycle 1[c]	5.97	-	--	-				
600	600	1/Cycle 1[f]					22.7	-	28.2	-
600	600	1/Cycle 1[g]					23.3	-	25.0	-

[a] AUC values expressed as $AUC_{0\text{-}t}$ for study [redacted] and [redacted]. For Exp. [redacted], $AUC_{0\text{-}5h}$ followed by those for $AUC_{0\text{-}inf.}$ [redacted], Cycle 1 values expressed as $AUC_{0\text{-}inf}$ Cycle 3 values expressed as $AUC_{0\text{-}7\ day.}$ [redacted] and [redacted] AUC expressed as $AUC_{0\text{-}inf.}$

[b] To obtain dose in μg/kg, for rats divided by 6, for primates divide by 12.

[c] [redacted]: Single infusions administered once every 3 weeks for total of three infusions. Samples collected after 1st and 3rd infusion.

[d] [redacted]: Single infusion administered for 3 or 24 hours.

[e] Exp. [redacted]: Single infusion administered for 3 hours. Study conducted with test material from [redacted] and [redacted] sources.

[f] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.

[g] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles. Repeated dose data may have been confounded by the injection site inflammation reaction and resulting secondary pathology. $AUC_{0\text{-}144\ h}$ is provided in the brackets

[h] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m²) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of cycles 3 and 4.

[i] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; this dose level not evaluated in females or sample not analyzed or parameter not calculated.

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion (µg/m²)[b]	Dose/cycle (µg/m²)[b]	Dose No./Dose Cycle	AUC[a] (ng•h/mL) Sprague-Dawley Rat Male 3h[f]	Male 24h[f]	Female 3h	Female 24h	Cynomolgus Monkey Male 3h	Male 24h	Female 3h	Female 24h
240	720	1/Cycle 1[c]					8.64	-	5.39	-
240	720	9/Cycle 3[c]					10.5	-	11.2	-
780	780	1/Cycle 1[d]					28.8	-	31.5	-
840	840	1/Cycle 1[c]					29.6	-	31.6	-
840	840	4/Cycle 4[c]					36.2	-	40.0	-
900	900	1/Cycle 1[e]					30.3	51.6	26.9	--
900	900	3/Cycle 3[e]					24.3	--	27.1	--
900	900	4/Cycle 4[e]					34.9	---	33.5	---
360	1080	1/Cycle 1[c]					--	-	12.9	-
360	1080	9/Cycle 3[c]					--	-	15.9	-
1200	1200	4/Cycle 4[e]					--	30.5	--	49.7
1440	1440	4/Cycle 4[e]					--	---	84.0	---

[a] [redacted] Cycle 3 AUC values expressed as AUC0-7day. [redacted] Cycle 1 AUC values and [redacted] and [redacted] AUC values -expressed as AUC0-inf

[b] To obtain dose in µg/kg, for primates, divide by 12.

[c] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 µg/m²) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of cycles 3 and 4.

[d] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles. Repeated dose data may have been confounded by the injection site inflammation reaction and resulting secondary pathology.

[e] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.

[f] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; sample not available or not analyzed or parameter not calculated.
--- Not applicable; dose level not evaluated via 24 hour infusion during Cycle 4.

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion ($\mu g/m^2$)[a]	Dose/cycle ($\mu g/m^2$)[a]	Dose No./Dose Cycle	C_{max} (ng/mL) Sprague-Dawley Rat Male 3h[h]	Sprague-Dawley Rat Male 24h[h]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
15	15	1/Cycle 1[b]	--	-	0.154	-				
60	60	1/Cycle 1[b]	0.947	-	0.483	-				
60	60	3/Cycle 3[b]	0.351	-	0.302	-				
150	150	1/Cycle 1[b]	0.814	-	0.481	-				
150	150	3/Cycle 3[b]	1.25	-	1.01	-				
300	300	1/Cycle 1[b]	1.63	-	1.30	-				
300	300	3/Cycle 3[b]	1.92	-	1.29	-				
300	300	1/[c]	0.804	0.131	0.994	0.188				
300	300	1/[d]	1.35	-	0.924	-				
300 ([redacted])	300 ([redacted])	1/[d]	1.07	-	1.14	-				
300	300	1/Cycle 1[e]					0.783	-	0.824	-
300	300	3/Cycle 3[e]					0.792	-	0.987	-
300	300	1/Cycle 1[f]					1.70	-	2.09	-
300	300	8/Cycle 8[f]					0.09	-	0.99	-
120	360	1/Cycle 1[g]					0.396	-	0.399	-
120	360	9/Cycle 3[g]					0.403	-	0.666	-
420	420	1/Cycle 1[f]					2.50	-	1.99	-
420	420	6/Cycle 6[f]					1.94	-	1.85	-
450	450	1/Cycle 1[b]	2.00	-	--	-				
600	600	1/Cycle 1[e]					2.80	-	6.80	-
600	600	3/Cycle 3[e]					5.29	-	2.86	-
600	600	1/Cycle 1[f]					2.96	-	3.76	-

[a] To obtain dose in µg/kg, for rats divided by 6, for primates divide by 12.
[b] [redacted]: Single infusions administered continuously once every 3 weeks for total of three infusions. Samples collected after 1st and 3rd infusion.
[c] [redacted]: Single infusion administered continuously for 3 or 24 hours.
[d] Exp. [redacted]: Single infusion administered continuously for 3 hours. Study conducted with test material from [redacted] and [redacted] sources.
[e] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.
[f] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles. Repeated dose data may have been confounded by the injection site inflammation reaction and resulting secondary pathology.
[g] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 $\mu g/m^2$) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of Cycles 3 and 4.
[h] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; sample not analyzed or parameter not calculated.

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion ($\mu g/m^2$)[a]	Dose/cycle ($\mu g/m^2$)[a]	Dose No./Dose Cycle	C_{max} (ng/mL) Sprague-Dawley Rat Male 3h[e]	Sprague-Dawley Rat Male 24h[e]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
240	720	1/Cycle 1[b]					0.945	-	0.589	-
240	720	9/Cycle 3[b]					1.100	-	1.170	-
780	780	1/Cycle 1[c]					3.71	-	5.23	-
840	840	1/Cycle 1[b]					2.63	-	5.29	-
840	840	4/Cycle 4[b]					3.95	-	6.19	-
900	900	1/Cycle 1[d]					3.24	1.76	2.58	1.04
900	900	3/Cycle 3[d]					1.66	1.75	1.38	1.66
900	900	4/Cycle 4[d]					3.66	---	5.08	---
360	1080	1/Cycle 1[b]					1.48	----	1.83	----
360	1080	9/Cycle 3[b]					1.85	----	3.41	----
1200	1200	4/Cycle 4[d]					--	0.84	5.62	1.21
1440	1440	4/Cycle 4[d]					4.27	---	5.68	---

[a] To obtain dose in µg/kg, for primates, divide by 12.

[b] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 $\mu g/m^2$) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of Cycles 3 and 4.

[c] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles.

[d] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.

[e] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; sample not analyzed or parameter not calculated
--- Not applicable; dose level not evaluated via 24 hour infusion during Cycle 4.
---- Not applicable; dose level not evaluated via 24 hour infusion.

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion (μg/m²)[a]	Dose/cycle (μg/m²)[a]	Dose No./Dose Cycle	t_{max} (h) Sprague-Dawley Rat Male 3h[f]	Sprague-Dawley Rat Male 24h[f]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
15	15	1/Cycle 1[b]	--	-	3.2	-				
60	60	1/Cycle 1[b]	3.2	-	3.0	-				
60	60	3/Cycle 3[b]	2.7	-	2.6	-				
150	150	1/Cycle 1[b]	2.7	-	2.5	-				
150	150	3/Cycle 3[b]	3.2	-	3.1	-				
300	300	1/Cycle 1[b]	0.65	-	2.5	-				
300	300	3/Cycle 3[b]	0.73	-	3.1	-				
300	300	1/[c]	0.58	23.2	0.47	22.9				
300	300	1/Cycle 1[d]					1.50	-	2.00	-
300	300	8/Cycle 8[d]					2.50	-	2.50	-
120	360	1/Cycle 1[e]					2.83	-	2.83	-
120	360	9/Cycle 3[e]					2.83	-	1.0	-
420	420	1/Cycle 1[d]					2.50	-	2.00	-
420	420	6/Cycle 6[d]					73.4	-	1.75	-
450	450	1/Cycle 1[b]	2.7	-	--	-				
600	600	1/Cycle 1[d]					2.00	-	2.50	-
240	720	1/Cycle 1[e]					2.83	-	1.0	-
240	720	9/Cycle 3[e]					2.83	-	2.83	-
780	780	1/Cycle 1[d]					2.50	-	1.60	-
840	840	1/Cycle 1[e]					2.83	-	2.83	-
840	840	4/Cycle 4[e]					2.83	-	2.83	-
360	1080	1/Cycle 1[e]					1.0	-	2.83	-
360	1080	9/Cycle 3[e]					2.83	-	1.0	-

[a] To obtain dose in μg/kg, for rats divided by 6.
[b] [redacted]: Single infusions administered continuously once every 3 weeks for total of three infusions. Samples collected after 1st and 3rd infusion.
[c] [redacted]: Single infusion administered continuously for 3 or 24 hours.
[d] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles. Repeated dose data may have been confounded by the injection site inflammation reaction and resulting secondary pathology.
[e] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m²) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of cycle 1 or after last administration of cycles 3 and 4.
[f] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only
-- Not applicable; sample not analyzed or parameter not calculated.

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion (μg/m²)[a]	Dose/cycle (μg/m²)[a]	Dose No./Dose Cycle	$t_{1/2}$ (h) Sprague-Dawley Rat Male 3h[f]	Sprague-Dawley Rat Male 24h[f]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
300	300	1/[b]	4.4	-	--	-				
300 ([redacted])	300 ([redacted])	1/[b]	2.8	-	--	-				
300	300	1/Cycle 1[c]					41	-	81	-
300	300	3/Cycle 3[c]					48	-	83	-
300	300	1/Cycle 1[d]					45.1	-	60.1	-
120	360	9/Cycle 3[e]					63	-	85	-
420	420	1/Cycle 1[d]					--	-	36.7	-
600	600	1/Cycle 1[c]					77	-	77	-
600	600	3/Cycle 3[c]					173	-	229	-
600	600	1/Cycle 1[d]					63.7	-	84.1	-
240	720	1/Cycle 1[e]					60	-	73	-
240	720	9/Cycle 3[e]					49	-	74	-
780	780	1/Cycle 1[d]					53.0	-	70.9	-
840	840	1/Cycle 1[e]					61	-	42	-
840	840	4/Cycle 4[e]					64	-	45	-
900	900	1/Cycle 1[c]					74	109	96	--
900	900	3/Cycle 3[c]					63	--	231	--
900	900	4/Cycle 4[c]					92	---	99	---
360	1080	1/Cycle 1[e]					149	-	--	-
360	1080	9/Cycle 3[e]					--	-	138	-
1200	1200	4/Cycle 4[c]					62	81	--	74
1440	1440	4/Cycle 4[c]					--	---	137	---

[a] To obtain dose in μg/kg, for rats divided by 6, for primates divide by 12.

[b] Exp. [redacted]: Single infusion administered continuously for 3 hours. Study conducted with test material from [redacted] and [redacted] sources.

[c] [redacted]: ingle infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.

[d] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles.

[e] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m²) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of Cycles 3 and 4.

[f] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only
-- Not applicable; sample not analyzed or parameter not calculated.
--- Not applicable; dose level not evaluated via 24-hour infusion during Cycle 4

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion (μg/m²)[a]	Dose/cycle (μg/m²)[a]	Dose No./Dose Cycle	Cl (L•h/kg) Sprague-Dawley Rat Male 3h[f]	Sprague-Dawley Rat Male 24h[f]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
300	300	1/[b]	17.7	-	--	-				
300 ([redacted])	300 ([redacted])	1/[b]	18.6	-	--	-				
300	300	1/Cycle 1[c]					3.21	-	2.28	-
300	300	3/Cycle 3[c]					3.68	-	2.21	-
300	300	1/Cycle 1[d]					2.08	-	1.96	-
120	360	9/Cycle 3[e]					2.87	-	2.39	-
420	420	1/Cycle 1[d]					--	-	3.10	-
600	600	1/Cycle 1[c]					2.20	-	1.78	-
600	600	1/Cycle 1[d]					2.21	-	2.04	-
240	720	1/Cycle 1[e]					2.32	-	--	-
240	720	9/Cycle 3[e]					1.90	-	1.79	-
780	780	1/Cycle 1[d]					2.27	-	2.10	-
840	840	1/Cycle 1[e]					2.37	-	2.21	-
840	840	4/Cycle 4[e]					1.94	-	1.75	-
900	900	1/Cycle 1[c]					2.47	1.45	2.79	--
900	900	3/Cycle 3[c]					3.09	-	2.77	--
900	900	4/Cycle 4[c]					2.15	---	2.24	---
360	1080	1/Cycle 1[e]					--	-	2.32	-
360	1080	9/Cycle 3[e]					--	-	1.89	-
1200	1200	4/Cycle 4[c]					--	3.28	--	2.01
1440	1440	4/Cycle 4[c]					--	---	1.43	---

[a] To obtain dose in μg/kg, for rats divided by 6, for primates divide by 12.
[b] Exp. [redacted]: Single infusion administered continuously for 3 hours. Study conducted with test material from [redacted] and [redacted] sources.
[c] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.
[d] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles.
[e] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m²) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of cycle 1 or after last administration of Cycles 3 and 4.
[f] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; sample not analyzed or parameter not calculated.
--- Not applicable; dose level not evaluated via 24-hour infusion during Cycle 4

2.6.7.3 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（続き）

Test Article: R279741（Trabectedin）

Dose/infusion (μg/m^2)[a]	Dose/cycle (μg/m^2)[a]	Dose No./Dose Cycle	VD_{ss} (L/kg) Sprague-Dawley Rat Male 3h[f]	Sprague-Dawley Rat Male 24h[f]	Sprague-Dawley Rat Female 3h	Sprague-Dawley Rat Female 24h	Cynomolgus Monkey Male 3h	Cynomolgus Monkey Male 24h	Cynomolgus Monkey Female 3h	Cynomolgus Monkey Female 24h
300	300	1/[b]	35.9	-	--	-				
300 ([redacted])	300 ([redacted])	1/[b]	20.4	-	--	-				
300	300	1/Cycle 1[c]					142	-	197	-
300	300	3/Cycle 3[c]					193	-	200	-
300	300	1/Cycle 1[d]					82.9	-	92.5	-
420	420	1/Cycle 1[d]					--	-	116	-
600	600	1/Cycle 1[c]					161	-	80.7	-
600	600	1/Cycle 1[d]					131	-	147	-
240	720	1/Cycle 1[e]					137	-	--	-
780	780	1/Cycle 1[d]					116	-	121	-
840	840	1/Cycle 1[e]					160	-	121	-
840	840	4/Cycle 4[e]					132	-	94.4	-
900	900	1/Cycle 1[c]					176	106	287	--
900	900	3/Cycle 3[c]					230	--	534	--
900	900	4/Cycle 4[c]					212	---	171	---
360	1080	1/Cycle 1[e]					--	-	125	-
1200	1200	4/Cycle 4[c]					--	292	--	167
1440	1440	4/Cycle 4[c]					--	---	219	---

[a] To obtain dose in μg/kg, for rats divided by 6, for primates divide by 12.

[b] Exp. [redacted]: Single infusion administered continuously for 3 hours. Study conducted with test material from [redacted] and [redacted] sources.

[c] [redacted]: Single infusions administered once every three weeks (i.e. a cycle) for 3 cycles. A 4th cycle was administered at a higher dose.

[d] [redacted]: Single infusion administered once every three weeks for 1 to 8 cycles.

[e] [redacted]: Three hour infusions administered once/week for three weeks followed by a one week recovery period (i.e. a cycle); repeated three times. The high dose (840 μg/m^2) was administered once every three weeks; repeated 4 times. Samples collected after the first administration of Cycle 1 or after last administration of Cycles 3 and 4.

[f] Duration of intravenous infusion.

- Not applicable; animals were administered compound via 3-hour i.v. infusion only.
-- Not applicable; sample not analyzed or parameter not calculated.
--- Not applicable; dose level not evaluated via 24-hour infusion during Cycle 4

2.6.7.4 毒性試験：被験物質（バッチごと）一覧

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
Proposed Specification[b]						
DS: [redacted] – [redacted] R279741	[redacted]	Single impurity [redacted] -- --	[redacted] -- --	[redacted]	Single Dose Intravenous Toxicity in Mice with Recovery	4.2.3.1.1
DS: [redacted] - [redacted] R279741	[redacted]	Single impurity [redacted]	[redacted]	[redacted]	Single Dose Intravenous in Fisher 344 Rats	4.2.3.1.2
				[redacted]	Single Dose Intravenous Toxicity in Beagle Dogs	4.2.3.1.6
				[redacted]	5-Day Intravenous Toxicity Study in CD_2F_1 Mice	4.2.3.2.1

[a] Assay of ET-743 (R279741)
[b] Detailed in Drug Master File (3.2.S.4.1 Specification - Trabectedin)

-- = not available; DS = drug substance; form = formulation
Note: drug substance = unformulated drug; drug product = lyophilized drug for reconstitution or aqueous solutions

2.6.7.4　毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted]	[redacted]	Single Dose Intravenous Toxicity with 2-Week Recovery in Rats	4.2.3.1.3
				[redacted]	6-Week Intermittent Intravenous Toxicity Study with a 3-Week Recovery in Rats	4.2.3.2.2
				[redacted]	Acute Intravenous and Paravenous Irritation Potential Study in Rabbits	4.2.3.6.1
				[redacted]	Single Dose Intravenous MTD Comparative Study of ET-743 and ET-729 in Mice	4.2.3.7.5.1
DP: [redacted] form (DS: 000, [redacted] and [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted][b]	[redacted][c]	Single Dose Intravenous Toxicity Study with 3-Week Recovery in Rats	4.2.3.1.4
				[redacted]	Single Dose Intravenous Toxicity Study with 3-Week Recovery in Rats	4.2.3.7.6.1
				[redacted]	Dose Range-Finding following 4-Cycles of Intravenous Infusion to Cynomolgus Monkeys	4.2.3.2.5

[a] Assay of ET-743 (R279741)
[b] Total degradation products
[c] 不純物 B* spiked to [redacted]%

DP = drug product; DS = drug substance; form = formulation

2.6.7.4 毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted][b]	[redacted]	Single Dose Intravenous Toxicity Study with 3-Week Recovery in Rats	4.2.3.7.6.1
DS: [redacted] R279741	[redacted][c,d]	--	--	[redacted]	5-Day Intravenous Toxicity Study in Beagle Dogs	4.2.3.2.4
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted][c]	[redacted]	DRF Toxicity Following 3 or 4-Cycles of IV Infusion to Cynomolgus Monkeys	4.2.3.2.7
DS: [redacted] R279741	[redacted]	Single impurity [redacted]	[redacted]	[redacted]	Salmonella/Escherichia Coli Plate Incorporation Mutagenic Assay	4.2.3.3.1.1
DS: [redacted] R279741	[redacted]	Single impurity [redacted]	[redacted]	[redacted]	In Vitro Mammalian Chromosome Aberration Assay	4.2.3.3.1.2

[a] Assay of ET-743 (R279741)
[b] Total degradation products
[c] Information derived from stability analysis
[d] Capped vials stored up to [redacted] at [redacted] °C

-- = not available; DRF = dose range finding; DRF = dose range finding; DP = drug product; DS = drug substance; form = formulation; ND = not detected

2.6.7.4　毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	--	--	[redacted]	Mammalian Erythrocyte Micronucleus Test	4.2.3.3.2.1
				[redacted]	Intravenous DRF Developmental Toxicity Study in Rats	4.2.3.5.2.1
				[redacted]	Intravenous Developmental Toxicity Study in Rats	4.2.3.5.2.2
				[redacted]	Intravenous DRF Developmental Toxicity Study in Rabbits	4.2.3.5.2.3
				[redacted]	Intravenous Developmental Toxicity Study in Rabbits	4.2.3.5.2.4
DP: [redacted] form ([redacted] R279741 w/ 不純物 C* impurity)	[redacted]	不純物 C*: [redacted][b]	[redacted][c]	[redacted]	Single Dose Intravenous Toxicity Study with 3-Week Recovery in Rats	4.2.3.7.6.1

[a] Assay of ET-743 (R279741)
[b] Final concentration in prepared solution [redacted]%
[c] Spiked with 不純物 F* [redacted]%

DP = drug product; DRF = dose range-finding; DS = drug substance; form = formulation
Note: 不純物 C* = 不純物 C*

＊新薬承認情報提供時に置き換え

2.6.7.4　毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form[b] DP: [redacted] form[b] (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted][c]	[redacted]	Local tolerability /tissue reaction study in female New-Zealand white rabbits.	4.2.3.6.2
				[redacted]	Single dose intravenous infusion (3h) toxicity study in rats followed by a 3-day or 3-week treatment-free period	4.2.3.7.6.3
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted]	[redacted]	[redacted]	Single dose intravenous infusion (3h) toxicity study in rats followed by a 3-day or 3-week treatment-free period	4.2.3.7.6.3
DP: [redacted], stressed form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted] 不純物 I*: [redacted]	[redacted]	[redacted]	Single dose intravenous infusion (3h) toxicity study in rats followed by a 3-day or 3-week treatment-free period	4.2.3.7.6.3

[a] Assay of ET-743 (R279741)
[b] [redacted] and [redacted] are the same batches; [redacted] was used to differentiate formulations used in [redacted]
[c] Total degradation products

-- = not available; form = formulation; DP = drug product; DS = drug substance; ND = not detected

2.6.7.4　毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted][b]	[redacted]	Chronic toxicity study following 4-cycles of administration by intravenous infusion to cynomolgus monkeys followed by an 3-week treatment-free period	4.2.3.2.9
				[redacted]	Local tolerability /tissue reaction study of trabectedin in female New-Zealand white rabbits.	4.2.3.6.2
DS: [redacted] R279741	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted]	--	[redacted]	Cytoxicity of ET-743 and ET-729 on hepatocytes	4.2.3.7.3.2

[a] Assay of ET-743 (R279741)
[b] Total degradation products

-- = not available; DP = drug product; DS = drug substance; form = formulation

2.6.7.4　毒性試験：被験物質（バッチごと）一覧（続き）

Test Article: R279741（Trabectedin）

Batch No.	Purity (%)[a]	Specified Impurities (%)		Study No.	Type of Study	Location in CTD
		Individual Impurities	Total Impurity			
DP: [redacted] form (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted]	[redacted]	Chronic toxicity study following 4 to 8-cycles of administration by intravenous infusion to cynomolgus monkeys followed by an 8-week treatment-free period	4.2.3.2.10
DP: [redacted][b] (DS: [redacted] R279741)	[redacted]	不純物 A*: [redacted] 不純物 B*: [redacted] 不純物 H*: [redacted]	[redacted]	[redacted]	Tox Qualification (不純物 D*+E* and 不純物 A*)[b]	4.2.3.7.6.2
--	--	--	--	[redacted]	Cytoxicity of ET-743 on hepatocytes	4.2.3.7.3.1

[a] Assay of ET-743 (R279741)
[b] Spiked with 不純物 D* ([redacted]%), 不純物 E* ([redacted]%), 不純物 A* ([redacted]%)

-- = not available; DP = drug product; DS = drug substance; form = formulation; NS = not specified

2.6.7.5 単回投与毒性試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group/Sacrifice Schedule	Route (Vehicle/ Formulation)	Doses μg/m^2 (μg/kg)	Observed Maximum Non-Lethal Dose μg/m^2 (μg/kg)	Approximate Lethal Dose μg/m^2 (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Mouse/MF1 Male-15/groups I, II and III Male-30, group IV 5/group sacrificed 14 days post treatment. (Groups I, II, III) 10/group sacrificd 14 days post-treatment (Group IV) 5/group sacrificed 42 days post treatment (Groups I, II and III). 10/group (Group IV) sacrificed 42 days post treatment. All survivors sacrificed 56 days post treatment.	Intravenous injection/(0.9% saline/ R279741 plus vehicle) (Single injection administered)	0 300 (100) 450 (150) 600 (200)	300 (100)	Between 300 (100) and 450 (150)	Dosing solution concentrations were between 106 and 108.5% of the nominal concentration. 0 μg/m^2: Piloerection noted in 7 mice. 300 μg/m^2: Piloerection noted in 13 mice, and discolored scabrous tails in 6 mice. Hematology-Day 14: ↓ HCT, PLC, ↑ MCHC; Hematology-Day 42: ↓ MCV; Hematology-Day 56: No noteworthy findings; Clinical Chemistry-Day 14, 42, 56: No noteworthy findings; Organ weights Day 14: ↑ brain/body weight ratio, Day 42: ↑ thymus weight, ↓ heart and testes/body weight ratios; Day 56: No noteworthy findings. 450 μg/m^2: Two mice sacrificed moribund (Days 22 and 30), piloerection in 10 mice, discoloration and lesions of tail seen frequently. Hematology-Day 14: ↓ HCT, PLC, ↑ MCHC; Hematology-Day 42: ↓ MCV; Hematology-Day 56: No noteworthy findings; Clinical Chemistry-Days 14 and 42: ↓ CREAT; Clinical Chemistry-Day 56: No noteworthy findings; Organ weights Day 14: ↑ brain/body weight ratio, Day 42: ↓ heart and testes/body weight ratios; Day 56: No noteworthy findings. 600 μg/m^2: Two mice found dead Day 2, 8 mice sacrificed between Days 1 and 10 due to poor condition, piloerection and tail lesions commonly observed. ↓ body weight through Day 3 and 7, Hematology-Day 14: ↓ RBC, HCT, HGB; Hematology-Day 42: ↓ MCH; Hematology-Day 56: No noteworthy findings; Clinical Chemistry-Day 14: ↓ ALP; Clinical Chemistry-Days 42, 56: No noteworthy findings; Organ weights Day 14: ↓ thymus weight and thymus/body weight ratio, Day 42 ↑ kidney weight/body weight ratio, ↑ thymus weight and thymus/body weight ratio, ↓testes/body weight ratios, Day 56: No noteworthy findings. Microscopic lesions observed : congestion and depletion.	[redacted] 4.2.3.1.1

↓ = decrease, ↑ = increase, ALP = alkaline phosphatase, CREAT = creatinine, HCT = hematocrit, HGB = hemoglobin, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean cell volume, PLC = platelet count, RBC = red blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					600 µg/m^2 (Cont): Treatment related microscopic alterations observed in the liver of animals dying or sacrificed through Day 14 included congestion, coagulative cell necrosis and increased mitotic figures. No treatment related effects evident in the liver at Days 42 and 56. Treatment related microscopic alterations observed in the heart of animals dying or sacrificed through Day 14 included myocardial necrosis, calcification and inflammatory cell infiltrate. At Day 42 calcification was evident in 1 animal, no findings evident at 56 days. Increased extramedullary hematopoiesis was observed on Day 14; recovery was evident by study Day 42. Mice that died early exhibited lymphocyte necrosis in the thymus, lymph nodes, and spleens, and bone marrow depletion and congestion. These findings not evident in animals that survived to scheduled necropsy.	[redacted] [redacted] 4.2.3.1.1

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group/Sacrifice Schedule	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat/Fischer 344 Male and Female/ 10/sex/group 5/sex/group sacrificed Day 8 Survivors sacrificed Day 29	Intravenous injection/ (0.05 mol/L potassium phosphate buffer (pH 4.0)/ R279741 plus vehicle) (Single injection administered)	0 45 (9) 450 (75) 540 (90)	Males: 540 (90) Females: 45 (9)	Males: >540 (90) Females: Between 45 (9) and 450 (75)	Dosing solution concentrations were between 93.3 and 99.9 % of the nominal concentration. 0 µg/m^2: No noteworthy findings 45 µg/m^2: ↓ RETIC males and females (43 – 44% on Day 8), ↑ RETIC (Days 15, 29), ALT ↑ 3.3-fold in females at Day 5. 450 µg/m^2: Five females sacrificed moribund, males exhibited diarrhea, exudates from eyes and/or nose, chromodacryorrhea, hunched posture, rough coat and alopecia. Females exhibited exudates from eyes and/or nose, chromodacryorrhea, hunched posture, rough coat and alopecia, discolored urine, prostration, hypoactivity, cloudy eyes, yellow ears, dyspnea, abnormal gait, and emaciation. Clinical findings more severe in females than in males. ↓ Body weights. ↓WBC in males and females (19-25%) on Day 5. ↓ RBC in males (16%) and females (42%) on Day 15, remained reduced Day 29. ↓ RETIC male and female (95-100%) on Days 5. ↓ PLC in males on Days 5 and 8 (43-53%). ↑ PLC in males on Days 15 and 22 (1.5-fold), males recovered by Day 29. Females ↓ on Day 15 (19%), ↑ Day 22 (1.3-fold). ↓ Day 15 HGB (41%) and HCT (41%) in females. ↑ MCV in males on Day 15, peaked on Day 22 (↑15%), remained elevated through Day 29. ↑ MCV in females on Day 22 (28%).↑ NRB observed in male and female rats Day 15 through Day 22. ↓ LYMPH (20%) and ↓MONO (86-91%) counts observed on Day 5, remained ↓ through Day 29. ↓ASN 56% on Day 8 in males and ↑ 2.6-fold in females on Day 22. Levels markedly increased in males prior to returning to normal at Day 29.	[redacted] 4.2.3.1.2

↑ = increase, ↓ = decrease, ASN = absolute segmented neutrophils, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCV = mean cell volume, MONO = monocytes, NRB = nucleated red blood cells, PLC = platelet count, RBC = red blood cells, RETIC = reticulocytes,WBC = white blood cells, ALT = serum alanine aminotransferase

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					AST ↑ 5.5 and 4.6-fold in males and females at Day 5, remained slightly elevated through Day 29. ALT ↑ 7.5 and 7.8-fold in males and females at Day 5. Glucose ↓in females (30%) on Day 5. TBI and DBI ↑ 10-fold or more in males and females from Day 16 (first evaluation interval) through termination. ↓ Thymus size-5 of 10 females, yellow ears-3 of 10 females, dark kidney cortex-3 of 10 females, yellow/brown liver - 4 of 10 females, swollen tail – one of 10 females. Microscopic lesions observed in males and females included: bone marrow depletion; inflammation, gland dilation and epithelial hyperplasia of the colon; cholangitis, necrosis, inflammation of the liver; depletion of mesenteric lymph node and spleen, and atrophy of the thymus. 540 µg/m^2: One female sacrificed moribund, 4 females found dead, males exhibited exudates from eyes and/or nose, diarrhea, chromodacryorrhea, hunched posture, rough coat and alopecia. Females exhibited exudates from eyes and/or nose, diarrhea, chromodacryorrhea, hunched posture, rough coat and alopecia, discolored urine, hypoactivity, cloudy eyes, yellow ears, abnormal gait, and emaciation. Clinical findings more severe in females than in males and in high dose than in mid dose. ↓ Body weights. ↓WBC in males and females (34-43%) on Day 5. ↓ RBC in males (31%) and females (49%) on Day 15, remained reduced Day 29. ↓RETIC male (100%) and female (100%) on Days 5.	[redacted] 4.2.3.1.2

↑ = increase, ↓ = decrease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ASN = absolute segmented neutrophils, DBI = direct bilirubin, HGB = hemoglobin, HCT = hematocrit, LYMPH = lymphocytes, MCV = mean cell volume, MONO = monocytes, NRB = nucleated red blood cells, PLC = platelet count, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses $\mu g/m^2$ (μg/kg)	Observed Maximum Non-Lethal Dose $\mu g/m^2$ (μg/kg)	Approximate Lethal Dose $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
					↓ PLC in males and females on Days 5 and 8 (79-85%). ↑ PLC in males on Days 15 and 22 (1.6-fold), males recovered by Day 29. Females ↓ on Day 15 (36%), ↑ Day 22 (1.4-fold) and remained elevated on Day 29.	[redacted]
					↓ Day 15 HGB (26%) and HCT (23%) in male. ↓ Day 15 HGB (48%) and HCT (49%) in female . HGB/HCT remained low in females through Day 29. Returned to normal in males by Day 22. ↑ MCV in males on Day 15, peaked on Day 22 (27%), remained elevated through Day 29. ↑ MCV in females on Day 22 (28%), remained elevated through Day 29.	4.2.3.1.2
					Small ↑ NRB observed in male and female Day 15 through Day 22, returning to normal by Day 29. ↓ LYMPH (36-38%) and ↓MONO (87-88%) counts observed on Day 5, elevated on Day 15 and Day 22. ↓ASN Day 8(94%) in males and Day 5 (63%) and Day 8(89%) in females. Levels markedly increased in males prior to returning to normal at Day 29. Female value remained high at Day 29.	
					↑AST 6.5 and 5.3-fold in males and females at Day 5, remained slightly elevated through Day 29. ↑ALT 9.2 and 8.9-fold in males and females at Day 5, remained slightly elevated through Day 29. ↓Glucose 22% in males and 28% females on Day 5. ↑TBI and DBI 10-fold or more in males and females from Day 16 (first evaluation interval) through termination.	
					↓ Thymus size-3 of 10 females, 3 of 10 males, yellow ears-1 of 10 females, and red inflamed colon 1 of 10 males, tail lesion1 of 10 females	

↑ = increase, ↓ = decrease, ALT = alanine aminotransferase, ASN = absolute segmented neutrophils, AST = aspartate aminotransferase, DBI = direct bilirubin, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCV = mean cell volume, MONO = monocytes, NRB = nucleated red blood cells, PLC = platelet count, TBI = total bilirubin

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m² (µg/kg)	Observed Maximum Non-Lethal Dose µg/m² (µg/kg)	Approximate Lethal Dose µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Microscopic lesions observed in males and females included: bone marrow depletion; inflammation, gland dilation and epithelial hyperplasia of the colon; cholangitis, necrosis, inflammation of the liver; depletion of mesenteric lymph node and spleen, and atrophy of the thymus. In summary: Maximum Tolerated Dose – Males: 540 µg/m² Females: Between 45 and 450 µg/m² No Observed Effect Level – Males and Females: Approximately 45 µg/m² Primary Target Organs of Toxicity: Liver, bone marrow, lymphoid tissue, and colon.	[redacted] 4.2.3.1.2
Rat/Sprague-Dawley Males and Females 3/sex/group	Intravenous 3 hour infusion (Single administration/2 week recovery period)	Males: 450 (75) 600 (100) Females: 300 (50) 600 (100)	Males: 450 (75) Females: 300 (50)	Males: between 450 (75) and 600 (100) Females: between 300 (50) and 600 (100)	300 µg/m² (females): slight ↓ body weight week 1 incomplete recovery (week 2), week 1 food consumption slightly lower than week 2. Day 4 post dosing: pronounced ↓ WBC, EOSIN, RETIC, MONO, slight ↓ NEUT, LYMPH, Day 14 post dosing: pronounced ↑ RETIC, MCV, moderate ↑ NORM, slight ↑ MCH pronounced ↓ HCT, RBC, EOSIN, HGB and THROMB. Day 4 post dosing: pronounced ↑ TBI, TRI, AST, ALT, slight-moderate ↑ ALP, CHOL, slight ↓ BUN, CREAT. At 14 days post dosing: pronounced ↑ TBI, AST, TRI, moderate ↑ BUN, ALT, ALP, CHOL, slight ↓ SOD. At necropsy swollen livers noted in 2 animals, microscopically focal liver necrosis observed in 2 animals.	[redacted] 4.2.3.1.3

↑ = increase, ↓ = decrease, ALP = alkaline phosphate, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CREAT = creatinine, CHOL = cholesterol, EOSIN = eosinophils, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean cell hemoglobin, MCV = mean cell volume, MONO = monocytes, NEUT = neutrophils, NORM = normoblasts, RBC = red blood cells, RETIC = reticulocytes, SOD = sodium, TBI = total bilirubin, THROMB = thrombocytes, TRI = triglyceride, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					450 µg/m^2 (males): slight transient ↓ body weight (week 1), week 1 food consumption slightly lower than week 2, Day 4 post dosing: moderate to pronounced ↓ EOSIN, RETIC, MONO, Day 14 post dosing: moderate ↑ RETIC, slight ↑ MCV and MCH, moderate ↓ HCT, RBC, EOSIN, and HGB, slight ↓ THROMB. Day 4 post dosing: marginal ↑ POT, ALP, AST, slight to moderate ↓ TP, CREAT, ALB, marginal ↓ BUN. Day 14 post dosing: pronounced ↑ AST, ALT, slight-moderate ↑ TBI, ALP, TRI, marginal ↓ BUN. Three animals exhibited focal liver necrosis. 600 µg/m^2 (males/females): 3 males and 3 females died or sacrificed moribund by Day 4 or 7, one or more males exhibited piloerection, red stained nares, soft feces, thin, poor condition, crusty nose, dyspnea, wet urogenital region, one or more females exhibited piloerection, thin, soft feces, red nares, wet urogenital region, decreased general activity. Male body weight moderately ↓ week 1, no male survivors week 2, no female survivors week 1. Moderate ↓ in food consumption in males during week 1. Food consumption not evaluated in females due to mortality. Day 4 post dosing (males): pronounced ↓ WBC, EOSIN, RETIC, MONO, LYMPH, moderate ↓ BASO, In the unscheduled sacrifice animals pronounced ↓ in all hematology parameters except MCH which was normal and MHC which was ↑. Day 4 post dosing slight-moderate ↓ CHL, TP, ALB, marginal ↓ BUN, CREAT, pronounced ↑ CHOL, TRI, AST, ALT, ALP, TBI, slight ↑ glucose. In the unscheduled sacrifice animals: slight-moderate ↓ SOD, TP, CREAT, pronounced ↓ ALB, slight ↑ POT, glucose, pronounced ↑ CHOL, TRI, BUN, TBI, AST, ALT, ALP, and moderate ↑ INP.	[redacted] 4.2.3.1.3

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphate, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHL = chloride, CHOL = cholesterol, CREAT = creatinine, EOSIN = eosinophils, HCT = hematocrit, HGB = hemoglobin, INP = inorganic phosphate, LYMPH = lymphocytes, MCH = mean cell hemoglobin, MCV = mean cell volume, MHC = mean hemoglobin concentration, MONO = monocytes, POT = potassium, RBC = red blood cells, RETIC = reticulocytes, SOD = sodium, TBI = total bilirubin, THROMB = thrombocytes, TP = total protein, TRI = triglyceride, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Day 4 post dosing (females): pronounced: ↓ WBC, EOSIN, RETIC, MONO, LYMPH, NEUT, THROMB, and BASO. Females not evaluated at study termination due to mortality. Slight-moderate ↓ TP, CREAT, CHOL, pronounced ↑ AST, ALT, ALP, TBI. BUN ↑ in one rat and ↓ in two rats. Females not evaluated at study termination due to mortality. Gross pathology changes included: cachexia, dehydration, swollen liver and adrenal glands, bloody content of large intestine, thin wall of small intestine, changes in the stomach, yellow subcutis. In addition a few rats exhibited crusty nose, pale liver, hemorrhagic adrenal glands and large intestine, dilated small intestine with watery content. Microscopically bone marrow depletion, liver necrosis and other liver findings indicative of liver toxicity were observed as well as intestinal epithelial atrophy and ulcerations. The intestinal lesions were considered the primary cause of mortality. In summary: Maximum Tolerated Dose – Males: 450 µg/m^2 Females: 300 µg/m^2	[redacted] 4.2.3.1.3

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphate, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHL = chloride, CHOL = cholesterol, CREAT = creatinine, EOSIN = eosinophils, LYMPH = lymphocytes, MONO = monocytes, NEUT = neutrophils, POT = potassium, RETIC = reticulocytes, SOD = sodium, TBI = total bilirubin, THROMB = thrombocytes, TP = total protein, WBC = white blood cells

2.6.7.5　単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses $\mu g/m^2$ (μg/kg)	Observed Maximum Non-Lethal Dose $\mu g/m^2$ (μg/kg)	Approximate Lethal Dose $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat/ Sprague-Dawley Male and Female, 10/sex/group Duration of treatment: Group 1 – 3 hrs Group 2 – 24 hrs Group 3 – 3 hrs Group 4 – 24 hrs Group 5 – 3 hrs 5/sex/group sacrificed 3 days post dosing; 5/sex/group were allowed a three-week recovery period post dosing.	Intravenous Infusion (Sterile water - saline/ R279741-plus vehicle or Sterile water - saline/R279741 and 不純物 B* (impurity) plus vehicle)	Group 1 0 (vehicle control) Group 2 0 (vehicle control) Group 3 300 (50) R279741 Group 4 300 (50) R279741 Group 5 291 (48.5)/ 9 (1.5) R279741/ 不純物 B* (impurity)	300 (50) R279741 291 (48.5)/ 9 (1.5) R279741/ 不純物 B* (impurity)	>300 (50)g R279741 >291 (48.5)/ 9 (1.5) R279741/ 不純物 B* (impurity)	<u>*Summary*</u> Single dose intravenous administration of R279741 by 3-hour infusion might be more toxic than by 24-hour infusion as suggested by the depletion of bone marrow cellularity. No clear differences in toxicity were observed between R279741 and R310330 plus the impurity 不純物 B* when administered as a three-hour infusion. 0 $\mu g/m^2$/cycle - 3 hour infusion: Males: No noteworthy findings. Females: No noteworthy findings. 0 $\mu g/m^2$/cycle - 24 hour infusion: Males: No noteworthy findings. Females: No noteworthy findings. 300 $\mu g/m^2$/cycle R279741 - 3 hour infusion: Males: Slight ↓ body weight, body weight gain and food consumption during week 1. *Post Dosing Hematology*: Slight ↓ HCT, moderate ↓ WBC, pronounced ↓ RETIC, slight ↓ BASO, moderate ↓ LYMPH, marginal ↓ EOSIN, moderate ↓ MONO. *End of Recovery Hematology:* marginal ↓ RBC, slight ↓ WBC, slight ↑ RETIC, MCV, slight ↓ BASO and LYMPH. *Post Dosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate, total protein and creatinine. *End of Recovery Clinical Chemistry:* No noteworthy findings. No noteworthy macroscopic findings.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, BASO = basophils, EOSIN = eosinophils, HCT = hematocrit, LYMPH = lymphocytes, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETIC = reticulocytes, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Females: Dark urine noted in 6 of 10 prior to interim kill and in 3 of 5 recovery animals. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week post dosing, by end of second week ↓ was slight. *Post Dosing Hematology*: Slight ↓ THROM, pronounced ↓ RETIC, slight ↓ LYMPH, BASO and EOSIN. *End of Recovery Hematology:*Moderate ↓ HCT, HGB, RBC, moderate ↑ THROM, MCV, MCH, slight ↓ MCHC, pronounced ↑ RETIC, slight ↑ MONO. *Post Dosing Clinical Chemistry:* Slight ↑ CA, moderate ↓ chloride, ALB, pronounced ↑ GGT, ALP, AST, ALT, TBI, CHOL, TRI. *End of Recovery Clinical Chemistry:* Slight ↑ CA, marginal ↑ BUN, pronounced ↑ GGT, TBI, CHOL, TRI, moderate ↑ ALT, ALP, AST. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen and thymus weight observed 3 days post dosing. Following 3 weeks recovery liver weight increase more pronounced and spleen weight slightly increased. Slight ↑ in absolute and relative weight of the pancreas and kidneys observed at end of recovery only. *Post Dosing Macroscopic Pathology:* General anemia, yellow abdominal mesothelium, yellow subcutis, pale liver, swollen liver, hemorrhagic stomach content, a dark focus on the stomach, yellow urinary bladder content. *Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale/yellow-stippled liver, swollen liver and pancreas, yellow tissue mass at dose site and swollen spleen. 300 µg/m^2/cycle R279741- 24 hour infusion: Males: Slight-moderate ↓ body weight, body weight gain and food consumption during week 1. *Post Dosing Hematology:* Marginal ↓ RBC, slight ↓ HCT, WBC, BASO, LYMPH, pronounced ↓ RETIC. *End of Recovery Hematology:* Slight ↓ RBC, slight ↑ RETIC and MCV. *Post Dosing Clinical Chemistry:* Slight ↓ CA, IP, TP, ALB. *End of Recovery Clinical Chemistry:* Slight ↑ CA, IP. No noteworthy macroscopic findings.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CA = calcium, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, IP = inorganic phosphorous, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, THROM = thrombocytes, TP = total protein, TRI = triglycerides, WBC = white blood cells

2.6.7.5　単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses $\mu g/m^2$ (μg/kg)	Observed Maximum Non-Lethal Dose $\mu g/m^2$ (μg/kg)	Approximate Lethal Dose $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Females: Dark urine noted in 5 of 10 prior to interim kill and in 2 of 5 recovery animals. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week post dosing, by end of second week ↓ was slight. *Post Dosing Hematology:* Pronounced ↓ RETIC, slight ↓ BASO. *End of Recovery Hematology:* Pronounced ↑ RETIC, moderate ↓ HCT, HGB and RBC. Moderate ↑ THROM, MCV, MCH, slight ↑ MONO. *Post Dosing Clinical Chemistry:* Moderate↓ chloride, ALB, slight ↑ calcium, pronounced ↑ CHOL, TRI, TBI, GGT, ALT, moderate ↑ ALP, AST, marginal ↓ BUN. *End of Recovery Clinical Chemistry:* Slight ↑ calcium, potassium, pronounced ↑ CHOL, TRI, GGT, moderate ↑ ALT, ALP, AST, TBI, marginal ↑ BUN. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen weight observed 3 days post dosing. Following 3 weeks recovery liver weight increase more pronounced and spleen weight slightly increased. Slight ↑ in absolute and relative weight of the pancreas and kidneys observed at end of recovery only. *Post Dosing Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, more pronounced liver lobulation, and swollen liver. *Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale liver, swollen liver, swollen pancreas and swollen spleen. 291 $\mu g/m^2$/9 $\mu g/m^2$/cycle R279741/ 不純物 B* (impurity) - 3 hour infusion: Males: Slight-moderate ↓ body weight, body weight gain and food consumption during week 1. *Post Dosing Hematology:* Moderate ↓ WBC, pronounced ↓ RETIC, slight ↓ LYMPH, MONO, marginal ↓ BASO and EOSIN. *End of Recovery Hematology:* Marginal ↓ RBC, slight ↓ WBC, slight ↑ RETIC and MCV. *Post Dosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate, TP, creatinine. *End of Recovery Clinical Chemistry:* No significant findings. No noteworthy macroscopic findings.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, THROM = thrombocytes, TP = total protein, TRI = triglycerides, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Females: Dark urine noted in 6 of 10 prior to interim kill and in 3 of 5 recovery animals. Feed wastage noted in 2 of 5 during recovery. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week post dosing, by end of second week ↓ was slight. *Post Dosing Hematology:* Slight ↓ LYMPH, BASO and EOSIN. Pronounced ↓ RETIC. *End of Recovery Hematology:* Slight ↓ MCHC, moderate ↓ HCT, HGB, RBC, moderate ↑ THROM, RETIC, MCV, MCH. *Post Dosing Clinical Chemistry:* Moderate↓ chloride, ALB, slight ↑ calcium, pronounced ↑ CHOL, TRI, TBI, GGT, ALT, moderate ↑ ALP, AST, marginal ↓ BUN. *End of Recovery Clinical Chemistry:* Slight ↑ calcium, pronounced ↑ GGT, CHOL, moderate ↑ TRI, TBI, ALP, AST, ALT, marginal ↑ BUN. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen and thymus weight observed 3 days post dosing. Following 3 weeks recovery liver weight increase moderate and spleen weight slightly increased. Slight ↑ in absolute and relative weight of the pancreas and kidneys observed at end of recovery only. *Post Dosing Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, , more pronounced liver lobulation, swollen liver, dilated stomach, yellow urinary bladder content. *Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale liver, swollen liver, swollen pancreas, swollen spleen. *Histopathology Findings (All Treated Groups):* *Administration Sites*: Irritation, some with necrosis of the vessel wall, especially in animals killed after dosing. *Bone Marrow:* Decreased cellularity, especially after 3 hour infusion. Recovery almost complete after the recovery period. *Gastrointestinal Tract:* Single cell necrosis of epithelial crypt cells of the rectum, glandular stomach, small and/or large intestine present in most males and females killed after dosing. No gastrointestinal effects observed following recovery. *Pancreas:* Male groups after dosing exhibited increased minimal pancreatic acinar single cell necrosis. In female recovery groups the presence of intracytoplasmatic zymogen in the pancreatic acinar cells was minimally augmented.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean cell volume, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, THROM = thrombocytes, TRI = triglycerides

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					Histopathology Findings (All Treated Female Groups): *Liver*: Moderate hepatotoxicity in females killed after dosing characterized by: swelling of hepatocytes, hepatocellular necrosis, proliferative/inflammatory and epithelial changes of bile ducts and Kupffer cell proliferation. Following recovery, a moderate diffuse chronic hepatotoxicity characterized by diffuse chronic inflammation, pigmentation of sinusoidal lining cells, proliferative and epithelial changes of bile ducts and hepatocellular necrosis. *Kidney*: In female recovery groups, clear vacuolization with pigmentation of the renal corticotubular cytoplasm. *Spleen*: In female recovery groups, splenic hyperplastic changes increased with more prominent erythropoiesis and granulopoiesis, probably related to the primary hepatotoxic inflammatory changes and as a regenerative hematopoietic impulse during the recovery period.	[redacted] 4.2.3.1.4

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
Dog/Beagle Male and Female 2/sex/group Single bolus injection, 8 and 29 day recovery periods	Intravenous injection (0.05 mol/L potassium phosphate buffer (pH 4.0)/R279741 plus vehicle	0 200 (10) 540 (27) 700 (35)	700 (35)	>700 (35)	0 µg/m^2: Body weight gain between Days 1 and 8 was 0 to 2%. All survivors gained weight between Day 11 and 29. 200 µg/m^2: Body weight gain between Days 1 and 8 was -3 to 4%. All survivors gained weight between Day 11 and 29. Food consumption ↓ Days 1-3, returned to predose level by Day 4. Mild ↓ RBC in males on Day 8, recovered by Day 22. ↓ RETIC by Day 4, returned to normal by Day 15 or 22. ALT ↑ 5-fold in one female on Day 4. 540 µg/m^2: One male vomited on Day 2 (6 hours postdose). Body weight gain between Days 1 and 8 was -5 to -1%. All survivors gained weight between Day 11 and 29. The female had an overall weight loss of 2%. Food consumption ↓ Days 1-3, returned to predose level by Day 4. Mild ↓ RBC in both males and in one female on Day 8, recovered by Day 22. Mild ↓ HGB and HCT on Day 8, recovered by Day 15 or 22. ↓ RETIC on Day 4, returned to normal by Day 15 or 22. ↓ PLAT in one male (35%) and one female (61%) on Day 8, returned to normal by Day 15. WBC ↓ in one male (36%, Day 4) and one female (40% Day 4 and 8). ANS ↓ 36% and 45% in one male and one female on Day 4. ALT ↑ 14-56-fold in two males and 24-fold in one female, values generally peaked on Day 4 or 8 and recovered. AST ↑ 11-fold in one male (Day 4) and 3-fold in one female (Day 8) and recovered by the next interval. ALP ↑ 2-7-fold in two males and 4-fold in one female, values generally peaked on Day 8 or 15 and recovered. At necropsy the liver of one female was mottled, yellow-tan with a prominent centrilobular pattern. Microscopic findings, considered treatment related on Day 8 in males and females, were observed in the liver (mild acute cholangitis), gallbladder (moderate chronic cholecystitis), sternal bone marrow (depletion), and pancreas (mild to moderate increase in apoptosis and acinar cell atrophy). At Day 29 only liver and gallbladder effects were still evident in the males and females. The gallbladder effects were either absent or reduced in severity at Day 29 suggesting reversibility.	[redacted] 4.2.3.1.6

↑ = increase, ↓ = decrease, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANS = absolute segmented neutrophils, AST = aspartate aminotransferase, HCT = hematocrit, HGB = hemoglobin, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, WBC = white blood cells

2.6.7.5 単回投与毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Doses µg/m^2 (µg/kg)	Observed Maximum Non-Lethal Dose µg/m^2 (µg/kg)	Approximate Lethal Dose µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
					700 µg/m^2: Two males and 1 female vomited on Day 1 (6 hours postdose) and/ or Day 2 (>24 hours postdose). Body weight gain between Days 1 and 8 was -12 to -4%. All survivors gained weight between Day 11 and 29. The female had an overall weight loss of 5%. Food consumption ↓ Days 1-3, returned to predose level by Day 5 (male) and Day 15 (female). Mild ↓ RBC in males and females on Day 8, recovered by Day 22. Mild ↓ HGB and HCT on Day 8, recovered by Day 15 or 22. ↓ RETIC by Day 4, returned to normal by Day 15 or 22. ↓ PLAT in males (53%) and females (57%) on Day 8 and Day 11 (89-93%), returned to normal by Day 15. WBC ↓ 68% in males and 41% in females on Day 8. ANS ↓ 89% and 73% in males and females on Day 8. ALT ↑ 105-85-fold in two males and 26 - 55-fold in two females, values generally peaked on Day 4 or 8 and recovered, one male did not completely recover. AST ↑ 6 and 12-fold in 2 males (Day 4 and 8) and 9-fold in 1 female (Day 4 and 8) and recovered by the next interval. ALP ↑ 13 - 15-fold in males and 7-51-fold in females, values generally peaked on Day 8 or 15 and recovered with the exception of 1 male dog in which ALP did not recover. At necropsy the liver of one male was mottled, yellow-tan with a prominent centrilobular pattern. Microscopic findings, considered treatment related on Day 8 in males and females, were observed in the liver (mild acute cholangitis), gallbladder (moderate chronic cholecystitis), sternal bone marrow (depletion), and pancreas (mild to moderate increase in apoptosis and acinar cell atrophy). At Day 29 only liver and gallbladder effects were still evident in the males and females. The gallbladder effects were either absent or reduced in severity at Day 29 suggesting reversibility. In summary: Maximum Tolerated Dose – Males and Females: 540 µg/m^2	[redacted] 4.2.3.1.6

↑ = increase, ↓ = decrease, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANS = absolute segmented neutrophils, AST = aspartate aminotransferase, HCT = hematocrit, HGB = hemoglobin, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, WBC = white blood cells

Test Article: R279741（Trabectedin）

2.6.7.6 反復投与毒性試験：重要な試験以外の試験

2.6.7.6.1 げっ歯類を用いた反復投与毒性試験

2.6.7.6.1.1 マウス 5 日間反復投与試験

Report Title: Five Daily Dose Toxicity Study of Ecteinascidin 743 (NSC-648766) in CD_2F_1 Mice **Test Article: R279741（Trabectedin）**

Species/Strain: Mouse/CD_2F_1 **Duration of Dosing:** 5 days **Study No.:** [redacted]

Age at First Dose: Males: 7 weeks; Females: 6 weeks **Duration of Recovery:** 17 days **Location in CTD:** 4.2.3.2.1

Date of First Dose: [redacted] **Route:** Intravenous Injection (bolus)

Vehicle/Formulation: 0.05 M potassium phosphate buffer solution, deionized water, pH 4/R279741 plus vehicle **GLP Compliance:** Yes

Special Features: None

No Observed Adverse Effect Level: <120 μg/m^2 (40 μg/kg)

DOSING PERIOD

Dose μg/m^2 (μg/kg)	**0 (Control)**		**120 (40)**		**180 (60)**		**240 (80)**	
No. of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Toxicokinetics[a]**:**								
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	1	0	2	0	1	1
Body Weight[b] (Day 5) (g)	23.2	19.3	1.00	0.96	0.94*	0.93*	0.91**	0.90**
Clinical Observations[c] (Immediately postdose)								
Ataxia	-	1/10	-	-	-	-	3/10	1/10
Prostration	-	1/10	1/10	-	4/10	2/10	3/10	2/10
Dyspnea	-	1/10	1/10	-	3/10	1/10	2/10	1/10
Convulsions	-	-	3/10	-	5/10	2/10	3/10	1/10

[a] Toxicokinetics not evaluated

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

[c] Number with finding/Number examined

- = no noteworthy findings

Note: Dose conversion to μg/m^2: multiply μg/kg by 3 for mice.

* p<0.05, ** - p<0.01 (Analysis of Variance, Dunnett's test)

2.6.7.6.1.1 マウス 5 日間反復投与試験（続き）

Report Title: Five Daily Dose Toxicity Study of Ecteinascidin 743 (NSC-648766) in CD_2F_1 Mice **Test Article: R279741（Trabectedin）**

DOSING PERIOD

Dose ug/m^2 (μg/kg)	**0 (Control)**		**120 (40)**		**180 (60)**		**240 (80)**	
No. of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Hematology[a] (Day 8)								
White blood cell count (×10^3/mm^3)	4.5	3.6	0.98	1.03	0.51**	0.89	0.69	0.81
Red blood cell count (×10^6/mm^3)	9.04	8.9	0.88**	0.84**	0.82**	0.80**	0.84**	0.82**
Hemoglobin (g/dl)	13.3	13.1	0.89**	0.82**	0.79**	0.78**	0.83**	0.80**
Hematocrit (%)	39.3	38.3	0.88**	0.85**	0.81**	0.80**	0.86**	0.83**
Reticulocyte count (%RBC)	2.2	2.5	0.36**	0.96	0.00**	0.44*	0.09**	0.00**
Neutrophils, segmented (mm^3)	1439	853	0.64	0.64	0.11**	0.64	0.20**	0.21
Eosinophils (mm^3)	127	76	0.00**	0.30	0.00**	0.12*	0.00**	0.00*
Serum Chemistry[a] (Day 8)	-	-	-	-	-	-	-	-
Gross Pathology (Day 8)	-	-	-	-	-	-	-	-
Number Examined	5	5	5	5	4	5	5	4
Histopathology (Day 8 and Early Deaths)								
Tissue Examined: Bone Marrow (femur)								
Number Examined	5	5	1	0	2	0	6	5
depletion	0	0	0		2		5	4
Score 2	“	“	“		0		1	0
Score 3	“	“	“		2		3	1
Score 4	“	“	“		0		1	3
hyperplasia	0	0	0		0		0	1
Score 4	“	“	“		“		“	1

[a] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

- = no noteworthy findings
* p<0.05, ** p<0.01 (Analysis of Variance, Dunnett’s test)
“ = finding not present, score not applicable

2.6.7.6.1.1 マウス５日間反復投与試験（続き）

Report Title: Five Daily Dose Toxicity Study of Ecteinascidin 743 (NSC-648766) in CD_2F_1 Mice **Test Article: R279741（Trabectedin）**

DOSING PERIOD

Dose ug/m^2 (μg/kg)	**0 (Control)**		**120 (40)**		**180 (60)**		**240 (80)**	
No. of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Histopathology (Day 8 and Early Deaths)								
Tissue Examined: Spleen								
Number Examined	5	5	1	0	2	0	6	5
depletion extramedullary hematopoietic cells	0	0	0		0		5	5
Score 1	“	“	“		“		1	0
Score 2	“	“	“		“		4	5
Tissue Examined: Liver								
Number Examined	5	5	1	0	2	0	6	5
extramedullary hematopoiesis	3	5	1		2		1	3
Score 1	3	5	1		2		1	3

“ = finding not present, score not applicable

2.6.7.6.1.1 マウス５日間反復投与試験（続き）

Report Title: Five Daily Dose Toxicity Study of Ecteinascidin 743 (NSC-648766) in CD_2F_1 Mice **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD

Dose ug/m^2 (μg/kg)	**0 (Control)**		**120 (40)**		**180 (60)**		**240 (80)**	
No. of Animals	M:5	F:5	M:5	F:5	M:5	F:5	M:5	F:5
Noteworthy Findings During Recovery								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight[a] (Day 22**)** (g)	25.0	21.1	0.99	0.98	0.99	0.97	1.0	0.89*
Clinical Observations[b]								
edema- tail	-	-	3/4	2/5	2/4	5/5	4/4	5/5
lesion-tail	-	-	1/4	2/5	1/4	2/5	3/4	5/5
erythema-tail	-	-	1/4	2/5	2/4	5/5	3/4	5/5
necrosis-tail	-	-	-	-	-	-	-	4/5
hunched posture	-	-	-	-	-	-	-	3/5
Hemotalogy[a] (Day 22)								
White blood cell count (×10^3/mm^3)	5.2	3.9	0.94	1.67	1.40	1.82	1.33	2.38*
Reticulocyte count (%RBC)	1.1	0.9	1.09	1.44	1.27	1.33	2.27	5.78**
Serum Chemistry[a] (Day 22)	-	-	-	-	-	-	-	-

[a] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).
[b] Number with finding/Number examined

- = no noteworthy findings
* p<0.05, ** p<0.01(Analysis of Variance, Dunnett's test)

2.6.7.6.1.1 マウス５日間反復投与試験（続き）

Report Title: Five Daily Dose Toxicity Study of Ecteinascidin 743 (NSC-648766) in CD_2F_1 Mice **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD

Dose ug/m^2 (μg/kg)	**0 (Control)**		**120 (40)**		**180 (60)**		**240 (80)**	
No. of Animals	M:5	F:5	M:5	F:5	M:5	F:5	M:5	F:5
Gross Pathology[a] (Day 22)								
Number Examined								
spleen moderately enlarged	0/5	0/5	1/4	0/5	1/4	1/5	0/4	4/5
Histopathology (Day 22)								
Tissue Examined: Bone Marrow (femur)								
Number Examined	5	5	0	0	0	0	4	5
hyperplasia	0	0					3	5
Score 4	“	“					3	5
Tissue Examined: Spleen								
Number Examined	5	5	0	0	0	0	4	5
hyperplasia extramedullary hematopoietic cells	0	0					4	5
Score 4	“	“					4	5
Tissue Examined: Liver								
Number Examined	5	5	0	0	0	0	4	5
extramedullary hematopoiesis	3	3					2	3
Score 1	3	3					2	3

[a] Number with finding/Number examined

“ = finding not present, score not applicable

2.6.7.6.2 非げっ歯類を用いた反復投与毒性試験

2.6.7.6.2.1 イヌ 5 日間反復投与試験

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

Species/Strain: Dog/Beagle
Duration of Dosing: The animals were administered five consecutive daily intravenous bolus injections. Groups of four animals (2/sex/group) were administered the test article at 100 (5), 160 (8) or 220 (11) μg/m^2 (μg/kg).
Study No.: [redacted]
Age at First Dose: Approximately 8-9 months of age
Duration of Recovery: One animal/sex/group was sacrificed on Day 11 (recovery Day 6) and the remaining animals (1/sex/group) were sacrificed on Day 36 (recovery Day 31).
Location in CTD: 4.2.3.2.4
Date of First Dose: [redacted]
Route: Intravenous Injection (bolus)
Vehicle/Formulation: Sterile potassium phosphate buffer/ R279741 plus vehicle
GLP Compliance: No
Special Features: None
No Observed Adverse Effect Level: <100 μg/m^2 (5 μg/kg)

DOSING PERIOD

Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Toxicokinetics[a]								
Noteworthy Findings								
Body Weight[b] **(kg)**								
Day 1	11.7	9.5	0.94	1.04	1.05	1.01	1.02	0.96
Day 4	11.6	9.3	0.94	1.04	1.04	1.02	0.97	0.95
Food Consumption[b] **(g)**								
Day 1	400	324	1.00	1.23	1.00	1.23	1.00	0.90
Day 2	400	349	0.90	1.08	1.00	1.14	1.00	0.58
Day 5	400	349	0.91	0.96	0.57	0.91	0.71	0.21
Rectal Body Temperature (°F)	-	-	-	-	-	-	-	-

[a] Companion toxicokinetics report (Study No. [redacted]). Most samples were below the lower limit of quantification (<1 ng/mL); analytical method not sensitive enough to quantify the amount of drug in sample.

[b] For controls, group means are shown. For treated groups, multiples of controls are shown.

- No noteworthy findings

Note: Dose conversion to μg/m^2: multiply μg/kg by 20 for dogs.

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

DOSING AND RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F: 2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings During Dosing								
Clinical Observations[a]	-	-	-					
Foreleg swelling				1/2	1/2	1/2	1/2	
Foreleg alopecia				1/2	1/2	1/2	1/2	
Emesis					1/2		1/2	1/2
Diarrhea							1/2	1/2
Hematology[b]								
Day 3	-	-	-	-	-	-	-	-
Clinical Chemistry[b]								
Day 3								
Alanine aminotransferase (IU/L)	35.0	45.5	1.14	1.04	0.81	0.90	3.06	0.57
Aspartate aminotransferase (IU/L)	29.0	35.0	1.41	0.99	1.09	0.89	2.74	0.74
Total protein (g/dL)	5.9	5.8	1.01	0.97	0.97	0.95	0.92	0.97
Albumin (g/dL)	3.2	2.9	0.94	1.07	0.95	1.03	0.97	1.05
Albumin/Globulin ratio	1.17	1.02	0.87	1.24	0.98	1.18	1.13	1.15
Alkaline phosphatase (IU/L)	84.5	103.0	1.14	0.74	1.19	1.08	1.14	0.67
Gamma glutamyl transpeptidase (IU/L)	2.5	4.0	0.80	1.00	1.00	0.50	1.20	0.63
Cholesterol (mg/dL)	173.5	202.0	0.94	0.95	0.83	0.86	0.99	1.10
Noteworthy Findings During Recovery								
Body Weight[b] **(kg)**								
Day 11 (Recovery Day 6)	11.7	9.1	0.93	1.07	1.00	1.04	0.91	0.88
Day 35 (Recovery Day 30)	11.7	10.1	1.01	1.02	1.10	1.03	0.93	0.83
Food Consumption[b] **(g)**								
Day 9 (Recovery Day 4)	400	341	0.99	1.09	0.89	1.07	0.43	0.26
Day 35 (Recovery Day 30)	400	306	1.00	0.87	1.00	1.31	1.00	0.49

[a] Number with observation/Number observed

[b] For controls, group means are shown. For treated groups, multiples of controls are shown.

- No noteworthy findings

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5,		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Hematology[a]								
Day 8 (Recovery Day 3)								
White blood cell count (10^3/mm^3)	7.0	10.5	1.34	0.70	0.96	0.57	0.53	0.47
Mature Neutrophil count (10^3/mm^3)	4.6	6.7	1.35	0.73	1.17	0.58	0.48	0.37
Lymphocyte count (10^3/mm^3)	1.9	3.2	1.34	0.56	0.63	0.55	0.74	0.72
Platelet Count (10^3/mm^3)	253	302	1.27	0.98	0.78	1.22	0.91	0.67
Day 11 (Recovery Day 6)								
White blood cell count (10^3/mm^3)	6.4	7.1	1.05	1.03	0.59	0.76	0.34	0.43
Mature Neutrophil count (10^3/mm^3)	4.4	4.2	0.91	1.02	0.45	0.71	0.13	0.27
Lymphocyte count (10^3/mm^3)	1.8	2.6	1.31	0.88	0.89	0.77	0.89	0.67
Platelet Count (10^3/mm^3)	265	304	1.00	0.98	0.47	0.99	0.38	0.31
Day 16 (Recovery Day 11)								
White blood cell count (10^3/mm^3)	6.7	8.5	1.06	0.89	1.18	0.96	0.39	0.71
Mature Neutrophil count (10^3/mm^3)	4.3	5.8	1.16	1.02	1.26	0.91	0.23	0.47
Lymphocyte count (10^3/mm^3)	2.1	2.3	0.95	0.65	0.90	1.22	0.76	1.35
Platelet Count (10^3/mm^3)	286	265	0.78	1.09	0.80	0.94	0.07	0.67
Days 22 (Recovery Day 17)								
White blood cell count (10^3/mm^3)	6.3	9.0	1.35	0.72	0.90	0.76	0.81	0.67
Mature Neutrophil count (10^3/mm^3)	4.3	5.0	1.28	0.98	0.58	0.86	0.79	0.70
Lymphocyte count (10^3/mm^3)	1.8	3.5	1.39	0.46	1.67	0.69	0.83	0.63
Platelet Count (10^3/mm^3)	263	290	1.53	1.02	1.62	1.66	0.90	1.47

[a] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Hematology[a]								
Days 29 (Recovery Day 24)								
White blood cell count (10^3/mm^3)	7.0	8.7	1.44	1.10	1.10	0.93	1.21	0.72
Mature Neutrophil count (10^3/mm^3)	3.7	4.6	1.65	1.30	1.14	1.26	1.78	0.78
Lymphocyte count (10^3/mm^3)	2.7	3.5	1.33	0.80	1.04	0.63	0.67	0.66
Platelet Count (10^3/mm^3)	218	218	1.54	1.30	1.51	1.97	1.92	1.34
Day 36 (Recovery Day 31)								
White blood cell count (10^3/mm^3)	7.7	9.2	1.14	0.74	0.91	0.86	1.18	0.74
Mature Neutrophil count (10^3/mm^3)	5.2	4.9	1.25	0.96	0.90	1.18	1.33	0.98
Lymphocyte count (10^3/mm^3)	1.9	3.9	0.95	0.44	1.05	0.44	1.00	0.51
Platelet Count (10^3/mm^3)	296	280	1.07	1.06	0.94	1.75	1.23	1.18

[a] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: **Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs** **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Clinical Chemistry[a]								
Day 8 (Recovery Day 3)								
Alanine aminotransferase (IU/L)	29.5	33.5	1.39	1.99	3.44	10.63	63.93	25.66
Aspartate aminotransferase (IU/L)	29.5	37.5	1.37	0.96	1.02	1.03	16.76	8.20
Total protein (g/dL)	6.4	6.3	0.95	1.01	0.95	0.94	0.87	0.80
Albumin (g/dL)	3.2	2.8	0.89	1.07	0.95	1.04	0.83	0.89
Albumin/Globulin ratio	0.97	0.80	0.91	1.13	1.03	1.21	0.94	1.23
Alkaline phosphatase (IU/L)	85.5	100.5	1.11	0.81	1.18	1.65	6.58	2.02
Gamma glutamyl transpeptidase (IU/L)	3.5	3.0	0.86	0.83	0.86	2.17	3.71	3.50
Cholesterol (mg/dL)	177.5	205.5	0.93	0.90	0.98	0.95	1.18	1.15
Day 11 (Recovery Day 6)								
Alanine aminotransferase (IU/L)	29.0	30.5	1.40	1.48	3.40	5.61	68.95	16.82
Aspartate aminotransferase (IU/L)	27.5	30.5	1.35	1.13	0.93	1.02	5.25	1.30
Total protein (g/dL)	6.3	6.2	1.01	1.04	1.00	1.00	0.90	0.86
Albumin (g/dL)	3.2	3.2	1.00	1.02	0.97	1.00	0.86	0.81
Albumin/Globulin ratio	1.01	1.06	1.00	0.96	0.96	1.01	0.94	0.90
Alkaline phosphatase (IU/L)	86.0	95.5	1.19	0.79	1.25	1.61	9.77	2.36
Gamma glutamyl transpeptidase (IU/L)	4.0	4.0	0.63	1.00	1.13	1.25	5.63	3.25
Cholesterol (mg/dL)	164.5	200.5	1.02	0.94	1.03	0.94	1.54	1.12
Day 16 (Recovery Day 11)								
Alanine aminotransferase (IU/L)	29.0	21.0	1.69	1.76	0.83	4.29	29.17	8.67
Aspartate aminotransferase (IU/L)	32.0	34.0	1.41	1.03	0.97	1.53	1.94	1.00
Total protein (g/dL)	5.7	5.6	1.00	1.11	1.04	1.02	0.98	1.02
Albumin (g/dL)	2.9	3.0	1.03	1.07	1.03	1.00	0.86	0.93
Albumin/Globulin ratio	1.04	1.15	1.07	0.93	0.99	0.97	0.78	0.84
Alkaline phosphatase (IU/L)	87.0	81.0	1.37	0.72	1.05	1.70	8.93	2.89
Gamma glutamyl transpeptidase (IU/L)	7.0	5.0	0.57	1.00	0.43	1.20	2.29	2.80
Cholesterol (mg/dL)	139.0	227.0	0.94	0.77	0.93	0.63	1.69	1.12

[a] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: **Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs** **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Clinical Chemistry(Cont.)[a]								
Days 22 (Recovery Day 17)								
Alanine aminotransferase (IU/L)	29.0	24.0	1.52	1.21	0.83	7.71	17.86	6.33
Aspartate aminotransferase (IU/L)	31.0	36.0	1.45	0.83	0.77	1.42	1.81	1.56
Total protein (g/dL)	5.9	5.7	1.00	1.00	1.02	1.02	0.95	1.00
Albumin (g/dL)	3.1	2.8	1.00	1.07	1.03	1.07	0.94	0.96
Albumin/Globulin ratio	1.11	0.97	1.00	1.14	1.03	1.10	0.96	0.93
Alkaline phosphatase (IU/L)	90.0	69.0	1.29	0.70	0.97	2.80	7.06	3.12
Gamma glutamyl transpeptidase (IU/L)	3.0	3.0	1.00	2.00	1.00	2.33	5.33	5.33
Cholesterol (mg/dL)	137.0	250.0	0.91	0.63	0.89	0.58	1.32	1.05
Days 29 (Recovery Day 24)								
Alanine aminotransferase (IU/L)	28.0	18.0	1.75	1.67	0.86	5.83	10.32	9.67
Aspartate aminotransferase (IU/L)	30.0	32.0	1.47	1.09	0.90	1.47	1.53	1.00
Total protein (g/dL)	6.0	6.0	1.02	1.02	1.05	1.00	1.02	1.02
Albumin (g/dL)	3.3	3.1	0.91	1.03	0.97	1.03	0.91	0.97
Albumin/Globulin ratio	1.22	1.07	0.80	1.03	0.84	1.07	0.80	0.91
Alkaline phosphatase (IU/L)	85.0	68.0	1.18	0.72	0.91	2.49	4.91	3.16
Gamma glutamyl transpeptidase (IU/L)	4.0	4.0	1.00	1.50	1.25	1.75	3.25	4.75
Cholesterol (mg/dL)	136.0	261.0	0.94	0.71	0.87	0.50	1.09	1.04

[a] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Clinical Chemistry (Cont.)[a]								
Day 36 (Recovery Day 31)								
Alanine aminotransferase (IU/L)	31.0	20.0	1.58	1.55	1.55	4.00	7.52	3.80
Aspartate aminotransferase (IU/L)	32.0	37.0	1.34	0.86	0.94	1.16	1.63	0.78
Total protein (g/dL)	6.2	6.0	1.08	1.08	1.03	1.03	1.00	1.05
Albumin (g/dL)	3.0	3.0	1.07	1.07	1.10	1.07	1.03	0.97
Albumin/Globulin ratio	0.94	1.00	0.97	0.97	1.13	1.07	1.06	0.85
Alkaline phosphatase (IU/L)	86.0	70.0	1.41	0.67	0.94	2.47	3.20	2.06
Gamma glutamyl transpeptidase (IU/L)	4.0	4.0	1.25	1.50	0.75	1.75	2.75	3.00
Cholesterol (mg/dL)	144.0	288.0	1.08	0.78	0.92	0.51	1.08	0.85
Gross Pathology[b]								
Injection Site	-	-	-					-
Alopecia				1/2	1/2		1/2	
Forearm enlarged						1/2	1/2	
Forearm thickened				1/2				
Histopathology (Recovery Day 6)								
Tissue Examined: Duodenum								
Number Examined	1	1	1	1	1	1	1	1
Abscess, crypt	0	0	1	1	0	0	1	0
Score 1	“	“	0	1	“	“	0	“
Score 2	“	“	1	0	“	“	1	“

[a] For controls, group means are shown. For treated groups, multiples of controls are shown.
[b] Number with observation/number observed

“ = finding not present, score not applicable
- No noteworthy findings

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: **Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs** **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 6) (C'ont)								
Tissue Examined: Kidney - Right	1	1	1	1	1	1	1	1
Number Examined	0	0	0	0	0	0	1	0
Pigment, brown, multifocal, medulla	“	“	“	“	“	“	1	“
Score 2								
Tissue Examined: Kidney - Left	1	1	1	1	1	1	1	1
Pigment, brown, multifocal, medulla	0	0	0	0	0	0	1	0
Score 1	“	“	“	“	“	“	1	“
Tissue Examined: Gall Bladder								
Number Examined	1	1	1	1	1	1	1	1
Subacute inflammation	0	0	0	0	1	1	1	1
Score 1	“	“	“	“	1	0	0	0
Score 2	“	“	“	“	0	1	0	1
Score 3	“	“	“	“	0	0	1	0
Edema	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	1

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 6) (Cont.)								
Tissue Examined: Ileum								
Number Examined	1	1	1	1	1	1	1	1
Necrosis, individual cell, crypt	0	0	0	0	0	1	0	1
Score 1	“	“	“	“	“	1	“	1
Tissue Examined: Liver								
Number Examined	1	1	1	1	1	1	1	1
Glycogen depletion	0	0	1	0	1	1	1	1
Score 1	“	“	0	“	0	1	0	1
Score 2	“	“	1	“	1	0	0	0
Score 3	“	“	0	“	0	0	1	0
Subacute periportal inflammation	0	0	0	0	1	1	1	1
Score 1	“	“	“	“	1	1	0	0
Score 2	“	“	“	“	0	0	1	1
Bile duct hyperplasia	0	0	1	0	1	0	1	0
Score 1	“	“	1	“	1	“	0	“
Score 2	“	“	0	“	0	“	1	“
Periportal edema	0	0	0	0	0	1	0	1
Score 1	“	“	“	“	“	1	“	1

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 6) (Cont.)								
Tissue Examined: Lymph Node, Bronchial								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	0	1	0	0	0	1	1
Score 1	“	“	1	“	“	“	0	0
Score 3	“	“	0	“	“	“	1	1
Hemorrhage	0	0	1	1	1	0	1	1
Score 1	“	“	0	1	0	“	0	0
Score 2	“	“	0	0	1	“	0	0
Score 3	“	“	1	0	0	“	1	1
Pigmentation, multifocal	0	0	0	0	0	0	0	1
Score 3	“	“	“	“	“	“	“	1
Tissue Examined: Lymph Node, Mandibular								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	0	1	1	0	1	1	1
Score 1	“	“	1	1	“	1	1	0
Score 2	“	“	0	0	“	0	0	1
Tissue Examined: Lymph Node, Mesenteric								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	0	1	0	0	0	1	1
Score 1	“	“	1	“	“	“	1	1

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: **Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs** **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 6) (Cont.)								
Tissue Examined: Lymph Node, Mesenteric								
Number Examined	1	1	1	1	1	1	1	1
Hemorrhage	0	0	0	0	0	0	0	1
Score 1	“	“	“	“	“	“	“	1
Tissue Examined: Bone Marrow (Rib)								
Number Examined	1	1	1	1	1	1	1	1
Depletion	0	0	1	0	1	1	1	1
Score 1	“	“	1	“	0	0	0	0
Score 2	“	“	0	“	0	1	0	0
Score 3	“	“	0	“	1	0	0	0
Score 4	“	“	0	“	0	0	1	1
Tissue Examined: Injection Site - Skin								
Number Examined	0	0	0	1	0	0	0	0
Hemorrhage				1				
Score 1				1				
Edema				1				
Score 3				1				
Tissue Examined: Skin - Elbow								
Number Examined	1	1	1	1	1	1	1	1
Hyperkeratosis	0	0	0	0	0	0	1	0
Score 2	“	“	“	“	“	“	1	“

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 6) (Cont.)								
Tissue Examined: Thymus								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	0	1	1	1	0	1	1
Score 1	“	“	1	0	1	“	0	0
Score 2	“	“	0	1	0	“	1	1
Hemorrhage, serosal	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	1
Histopathology (Recovery Day 31)								
Tissue Examined: Duodenum								
Number Examined	1	1	1	1	1	1	1	1
Abscess, crypt	0	0	0	1	0	0	0	0
Score 2	“	“	“	1	“	“	“	“
Tissue Examined: Kidney - Right								
Number Examined	1	1	1	1	1	1	1	1
Pigment, brown, multifocal, medulla	0	0	0	0	1	0	0	0
Score 1	“	“	“	“	1	“	“	“
Tissue Examined: Liver								
Number Examined	1	1	1	1	1	1	1	1
Subacute periportal inflammation	0	0	0	0	0	1	1	1
Score 1	“	“	“	“	“	1	1	1

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 31) (Cont.)								
Tissue Examined: Liver								
Number Examined	1	1	1	1	1	1	1	1
Bile duct hyperplasia	0	0	0	0	0	1	1	1
Score 1	“	“	“	“	“	1	1	1
Tissue Examined: Lymph Node, Bronchial								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	1	0	1	0	1	0	0
Score 2	“	0	“	1	“	1	“	“
Score 3	“	1	“	0	“	0	“	“
Tissue Examined: Lymph Node, Mesenteric								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	0	0	0	1	1	1	0
Score 1	“	“	“	“	1	1	0	“
Score 2	“	“	“	“	0	0	1	“
Hemorrhage	0	0	0	0	0	1	0	0
Score 1	“	“	“	“	“	1	“	“
Tissue Examined: Bone Marrow (Rib)								
Number Examined	1	1	1	1	1	1	1	1
Depletion	0	0	0	0	0	1	0	1
Score 1	“	“	“	“	“	1	“	1

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 31) (Cont.)								
Tissue Examined: Pancreas								
Number Examined	1	1	1	1	1	1	1	1
Atrophy, acinar	0	0	0	0	0	0	1	0
Score 2	“	“	“	“	“	“	1	“
Tissue Examined: Spleen								
Number Examined	1	1	1	1	1	1	1	1
Erythropoiesis	0	0	0	0	0	1	0	1
Score 1	“	“	“	“	“	1	“	1
Tissue Examined: Injection Site - Skin								
Number Examined	0	0	1	1	1	1	1	0
Hemorrhage			0	1	1	1	1	
Score 1			“	0	1	1	0	
Score 2			“	1	0	0	0	
Score 3			“	0	0	0	1	
Granulation Tissue				1	1	1	1	
Score 1				1	0	0	0	
Score 2				0	1	0	0	
Score 3				0	0	1	1	

“ = finding not present, score not applicable

2.6.7.6.2.1 イヌ 5 日間反復投与試験（続き）

Report Title: **Intravenous Toxicity Study of Ecteinascidin 743 (ET743) Administered for Five Consecutive Days in Beagle Dogs** **Test Article: R279741（Trabectedin）**

RECOVERY PERIOD								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		**100 (5)**		**160 (8)**		**220 (11)**	
Number of Days of Dosing	5		5		5		5	
Days of Treatment (Study Days)	1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5		1, 2, 3, 4, 5	
Number of Days of Recovery	6 and 31		6 and 31		6 and 31		6 and 31	
Sex: No. of Animals	M:2	F:2	M:2	F:2	M:2	F:2	M:2	F:2
Noteworthy Findings								
Histopathology (Recovery Day 31) (Cont.)								
Tissue Examined: Injection Site - Skin								
Number Examined	0	0	0	1	1	1	1	0
Inflammation, subacute, multifocal				0	1	1	1	
Score 1				“	1	0	0	
Score 2				“	0	0	0	
Score 3				“	0	1	1	
Edema				1	0	1	0	
Score 2				1	“	0	“	
Score 3				0	“	1	“	
Tissue Examined: Skin - Elbow								
Number Examined	1	1	1	1	1	1	1	1
Hyperkeratosis	0	0	0	0	1	0	1	0
Score 1	“	“	“	“	1	“	1	“
Tissue Examined: Thymus								
Number Examined	1	1	1	1	1	1	1	1
Lymphoid depletion	0	1	0	0	0	0	1	1
Score 1	“	1	“	“	“	“	0	1
Score 2	“	0	“	“	“	“	1	0

“ = finding not present, score not applicable

2.6.7.7 反復投与毒性試験：重要な試験

2.6.7.7.1 げっ歯類を用いた反復投与毒性試験

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

Species/Strain: Rat/ Sprague-Dawley
Duration of Dosing: Three infusion cycles, each cycle consisting of one 3-hour infusion followed by a 3-week treatment-free period. Treatment was administered as follows: Cycle 1 on Test Day 0; Cycle 2 on Test Day 21; Cycle 3 on Test Day 42.
Study No.: [redacted]
Age at First Dose: 10 weeks of age
Duration of Treatment-Free/Recovery: Each three-week cycle included one 3-hour infusion followed by a three-week treatment-free period. The last cycle was followed by a 3-day (5/sex/group) and a 3-week (5/sex/group) recovery period.
Location in CTD: 4.2.3.2.2
Date of First Dose: Males: [redacted], Females: [redacted]
Route: Intravenous Infusion
Vehicle/Formulation: Water for injection and sterile isotonic saline/ R279741 diluted with water and further diluted as necessary with saline
GLP Compliance: Yes
Special Features: Infusion line adsorption tests performed prior to study start indicated adsorption to the infusion line at the lowest dose and concentration ranges.
No Observed Adverse Effect Level: Females: <15 μg/m^2 (2.5 μg/kg)/cycle, Males: <60 μg/m^2 (10 μg/kg)/cycle

DOSING AND TREATMENT-FREE/RECOVERY PERIODS

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Number of Days of Recovery Following Last Infusion Cycle	3 Days (5/sex/group); 21 Days (5/sex/group)		3 Days (5 females); 21 Days (5 females)	3 Days (5/sex); 21 Days (5/sex)		3 Days (5/sex); 21 Days (5/sex)		3 Days (5/sex); 21 Days (5/sex)		3 Days (5 males); 21 Days (5 males)
Dose/infusion or cycle (μg/kg)	**0**[a]	**0**	**2.5**	**10**	**10**	**25**	**25**	**50**	**50**	**75**
Dose/infusion or cycle (μg/m^2)	**0**[a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Toxicokinetics[b]**:**										
C_{max} (ng/mL) 1st Cycle			0.15	0.95	0.48	0.81	0.48	1.63	1.30	2.00
C_{max} (ng/mL) 3rd Cycle			/	0.35	0.30	1.25	1.01	1.92	1.29	/
T_{max} (h) 1st Cycle			3.2	3.2	3.0	2.7	2.5	0.65	2.5	2.7
T_{max} (h) 3rd Cycle			/	2.7	2.6	3.2	3.1	0.73	3.1	/
AUC (ng.h/mL) 1st Cycle[c]			/	0.91	0.63	2.15	1.23	4.76	3.30	5.97
AUC (ng.h/mL) 3rd Cycle[c]			/	0.64	0.74	2.21	2.15	7.43	8.55	/

[a] Control animals received the vehicle
[b] Toxicokinetics Report [redacted], blood samples were taken from satellite animals (alternate sampling from two animals/sex for samples taken through 24 h after the first infusion; all four animals were sampled at other sampling times). Pharmacokinetic parameters were calculated on the mean values per time point/sex/infusion cycle/dose group.
[c] AUC_{0-t} calculated on times zero up to and including the last concentration above the LLOQ (Lower Limit of Quantitation)

Note: Dose conversion to μg/m^2: multiply μg/kg by 6 for rats.
/ = Could not be calculated or no sample

2.6.7.7.1.1 ラット３週間ごと１回（３サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3)
Cycle 3 Followed by 3 Day and 3 Week Recovery Periods

Group	**1**	**2**	**3**	**4**	**5**	**6**
Number of Doses Administered	3	3	3	3	3	3
Days of Treatment (Study Day)	Days 0, 21 and 42	Days 0, 21 and 42	Days 0, 21 and 42	Days 0, 21 and 42	Days 0, 21 and 42	Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Died or Sacrificed Moribund	0	0	0	0	0	0	0	1	8	7
Day of Death (Found dead/Moribund Sacrifice)								52	30, 32, 32, 33, 35, 39, 48, 49	7, 7, 10, 10, 10, 10, 54
Number Killed at Scheduled Sacrifice										
Day 45	5	5	5	5	5	5	5	5	1	2
Day 63	5	5	5	5	5	5	5	4	1	1
Body weight (g) [b]										
Cycle 1 (Post Dosing Day 6)	377	252	0.98	1.00	0.99	0.97	0.92**	0.92**	0.88***	0.76***
Cycle 1 (Post Dosing Day 20)	424	278	0.97	0.98	0.99	0.97	0.93*	0.94	0.94	0.95
Cycle 2 (Post Dosing Day 27)	447	289	0.97	0.94	0.97	0.95	0.88***	0.83***	0.72***	0.73**
Cycle 2 (Post Dosing Day 41)	486	306	0.97	0.95	0.97	0.95	0.93	0.88**	0.86**	0.85**
Cycle 3 (Post Dosing Day 44)	485	311	0.96	0.94	0.96	0.93	0.88**	0.84***	0.76**	0.80**
Cycle 3 (Post Dosing Day 55)	491	313	0.95	1.01	1.00	0.94	0.90*	0.84*	0.73	0.86

[a] Control animals received the vehicle

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p<0.05, ** = p<0.01, *** = p<0.001 (Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3)
Cycle 3 Followed by 3 Day and 3 Week Recovery Periods

Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Food Consumption (g) [b]										
Cycle 1 (Post Dosing Day 7)	184	155	0.97	1.02	0.95	0.89**	0.80***	0.81***	0.54***	0.34***
Cycle 1 (Post Dosing Day 21)	199	177	0.95	0.99	0.94	0.97	0.86*	1.02	0.98	1.08
Cycle 2 (Post Dosing Day 28)	185	169	0.88	0.88**	0.88	0.85***	0.59***	0.54***	0.35***	0.25**
Cycle 2 (Post Dosing Day 42)	194	156	1.04	1.00	1.04	0.93*	0.93	1.01	1.00	1.12
Cycle 3 (Post Dosing Day 49)	154	129	1.00	0.97	0.99	0.82*	0.67*	0.53**	0.76	0.56
Cycle 3 (Post Dosing Day 56)	196	152	1.13	0.98	1.08	0.90	0.88	0.83	0.83	1.06
Ophthalmology										
Day 42	-	-	NA	NA	NA	NA	NA	NA	-	-
Day 59 - 62	-	-	NA	NA	NA	NA	-	-	-	-
Clinical Observations [b]										
Day 1 to Day 45										
Anemia	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	6/10*	6/10*
Hypothermia	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	3/10
Rough Haircoat	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	5/10*
Nasal Discharge	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	2/10	5/10*
Feces, Soft	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	1/10	10/10***
Feces, Bloody	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	2/10
Feces, Small Amount	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	3/10	1/10
Urine Dark	0/10	0/10	0/10	0/10	0/10	0/10	2/10	2/10	10/10***	5/10*
Hyperactive to Touch	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	1/10	3/10
Bad Condition	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	1/10
Waste of Food	0/10	2/10	1/10	0/10	0/10	0/10	1/10	1/10	6/10	2/10
Wet Urogenital Region	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	3/10	0/10
Thin	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	5/10*	3/10
Day 43 to Day 63										
Urine Dark	0/5	0/10	0/10	0/5	0/10	0/5	2/10	3/5	4/4***	0/2
Waste of Food	0/5	1/10	1/10	0/5	0/10	0/5	0/10	1/5	3/4*	1/2

[a] Control animals received the vehicle

[b] Number with observation/Number examined

- = No noteworthy findings; NA = not applicable; * = p<0.05, ** = p<0.01, *** = p<0.001 (Food Consumption: Mann-Whitney U test, two tailed; Clinical Observations: Fisher Exact test)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Hematology [b]										
Week 2										
Hct (%)	50.7	47.1	0.98	1.00	0.98	0.97	0.93**	0.90***	0.71***	0.79**
Hgb (g/dl)	16.3	16.0	0.99	0.99	0.99	0.96*	0.93*	0.90***	0.69***	0.79**
RBC (10^6/mm^3)	8.49	8.10	0.98	1.01	0.98	0.98	0.93*	0.89**	0.71***	0.76**
WBC (1000/mm^3)	13.61	17.65	0.81	1.06	0.82	1.09	0.76*	0.87	0.77	0.61**
Reticulocytes (%)	2.6	2.5	1.12	0.85*	0.92	0.81**	1.68*	2.08*	3.92**	3.35**
Eosinophils (1000/mm^3)	0.14	0.18	0.94	1.21	1.06	0.79	0.78	0.57*	0.17***	0.50*
Basophils (1000/mm^3)	0.03	0.04	0.75	0.67	0.75	1.00	0.50	0.67*	0.50*	0.33*
Lymphocytes (1000/mm^3)	10.85	13.41	0.87	1.04	0.89	1.08	0.73*	0.80*	0.68**	0.50**
Thrombocytes (1000/mm^3)	1287	1421	1.03	0.88*	1.00	0.87*	1.06	1.05	0.76*	1.01
Week 7										
Hct (%)	50.8	48.0	0.88***	0.89**	0.99	0.94*	0.83***	0.81***	0.76**	0.84**
Hgb (g/dl)	16.7	16.9	0.85***	0.86***	0.98	0.93**	0.79***	0.80***	0.73**	0.80**
RBC (10^6/mm^3)	8.74	8.25	0.91***	0.91	0.98	0.93*	0.82***	0.72***	0.55**	0.64**
WBC (1000/mm^3)	10.92	9.87	1.28*	1.61**	1.20	1.03	1.55	0.99	0.42**	0.67
Reticulocytes (%)	2.2	1.8	1.61**	1.41*	0.83	0.41***	1.22	0.64**	1.06	0.5
Mean Cell Volume (fl)	58.2	58.2	0.97*	0.98	1.01	1.01	1.02	1.14***	1.43**	1.31**
Mean Cell Hemoglobin (pg)	19.1	20.5	0.94**	0.95*	0.99	1.00	0.97	1.13**	1.37**	1.26**
Mean Cell Hemoglobin Conc (g/dl)	32.9	35.3	0.97**	0.97*	0.99	0.99	0.95***	0.99	0.96*	0.96
Neutrophils (1000/mm^3)	2.10	1.46	2.87**	3.39**	1.81	1.44	4.93***	2.87	1.08	1.73
Eosinophils (1000/mm^3)	0.19	0.16	0.50**	0.74	1.38	0.53*	0.81	0.37**	0.12**	0.16**
Basophils (1000/mm^3)	0.02	0.02	1.00	1.00	0.50	1.00	0.50	0.50**	0.00**	0.50*
Lymphocytes (1000/mm^3)	8.30	7.91	0.98	1.15	1.07	0.92	0.90	0.52***	0.31**	0.42**
Monocytes (1000/mm^3)	0.30	0.32	1.75*	2.57***	1.66*	1.33	2.69	1.40	0.44**	0.83
Thrombocytes (1000/mm^3)	1112	1167	0.87*	0.83*	1.01	1.00	0.86	0.83	0.68	0.84

[a] Control animals received the vehicle

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p< 0.05, ** = p<0.01, *** = p<0.001 (Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Hematology[b] **(Cont)**										
Week 9										
Hct (%)	48.3	46.7	0.97	0.98	1.00	0.94	0.91*	0.85	0.86	0.77
Hgb (g/dl)	15.7	15.5	0.93*	0.92	0.99	0.90*	0.85*	0.82	0.76	0.72
RBC (10^6/mm^3)	8.45	8.10	0.97	0.98	0.97	0.91*	0.84*	0.72*	0.51	0.58
WBC (1000/mm^3)	11.11	11.15	1.17	1.64*	0.81	1.31*	1.63*	1.28	0.74	1.08
Reticulocytes (%)	2.2	1.9	1.37	1.50*	1.05	1.64*	2.53*	3.73	21.68	6.27
Mean Cell Volume (fl)	57.1	57.7	1.00	1.01	1.03	1.02	1.07*	1.21*	1.66	1.34
Mean Cell Hemoglobin (pg)	18.6	19.1	0.96	0.94	1.02	0.98	1.00	1.17	1.48	1.25
Mean Cell Hemoglobin Conc (g/dl)	32.7	33.1	0.95**	0.93**	0.99	0.96	0.94*	0.96	0.89	0.93
Neutrophils (1000/mm^3)	1.92	1.32	4.38	4.36*	1.21	1.84*	8.54*	3.94*	3.20	3.05
Eosinophils (1000/mm^3)	0.16	0.21	0.57	0.50	0.81	0.75	1.67	0.69	0.38	0.25
Basophils (1000/mm^3)	0.02	0.02	1.00	1.50	0.50*	1.50	0.00*	1.00	0.00	1.00
Lymphocytes (1000/mm^3)	8.65	9.15	0.72	1.05	0.75	1.20	0.64	0.68	0.39	0.61
Monocytes (1000/mm^3)	0.34	0.44	1.18	2.03	0.89	1.50	1.68	1.79	0.93	2.47
Thrombocytes (1000/mm^3)	1180	1225	0.91	0.89	1.05	1.15	1.14	1.08	1.14	1.79

[a] Control animals received the vehicle

[b] For controls, group means are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p<0.05, ** = p<0.01, *** = p<0.001 (Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Clinical Chemistry [b]										
Week 2										
Calcium (mg/dl)	10.5	10.2	1.01	0.99	1.02	1.02	1.06***	1.04*	1.12***	1.05**
Inorganic Phosphate (mg/dl)	9.2	8.5	1.00	0.96	0.96	0.99	0.92	0.97	0.95	0.92*
Albumin (g/dl)	4.4	4.5	0.98	0.95	1.00	1.00	1.00	0.95	0.87**	0.98
Glucose (mg/dl)	74	77	1.08	0.97	1.09	1.04	1.08	1.14**	1.22***	1.23*
Cholesterol (mg/dl)	60	83	0.92	1.03	0.95	1.17	1.59**	1.85***	2.45***	2.23**
Triglycerides (mg/dl)	66	47	1.02	0.88	0.98	1.20	1.26	0.94	3.21***	0.91
Blood Urea Nitrogen (mg/dl)	16.5	17.7	1.06	0.98	1.02	1.01	1.01	1.12	1.23**	0.98
Total Bilirubin (mg/dl)	0.16	0.18	1.00	0.94	1.00	0.94	2.78*	5.75***	24.11***	4.13**
Alkaline Phosphatase (U/l)	167	134	0.89	0.93	0.84	0.92	0.95	1.08	1.41*	1.13
Aspartate Aminotransferase (U/l)	157	169	0.90	1.03	0.89	0.88	0.96	1.56**	2.13***	1.23
Alanine Aminotransferase (U/l)	35	38	0.95	1.03	0.84	0.94	1.29	1.77***	2.21***	1.60*
Gamma Glutamyl Transferase [c] **(U/l)**	0.0	0.0	0.0	0.0	0.0	0.0	1.7**	3.5**	10.9***	10.8**
Week 7										
Calcium (mg/dl)	10.5	10.4	0.99	0.96	1.01	1.01	1.03	1.02	0.98	0.98
Inorganic Phosphate (mg/dl)	7.7	6.6	1.02	1.00	1.01	0.94	1.06	1.00	0.79**	0.92
Total Protein (g/dl)	6.7	7.4	0.97	0.97	0.99	1.03	0.95	1.00	0.85**	0.96
Albumin (g/dl)	4.4	4.9	0.76***	0.70**	0.94	0.95	0.67***	0.77***	0.71**	0.75**
Glucose (mg/dl)	85	79	1.06	1.02	1.01	0.94	1.00	1.09	1.66**	1.26
Cholesterol (mg/dl)	56	86	0.71**	0.73*	0.98	1.48*	1.20	2.32	3.67**	2.34
Triglycerides (mg/dl)	71	44	0.77	0.70	0.77*	1.23	1.48*	0.99	3.00**	0.96
Blood Urea Nitrogen (mg/dl)	13.2	14.1	1.11	1.15*	1.01	1.08	0.97	1.05	1.13	1.03
Creatinine (mg/dl)	0.51	0.57	1.02	1.00	1.00	1.02	0.93	0.98	0.81**	0.90
Total Bilirubin (mg/dl)	0.11	0.12	1.08	1.00	1.00	1.73**	6.00***	4.55**	15.75**	3.27**
Alkaline Phosphatase (U/l)	99	65	0.97	0.92	0.95	1.14	1.45**	1.48**	2.66**	1.82*
Aspartate Aminotransferase (U/l)	126	143	1.17	1.10	1.34*	2.06**	1.66***	1.73**	5.31**	2.25
Alanine Aminotransferase (U/l)	28	22	1.41**	1.00	2.45	4.21***	2.00	2.61**	9.27**	3.71**
Gamma Glutamyl Transferase [d] **(U/l)**	0.0	0.5	0.20	0.0	0.60	0.40	11.60	1.2*	53.00**	10.5

[a] Control animals received the vehicle
[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).
[c] Actual mean values presented. Control value of 0.0 precluded the calculation of the ratios of treated to control values.
[d] Actual mean values presented for males. Male Control value of 0.0 precluded the calculation of the ratios of treated to control values.

* = p<0.05, ** = p<0.01, *** = p<0.001 (Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Clinical Chemistry[b] **(Cont)**										
Week 9										
Calcium (mg/dl)	10.1	10.8	0.98	1.00	1.00	1.03	1.04	1.01	1.03	1.08
Inorganic Phosphate (mg/dl)	7.1	6.0	1.08	1.01	1.03	1.07	1.27**	1.06	1.22	1.15
Total Protein (g/dl)	6.8	7.4	0.99	1.04	1.01	1.07*	1.00	0.99	1.03	1.09
Albumin (g/dl)	4.3	5.0	0.84**	0.81**	1.00	0.88*	0.72**	0.79*	0.82	0.79
Glucose (mg/dl)	90	96	0.93	1.03	0.92	1.07*	0.80**	0.96	0.94	0.97
Cholesterol (mg/dl)	59	88	0.85	0.81	1.02	1.19	1.00	1.34	1.81	1.24
Triglycerides (mg/dl)	65	43	0.86	0.89	1.00	0.94	1.91	0.80	1.47	0.82
Blood Urea Nitrogen (mg/dl)	12.9	13.6	1.01	1.10	0.98	1.19	1.24	2.13	1.07	1.15
Creatinine (mg/dl)	0.56	0.62	1.00	1.11*	1.02	1.09*	1.00	1.13*	0.92	1.09
Total Bilirubin (mg/dl)	0.11	0.14	1.00	1.45	1.21	2.18	3.64	9.00*	6.36	4.09
Alkaline Phosphatase (U/l)	83	45	1.31	1.17	1.16	1.36	2.31**	2.23*	3.89	1.95
Aspartate Aminotransferase (U/l)	139	117	1.14	1.08	1.86	1.53	1.66	2.10	3.97	1.24
Alanine Aminotransferase (U/l)	35	26	1.19	1.17	2.42	1.83*	1.38	1.89	4.04	1.71
Gamma Glutamyl Transferase[c] **(U/l)**	0.0	0.4	0.0	0.4	1.0	0.8	13.0*	8.8*	10.0	3.0
Urinalysis	-	-	-	-	-	-	-	-	-	-
Organ Weights[b] **(End of Dosing: Day 45)**										
Liver (g)	10.39	7.14	1.39*	1.20*	1.04	1.10	1.42*	1.44*	NA	1.56
Liver (g/kg body weight)	22.61	25.67	1.33*	1.33*	1.06	1.18*	1.50*	1.60*	NA	1.91
Spleen (g)	0.72	0.61	3.07*	2.71*	0.93	1.11	2.17*	1.67*	NA	0.91
Spleen (g/kg body weight)	1.55	2.17	2.97*	3.03*	0.96	1.19	2.32*	1.87*	NA	1.11

[a] Control animals received the vehicle

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

[c] Actual mean values presented for males. Male Control value of 0.0 precluded the calculation of the ratios of treated to control values.

- = No noteworthy findings; NA = not applicable; * = p<0.05, ** = p<0.01, *** = p<0.001 (Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Organ Weights[b] (Cont) (End of Dosing: Day 45)										
Kidney (g)	2.64	1.80	1.04	1.03	0.96	1.04	1.05	1.07	NA	1.14
Kidney (g/kg body weight)	5.74	6.46	1.00	1.15*	0.98	1.12	1.10	1.19*	NA	1.39
Thymus (g)	0.36	0.32	1.16	0.86	1.09	1.02	0.86	0.87	NA	0.42
Thymus (g/kg body weight)	0.79	1.16	1.12	0.95	1.12	1.11	0.89	0.96	NA	0.51
Medial Iliac Lymph Node (g)	0.06	0.07	3.38	1.36	1.45	1.29	1.98	1.38	NA	0.66
Medial Iliac Lymph Node (g/kg body weight)	0.12	0.24	3.22	1.51	1.48	1.36	2.10	1.51	NA	0.79
Organ Weights[b] (Cont) (End of Recovery: Day 63)										
Liver (g)	11.58	7.31	1.08	1.11	1.03	1.04	1.39	0.98	NA	NA
Liver (g/kg body weight)	24.36	24.52	1.12	1.14	1.03	1.15*	1.52*	1.26	NA	NA
Spleen (g)	0.80	0.63	1.92	2.52*	0.93	1.88	2.08*	1.64	NA	NA
Spleen (g/kg body weight)	1.72	2.11	1.98	2.54*	0.93	2.02	2.26*	2.02	NA	NA
Kidney (g)	2.80	1.84	1.02	0.97	1.01	0.94	1.26*	0.96	NA	NA
Kidney (g/kg body weight)	5.95	6.19	1.05	0.98	1.01	1.02	1.39*	1.25	NA	NA
Thymus (g)	0.41	0.31	1.03	0.78	1.34*	0.74	0.89	0.56	NA	NA
Thymus (g/kg body weight)	0.86	1.05	1.06	0.79	1.34*	0.81	0.97	0.66	NA	NA
Medial Iliac Lymph Node (g)	0.07	0.09	1.36	1.85	0.84	1.36	1.41	1.93	NA	NA
Medial Iliac Lymph Node (g/kg body weight)	0.16	0.28	1.41	1.89	0.85	1.55	1.54	2.24	NA	NA

[a] Control animals received the vehicle

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

NA = not applicable; * = p<0.05, ** = p<0.01, *** = p<0.001 (organ weight data: Mann-Whitney U test, two tailed)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Gross Pathology[b] **(Scheduled Sacrifices)**										
End of Dosing (Day 45)										
Infusion Site – tissue mass	0/5	0/5	4/5	4/5	0/5	0/5	3/5	2/5	0/1	2/2
Infusion Site – adhesions	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/1	0/2
Lymph Node, medial iliac – adhesions	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/1	0/2
Lymph Node, medial iliac – swollen	0/5	1/5	3/5	1/5	1/5	0/5	2/5	1/5	0/1	0/2
Lymph Node, popliteal – swollen	4/5	2/5	2/5	2/5	3/5	2/5	3/5	2/5	0/1	1/2
Liver – pronounced lobulation	0/5	0/5	2/5	0/5	0/5	0/5	0/5	0/5	0/1	0/2
Liver – pale	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/1	0/2
Spleen – swollen	0/5	0/5	4/5	4/5	0/5	1/5	4/5	2/5	0/1	1/2
End of Recovery (Day 63)										
Infusion Site – tissue mass	0/5	0/5	4/5	5/5*	0/5	2/5	5/5*	4/4*	0/1	1/1
Infusion Site – adhesions	0/5	0/5	0/5	1/5	0/5	1/5	2/5	2/4	0/1	0/1
Lymph Node, medial iliac – adhesions	0/5	0/5	0/5	1/5	0/5	1/5	2/5	2/4	0/1	0/1
Lymph Node, medial iliac – swollen	0/5	1/5	3/5	2/5	0/5	2/5	1/5	2/4	0/1	0/1
Lymph Node, popliteal – swollen	2/5	2/5	4/5	4/5	3/5	4/5	0/5	1/4	1/1	1/1
Liver – pronounced lobulation	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/4	0/1	0/1
Spleen – swollen	0/5	0/5	3/5	5/5*	0/5	4/5	3/5	2/4	1/1	0/1

[a] Control animals received the vehicle

[b] Number with observation/Number examined

* = p<0.05, ** = p<0.01, *** = p<0.001 (gross necropsy data: Chi-square test)

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Gross Pathology[b] **(Found Dead/Moribund Sacrifices)**										
General – cachexia								1/1	4/8	5/7
General – anemia								1/1	6/8	5/7
General – dehydration								0/1	2/8	2/7
Adrenal Glands – swollen								0/1	2/8	4/7
Large Intestine – congested								0/1	0/8	2/7
Large Intestine – dilated								0/1	1/8	2/7
Large Intestine – focal hemorrhagic								0/1	1/8	2/7
Liver – pale								0/1	1/8	6/7
Lymph Node, cervical – hemorrhagic								0/1	0/8	4/7
Lymph Node, inguinal – hemorrhagic								0/1	1/8	0/7
Lymph Node, inguinal – swollen								0/1	3/8	0/7
Lymph Node, mesenteric – hemorrhagic								0/1	1/8	6/7
Lymph Node, medialiliac – hemorrhagic								0/1	0/8	5/7
Lymph Node, popliteal – swollen								0/1	2/8	3/7
Spleen – small								1/1	6/8	6/7
Subcutis – icterus								0/1	1/8	4/7
Testes – hemorrhagic								0/1		3/7
Histopathology End of Dosing (Day 45)										
Tissue Examined: Infusion Site										
Number Examined	4	5	5	5	5	5	5	5	1	2
Inflammation, acute (necrotizing)	0	0	4	4	0	0	3	5	0	2
Score 1	“	“	0	0	“	“	0	1	“	0
Score 2	“	“	1	0	“	“	0	2	“	0
Score 3	“	“	3	3	“	“	0	1	“	0
Score 4	“	“	0	1	“	“	3	1	“	2

[a] Control animals received the vehicle

[b] Number with observation/Number examined

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Infusion Site										
Number Examined	4	5	5	5	5	5	5	5	1	2
Inflammation, acute (adjacent tissue/muscle)	0	0	4	5	1	1	4	4	0	2
Score 1	“	“	0	1	1	1	1	0	“	0
Score 2	“	“	2	1	0	0	0	3	“	0
Score 3	“	“	2	3	0	0	1	1	“	0
Score 4	“	“	0	0	0	0	2	0	“	2
Necrosis (vessel wall)	0	0	4	5	3	2	1	3	1	2
Score 1	“	“	4	5	3	2	0	3	1	2
Score 2	“	“	0	0	0	0	1	0	0	0
Proliferation of fibro-angiomatous tissue	0	0	5	4	0	1	1	3	0	0
Score 1	“	“	0	1	“	1	0	0	“	“
Score 2	“	“	2	3	“	0	0	1	“	“
Score 3	“	“	3	0	“	0	1	2	“	“
Tissue Examined: Bone Marrow										
Number Examined	5	5	5	5	5	5	5	5	1	2
Amount of lipoid tissue/adipocytes	5	5	4	3	5	5	5	5	1	2
Score 1	4	3	4	3	3	0	2	0	0	0
Score 2	1	2	0	0	2	5	2	1	0	2
Score 3	0	0	0	0	0	0	1	4	1	0

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Bone Marrow										
Number Examined	5	5	5	5	5	5	5	5	1	2
Cellularity	5	5	5	5	5	5	5	5	1	2
Score 1	0	0	0	0	0	0	0	0	1	0
Score 2	0	0	0	0	0	4	1	4	0	2
Score 3	5	4	0	1	4	1	2	1	0	0
Score 4	0	1	5	4	1	0	2	0	0	0
Prominent granulopoiesis	0	0	2	5	0	0	3	1	0	2
Score 1	“	“	2	5	“	“	3	1	“	2
Prominent red blood cells	0	2	0	0	2	3	4	4	1	2
Score 1	“	2	“	“	2	3	2	0	0	1
Score 2	“	0	”	“	0	0	2	3	1	1
Score 3	“	0	”	“	0	0	0	1	0	0
Tissue Examined: Large Intestine - Colon										
Number Examined	5	5	0	0	0	0	5	5	1	2
Acute necrotizing inflammation (external muscle layer)	0	0					0	1	0	0
Score 3	“	“					“	1	“	“
Tissue Examined: Liver										
Number Examined	5	5	5	5	5	5	5	5	1	2
Bile duct proliferation (swollen epithelium)	0	0	4	0	1	0	0	4	0	0
Score 1	“	“	4	“	1	“	“	4	“	“

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Liver										
Number Examined	5	5	5	5	5	5	5	5	1	2
Hepatocytic necrosis (multifocal)	0	0	1	1	0	2	2	1	1	1
Score 1	“	“	1	1	“	1	1	0	1	1
Score 2	“	“	0	0	“	0	1	1	0	0
Score 3	“	“	0	0	“	1	0	0	0	0
Inflammation, round cells (Kiernan space)	0	0	5	5	3	2	5	2	0	0
Score 1	“	“	0	1	3	2	5	2	“	“
Score 2	“	“	4	3	0	0	0	0	“	“
Score 3	“	“	1	1	0	0	0	0	“	“
Kupffer cell proliferation	0	0	4	3	1	0	1	2	0	1
Score 1	“	“	1	2	1	“	1	2	“	1
Score 2	“	“	3	1	0	“	0	0	“	0
Kupffer cells swollen	0	0	3	3	0	0	1	3	0	0
Score 1	“	“	1	3	“	“	1	3	“	“
Score 2	“	“	2	0	“	“	0	0	“	“

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 And 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Liver										
Number Examined	5	5	5	5	5	5	5	5	1	2
Single cell necrosis	0	0	0	0	0	0	3	3	0	0
Score 1	“	“	“	“	“	“	3	1	“	“
Score 2	“	“	“	“	“	“	0	2	“	“
Tissue Examined: Lymph Node - Mesenteric										
Number Examined	5	5	5	5	5	5	4	5	1	2
Atrophy - diffuse	0	0	0	0	0	1	2	1	1	2
Score 1	“	“	“	“	“	1	2	1	0	0
Score 2	“	“	“	“	“	0	0	0	1	2
Tissue Examined: Lymph Node - Medial Iliac										
Number Examined	5	5	5	5	5	5	5	5	1	2
Atrophy (cortical lymphatic nodules)	0	0	0	0	0	2	1	3	0	1
Score 1	“	“	“	“	“	2	1	2	“	0
Score 2	“	“	“	“	“	0	0	1	“	1
Hyperplasia - diffuse	4	1	4	1	5	0	2	1	0	0
Score 1	4	1	1	1	5	“	2	1	“	“
Score 2	0	0	3	0	0	“	0	0	“	“

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 And 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (µg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Lymph Node - Medial Iliac										
Number Examined	5	5	5	5	5	5	5	5	1	2
Inflammation- acute	0	0	0	2	0	0	2	0	0	0
Score 1	“	“	“	2	“	“	0	“	“	“
Score 2	“	“	“	0	“	“	2	“	“	“
Tissue Examined: Lymph Node - Medial Iliac										
Number Examined	5	5	5	5	5	5	5	5	1	2
Inflammation-diffuse (adjacent tissue)	0	0	3	0	0	0	0	1	0	1
Score 1	“	“	1	“	“	“	“	0	“	0
Score 2	“	“	1	“	“	“	“	1	“	0
Score 3	“	“	1	“	“	“	“	0	“	1
Plasmacytosis (medulla)	2	4	5	5	4	4	5	5	1	2
Score 1	2	3	3	5	3	4	1	0	0	1
Score 2	0	0	1	0	1	0	4	5	1	1
Score 3	0	1	1	0	0	0	0	0	0	0
Tissue Examined: Lymph Node - Polpiteal										
Number Examined	5	4	5	5	5	5	5	5	1	2
Atrophy (cortical lymphatic nodules)	0	0	0	0	1	1	1	1	0	2
Score 1	“	“	“	“	1	1	1	1	“	0
Score 2	“	“	“	“	0	0	0	0	“	2

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Lymph Node - Polpiteal										
Number Examined	5	4	5	5	5	5	5	5	1	2
Plasmacytosis (medulla)	3	4	3	3	3	4	2	5	1	2
Score 1	2	4	2	3	2	4	1	3	1	2
Score 2	1	0	1	0	1	0	1	2	0	0
Prominent mast cells (medulla)	0	2	0	0	1	0	0	3	0	1
Score 1	"	2	"	"	1	"	"	3	"	1
Score 2	"	0	"	"	0	"	"	0	"	0
Tissue Examined: Small Intestine - duodenum										
Number Examined	5	5	0	5	0	5	5	5	1	2
Single cell necrosis (lamina propria)	0	0		0		0	0	2	0	0
Score 1	"	"		"		"	"	2	"	"
Tissue Examined: Spleen										
Number Examined	5	5	5	5	5	5	5	5	1	2
Atrophy - diffuse	0	0	0	0	0	0	0	0	1	1
Score 2	"	"	"	"	"	"	"	"	0	1
Score 3	"	"	"	"	"	"	"	"	1	0
Hyperplasia - diffuse	0	0	5	5	2	1	0	0	0	0
Score 1	"	"	3	4	2	1	"	"	"	"
Score 2	"	"	2	1	0	0	"	"	"	"

[a] Control animals received the vehicle

" = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology End of Dosing (Day 45) (Cont)										
Tissue Examined: Thymus										
Number Examined	5	5	5	5	5	5	5	5	1	2
Atrophy – diffuse	0	0	0	0	0	0	4	0	1	2
Score 1	“	“	“	“	“	“	2	“	0	0
Score 2	“	“	“	“	“	“	2	“	0	1
Score 3	“	“	“	“	“	“	0	“	0	1
Score 4	“	“	“	“	“	“	0	“	1	0
Starry sky appearance	1	0	2	3	2	2	2	4	0	0
Score 1	1	“	2	3	2	2	2	4	“	“
Histopathology Recovery (Day 63)										
Tissue Examined: Infusion Site										
Number Examined	5	5	5	5	5	5	5	4	1	1
Inflammation, acute (necrotizing)	0	0	4	4	0	2	5	4	0	1
Score 3	“	“	4	3	“	1	0	1	“	1
Score 4	“	“	0	1	“	1	5	3	“	0
Tissue Examined: Infusion Site										
Number Examined	5	5	5	5	5	5	5	4	1	1
Inflammation, acute (adjacent tissue/muscle)	0	0	4	5	0	2	5	4	0	1
Score 1	“	“	0	1	“	0	0	0	“	0
Score 2	“	“	1	0	“	0	1	0	“	0
Score 3	“	“	3	4	“	2	3	4	“	1
Score 4	“	“	0	0	“	0	1	0	“	0

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Recovery (Day 63) (Cont)										
Tissue Examined: Infusion Site										
Number Examined	5	5	5	5	5	5	5	4	1	1
Necrosis (vessel wall)	0	0	4	3	0	4	0	4	0	1
Score 1	“	“	4	3	“	4	“	4	“	1
Proliferation of fibro-angiomatous tissue	1	1	4	5	0	2	5	3	0	1
Score 1	1	1	0	0	“	0	0	0	“	0
Score 2	0	0	0	1	“	0	2	1	“	0
Score 3	0	0	4	4	“	2	3	2	“	1
Tissue Examined: Bone Marrow										
Number Examined	5	5	5	5	5	5	5	4	1	1
Amount of lipoid tissue/adipocytes	5	5	4	2	5	5	4	4	1	1
Score 1	4	2	4	2	3	3	4	4	0	1
Score 2	1	3	0	0	2	2	0	0	1	0
Cellularity	5	5	5	5	5	5	5	4	1	1
Score 2	0	0	0	0	0	0	0	0	1	0
Score 3	5	4	0	1	5	4	0	2	0	1
Score 4	0	1	5	4	0	1	5	2	0	0
Prominent granulopoiesis	0	0	1	3	0	0	3	1	0	0
Score 1	“	“	1	3	“	“	3	1	“	“

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (µg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Recovery (Day 63) (Cont)										
Tissue Examined: Liver										
Number Examined	5	5	5	5	5	5	5	4	1	1
Bile duct proliferation (swollen epithelium)	0	0	1	2	0	0	3	0	0	0
Score 1	“	“	1	1	“	“	3	“	“	“
Score 2	“	“	0	1	“	“	0	“	“	“
Hepatocytic necrosis (multifocal)	0	1	2	3	1	2	0	1	1	0
Score 1	“	1	1	3	1	0	“	0	1	“
Score 2	“	0	1	0	0	2	“	1	0	“
Inflammation, round cells (Kiernan space)	1	2	5	5	3	3	5	1	0	0
Score 1	1	2	4	2	3	2	5	1	“	“
Score 2	0	0	1	3	0	1	0	0	“	“
Kupffer cell proliferation	2	1	2	3	0	4	4	4	0	1
Score 1	2	1	0	0	“	1	3	1	“	0
Score 2	0	0	2	1	“	2	1	2	“	1
Score 3	0	0	0	2	“	1	0	1	“	0
Kupffer cells swollen	0	0	3	3	0	2	1	0	0	0
Score 1	“	“	3	0	“	0	0	“	“	“
Score 2	“	“	0	3	“	2	1	“	“	“

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (µg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Recovery (Day 63) (Cont)										
Tissue Examined: Liver										
Number Examined	5	5	5	5	5	5	5	4	1	1
Single cell necrosis	0	0	1	1	0	1	0	3	0	0
Score 1	“	“	1	1	“	1	“	1	“	“
Score 2	“	“	0	0	“	0	“	2	“	“
Tissue Examined: Thymus										
Number Examined	5	5	5	5	5	5	5	3	1	1
Atrophy – diffuse	0	0	1	2	0	0	1	1	1	0
Score 1	“	“	0	2	“	“	1	0	0	“
Score 3	“	“	1	0	“	“	0	1	1	“
Histopathology Found Dead/Moribund Sacrifices										
Tissue Examined: Infusion Site										
Inflammation, acute (necrotizing)								0	1	1
Score 3								“	1	1
Number Examined								1	8	7
Necrosis (vessel wall)								0	6	5
Score 1								“	6	5
Tissue Examined: Heart										
Number Examined								1	8	7
Hemorrhage								0	2	2
Score 1								“	2	1
Score 2								“	0	1

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Found Dead/Moribund Sacrifices (Cont)										
Tissue Examined: Liver										
Number Examined								1	8	7
Hepatocytic necrosis (multifocal)								1	7	7
Score 1								0	1	1
Score 2								0	2	2
Score 3								1	3	1
Score 4								0	1	3
Tissue Examined: Lymph Node - Mesenteric										
Number Examined								1	8	7
Atrophy - diffuse								0	4	5
Score 2								“	1	5
Score 3								“	2	0
Score 4								“	1	0
Tissue Examined: Lymph Node - Polpiteal										
Number Examined								1	8	7
Atrophy (cortical lymphatic nodules)								0	1	2
Score 1								“	1	0
Score 2								“	0	1
Score 3								“	0	1

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m²)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Found Dead/Moribund Sacrifices (Cont)										
Tissue Examined: Lymph Node - Polpiteal										
Number Examined								1	8	7
Atrophy - diffuse								1	5	4
Score 1								0	1	0
Score 2								1	1	1
Score 3								0	1	3
Score 4								0	2	0
Tissue Examined: Small Intestine – duodenum										
Number Examined								1	8	7
Ulceration								0	0	3
Score 1								“	“	2
Score 3								“	“	1
Tissue Examined: Spleen										
Number Examined								1	8	7
Atrophy - diffuse								1	8	7
Score 2								0	3	1
Score 3								0	4	2
Score 4								1	1	4
Tissue Examined: Stomach, glandular										
Number Examined								1	8	7
Acute necrotizing inflammation								0	0	3
Score 2								“	“	1
Score 3								“	“	2

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Found										
Dead/Moribund Sacrifices (Cont)										
Tissue Examined: Stomach, glandular										
Number Examined								1	8	7
Epithelial atrophy								0	4	2
Score 1								“	1	1
Score 2								“	1	1
Score 3								“	2	0
Hemorrhage								0	7	5
Score 1								“	3	2
Score 2								“	4	2
Score 3								“	0	1
Single cell necrosis/prominent cellular debris (mainly pylorus)								0	5	4
Score 1								“	3	2
Score 2								“	1	2
Score 3								“	1	“
Ulceration								0	0	3
Score 2								“	“	2
Score 3								“	“	1
Tissue Examined: Testes										
Number Examined								1		7
Degeneration (germinal epithelium) diffuse								1		1
Score 2								1		1

[a] Control animals received the vehicle

“ = Finding not present score not applicable

2.6.7.7.1.1 ラット３週間ごと１回（3 サイクル）反復投与試験（続き）

Report Title: 6-Week Intermittent Intravenous Toxicity Study with 3-Week Recovery in the Rat **Test Article: R279741（Trabectedin）**

	One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle (Cycles 1, 2 and 3) Cycle 3 Followed by 3 Day and 3 Week Recovery Periods									
Group	**1**		**2**	**3**		**4**		**5**		**6**
Number of Doses Administered	3		3	3		3		3		3
Days of Treatment (Study Day)	Days 0, 21 and 42		Days 0, 21 and 42	Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42		Days 0, 21 and 42
Dose/infusion or cycle (μg/m^2)	**0** [a]	**0**	**15**	**60**	**60**	**150**	**150**	**300**	**300**	**450**
Sex: No. of Animals	M: 10	F: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10
Noteworthy Findings										
Histopathology Found										
Dead/Moribund Sacrifices (Cont)										
Tissue Examined: Testes										
Number Examined								1		7
Spermatid giant cells								1		2
Score 1								0		2
Score 2								1		0
Tissue Examined: Thymus										
Number Examined								1	8	7
Atrophy - diffuse								1	8	7
Score 3								0	0	1
Score 4								1	8	6

[a] Control animals received the vehicle

2.6.7.7.2 非げっ歯類を用いた反復投与毒性試験

2.6.7.7.2.1 サル 3 週間ごと 1 回（4 サイクル）反復投与試験

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

Species/Strain: Primate/Cynomolgus

Duration of Dosing: Four infusion cycles, each cycle consisting of a one 3-hour or 24-hour infusion followed by a 3-week treatment-free period. Treatment was administered on Test Days 1, 22, 43 and 62.

Study No.: [redacted]

Age at First Dose: At least 24 months

Duration of Treatment-Free/Recovery: 3 weeks per dosing cycle. At the end of the fourth dosing cycle, the first surviving animal of each sex/group was kept for a 5- to 7-day recovery period before necropsy. The second animal/sex/group was kept for a 3-week recovery period before necropsy.

Location in CTD: 4.2.3.2.5

Date of First Dose: Males: [redacted]; Females: [redacted]

Route: Intravenous Infusion

Vehicle/Formulation: Water for injection and sterile isotonic saline/ R279741 diluted with water to 50 µg/mL and further diluted as necessary with saline.

GLP Compliance: Yes

Special Features: During acclimation the Group 5 animals were surgically implanted with a vascular access port. Note that the order of presentation of the Groups has been revised for Cycle 4 in order to present the data in ascending dose order.

No Observed Adverse Effect Level: <300 µg/m^2 (25 µg/kg) for Cycles 1-3/1440 µg/m^2 (120 µg/kg) for Cycle 4

DOSING AND TREATMENT-FREE/RECOVERY PERIODS

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/kg)	**0**[a]		**25**		**50**		**75**		**75**		**0**		**75**		**100**		**120**		**100**	
Dose/infusion or cycle (µg/m^2)	**0**[a]		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Toxicokinetics[c]**:**																				
C_{max} (ng/mL) 1st Cycle			0.78	0.82	2.80	6.80	3.24	2.58	1.76	1.04										
C_{max} (ng/mL) 3rd Cycle			0.79	0.99	5.29	2.86	1.66	1.38	1.75	1.66										
C_{max} (ng/mL) 4thCycle													3.66	5.08	/	5.62	4.27	5.68	0.84	1.21

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Toxicokinetics Report [redacted]

Note: Dose conversion to µg/m^2: multiply µg/kg by 12 for monkeys; / = Sample not available or not analyzed, or concentration not reliable, or parameter not calculated

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4							
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
$T_{1/2}$ (h) 1st Cycle			41	81	77	77	74	96	109	/										
$T_{1/2}$ (h) 3rd Cycle			48	83	173	229	63	231	/	/										
$T_{1/2}$ (h) 4thCycle													92	99	62	/	/	137	81	74
$AUC_{0\text{-}inf}$ (ng.h/mL) 1st Cycle			7.79	10.9	22.7	28.2	30.3	26.9	51.6	/										
$AUC_{0\text{-}inf}$ (ng.h/mL) 3rd Cycle			6.80	11.3	/	/	24.3	27.1	/	/										
$AUC_{0\text{-}inf}$ (ng.h/mL) 4thCycle													34.9	33.5	/	/	/	84.0	30.5	49.7
Died or Sacrificed Moribund	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	2	1	0	1
Day of Death (Found dead/Moribund Sacrifice)							61	59					80				66,67	79		75
No. Killed at Terminal Sacrifice (1/sex/group Days 70 or 71 and Days 88 or 89)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	2	1	2	1	1	0	1	2	1

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

/ = Sample not available or not analyzed, or concentration not reliable, or parameter not calculated; NA = not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (μg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Body Weight (g)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Electrocardiograms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ophthalmology	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Observations[c]																				
Dehydration	-	-	-	-	-	-	-	1/2	2/2	2/2	-	-	1/2	-	-	-	-	1/2	-	-
Hypoactivity	-	-	-	-	-	-	1/2	-	-	-	-	-	1/2	-	-	-	-	1/2	1/2	1/2
Injection Site Findings	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin Thickening	-	-	-	-	-	1/2	-	-	-	-	-	-	-	1/2	-	-	-	-	-	-
Open Wound	-	-	-	-	-	1/2	-	-	-	-	-	-	-	1/2	-	-	-	-	-	-
Hematology[d]																				
Day 5 (Post Cycle 1)																				
WBC (10^9/L)	13.06	15.12	0.50	0.65	0.44	0.97	0.46	0.37	1.25	0.80										
RBC (10^{12}/L)	6.21	6.83	0.97	0.83	0.96	1.00	0.87	0.81	0.92	0.90										
Hgb (g/dL)	12.1	12.75	0.99	0.89	0.96	0.98	0.88	0.86	0.91	0.93										
PCV (L/L)	0.40	0.43	0.98	0.87	0.96	0.95	0.88	0.86	0.93	0.91										
Retics (p. 1000)[d]	1.0	1.5	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.5										
Fibrinogen (g/L)	3.59	3.08	1.10	1.17	1.16	1.34	0.96	1.25	1.30	1.05										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

- = No noteworthy findings

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Hematology[c] (Cont)																				
Days 21-22 (Pre Cycle 2)																				
WBC (10^9/L)	11.04	11.71	0.73	0.92	0.71	0.80	0.87	0.47	2.00	1.48										
RBC (10^{12}/L)	6.40	6.78	0.96	0.87	0.87	0.94	0.77	0.51	0.73	0.84										
Hgb (g/dL)	12.9	13.0	0.97	0.94	0.88	0.95	0.81	0.55	0.74	0.89										
PCV (L/L)	0.43	0.44	0.94	0.92	0.86	0.92	0.78	0.55	0.73	0.84										
Retics (p. 1000)[c]	0.5	0.0	0.0	0.0	1.0	3.0	1.5	0.0	1.5	0.0										
Fibrinogen (g/L)	2.65	2.85	1.00	0.91	1.11	1.05	0.94	1.10	1.93	2.85										
Day 26 (Post Cycle 2)																				
WBC (10^9/L)	14.06	8.80	0.46	0.80	0.37	0.71	0.38	0.67	1.56	1.05										
RBC (10^{12}/L)	6.24	6.77	0.92	0.88	0.81	0.91	0.73	0.48	0.71	0.70										
Hgb (g/dL)	12.5	12.8	0.93	0.93	0.82	0.91	0.79	0.53	0.68	0.70										
PCV (L/L)	0.41	0.44	0.93	0.94	0.80	0.90	0.76	0.53	0.73	0.68										
Retics (p. 1000)[c]	0.0	3.0	0.0	0.5	0.0	0.5	0.0	2.0	4.5	1.0										
Fibrinogen (g/L)	3.61	2.54	1.05	1.27	1.01	1.25	1.00	2.94	1.93	2.97										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Hematology[c] (Cont)																				
Days 29-30 (Post Cycle 2)																				
WBC (10^9/L)	12.25	10.37	0.62	1.18	0.39	1.06	0.58	0.92	2.09	1.26										
RBC (10^{12}/L)	6.15	6.40	0.86	0.86	0.73	0.90	0.72	0.50	0.70	0.74										
Hgb (g/dL)	12.5	12.6	0.88	0.92	0.76	0.90	0.76	0.56	0.69	0.75										
PCV (L/L)	0.41	0.42	0.85	0.94	0.73	0.89	0.73	0.56	0.71	0.73										
Retics (p. 1000)[c]	0.5	0.0	0.0	0.0	0.0	0.0	0.0	2.0	4.0	0.5										
Fibrinogen (g/L)	2.62	2.30	1.00	1.23	1.20	1.72	1.11	2.48	2.47	2.16										
Days 40-41 (Pre Cycle 3)																				
WBC (10^9/L)	11.32	9.91	0.76	1.05	0.30	0.81	0.50	0.57	1.91	0.86										
RBC (10^{12}/L)	6.68	6.85	0.91	0.87	0.56	0.79	0.66	0.48	0.71	0.75										
Hgb (g/dL)	13.5	13.5	0.94	0.94	0.58	0.80	0.75	0.56	0.70	0.76										
PCV (L/L)	0.44	0.45	0.92	0.93	0.56	0.79	0.74	0.58	0.75	0.76										
Retics (p. 1000)[c]	0.0	0.5	0.0	0.0	1.0	1.5	1.0	3.0	4.0	0.5										
Fibrinogen (g/L)	2.52	2.33	1.04	1.11	2.54	2.34	1.04	1.39	1.16	1.80										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle ($\mu g/m^2$)	**0**[a]		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Hematology[c] **(Cont)** **Day 47 (Post Cycle 3)**																				
WBC (10^9/L)	9.02	11.94	0.64	0.77	0.79	0.54	0.36	0.53	1.93	0.99										
RBC (10^{12}/L)	6.49	6.59	0.83	0.85	0.52	0.76	0.63	0.50	0.67	0.67										
Hgb (g/dL)	13.0	12.8	0.89	0.91	0.55	0.78	0.72	0.60	0.63	0.68										
PCV (L/L)	0.43	0.43	0.85	0.91	0.52	0.78	0.70	0.62	0.69	0.69										
Retics (p. 1000)[c]	1.5	2.0	1.5	0.0	3.5	6.0	0.0	4.5	5.5	0.5										
Fibrinogen (g/L)	3.07	2.65	1.10	1.28	1.49	1.70	1.37	2.91	1.88	2.55										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Hematology[c] (Cont)																				
Days 59-62 (Pre Cycle 4)																				
WBC (10^9/L)											10.85	11.65	0.56	1.36	0.41	0.50	0.66	0.69	1.33	0.80
RBC (10^{12}/L)											6.52	6.68	0.70	0.70	0.43	0.46	0.88	0.86	0.83	0.80
Hgb (g/dl)											13.1	13.0	0.79	0.72	0.50	0.55	0.93	0.93	0.81	0.82
PCV (L/L)											0.44	0.44	0.77	0.70	0.47	0.57	0.90	0.90	0.84	0.80
Retics (p. 1000)[c]											0.5	1.5	11.0	4.5	6.5	1.5	2.0	3.0	5.0	2.0
Fibrinogen (g/L)											2.14	2.19	1.52	1.51	4.12	4.16	1.10	1.36	1.54	1.74
Days 67-68 (Post Cycle 4)											15.98	7.42	0.24	0.91	0.46	0.82	x	1.58	0.93	1.55
WBC (10^9/L)											6.47	6.60	0.64	0.63	0.63	0.65	x	0.80	0.74	0.71
RBC (10^{12}/L)											13.1	13.0	0.71	0.64	0.71	0.73	x	0.84	0.68	0.68
Hgb (g/dl)											0.44	0.43	0.69	0.65	0.68	0.81	x	0.86	0.70	0.70
PCV (L/L)											2.5	1.0	1.0	4.0	0.0	0.0	x	0.0	1.5	0.5
Retics (p. 1000)[c]											3.04	2.51	1.34	3.27	1.25	2.69	x	1.79	2.08	3.41
Fibrinogen (g/L)																				

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle ($\mu g/m^2$)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Hematology[c] (Con't)																				
Days 70-71 (Post Cycle 4)											10.26	10.54	0.38	0.67	0.47	0.30	x	0.24	1.90	1.13
WBC (10^9/L)											6.49	6.46	0.59	0.64	0.57	0.62	x	0.83	0.72	0.68
RBC (10^{12}/L)											13.3	12.7	0.64	0.63	0.62	0.70	x	0.88	0.65	0.67
Hgb (g/dL)											0.44	0.42	0.65	0.64	0.61	0.74	x	0.90	0.69	0.67
PCV (L/L)											0.0	0.5	0.0	2.5	0.0	0.0	x	0.0	4.5	10.5
Retics (p. 1000)[c]											2.17	2.11	2.03	3.64	1.74	3.01	x	3.14	2.35	2.51
Fibrinogen (g/L)																				
Days 88-89 (Post Cycle 4)																				
WBC (10^9/L)											8.65	5.69	x	1.58	x	x	x	x	1.15	x
RBC (10^{12}/L)											6.60	6.20	x	0.97	x	x	x	x	0.85	x
Hgb (g/dL)											14.0	12.2	x	0.90	x	x	x	x	0.83	x
PCV (L/L)											0.44	0.41	x	0.93	x	x	x	x	0.91	x
Retics (p. 1000)[c]											9.0	3.0	x	8.0	x	x	x	x	8.0	x
Fibrinogen (g/L)											2.53	1.57	x	1.89	x	x	x	x	1.07	x

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown. Actual reticulocyte values are presented for all groups.

x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Clinical Chemistry[c]																				
Day 5 (Post Cycle 1)																				
Alanine Aminotransferase (IU/L)	121.0	29.5	1.45	3.98	0.62	2.86	1.84	2.25	0.56	1.53										
Aspartate Aminotransferase (IU/L)	118.5	21.5	1.60	3.53	0.30	2.74	1.51	2.12	0.38	1.16										
Creatinine Kinase (IU/L)	679.0	74.0	1.75	5.13	0.21	3.89	1.09	2.32	0.34	1.04										
Days 21-22 (Pre Cycle 2)																				
Alanine Aminotransferase (IU/L)	26.0	17.0	1.19	1.94	1.00	1.65	1.88	1.41	1.23	1.21										
Aspartate Aminotransferase (IU/L)	31.0	17.0	0.92	1.50	0.61	1.21	0.82	1.18	1.13	1.15										
Creatinine Kinase (IU/L)	85.0	50.5	0.81	1.27	0.69	1.01	1.17	1.13	4.47	1.13										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Clinical Chemistry[c]																				
Day 26 (Post Cycle 2)																				
Alanine Aminotransferase (IU/L)	57.0	21.5	0.88	2.33	0.68	2.12	1.16	1.42	0.46	1.35										
Aspartate Aminotransferase (IU/L)	36.0	16.0	0.94	1.88	0.51	1.28	0.76	1.44	0.44	1.28										
Creatinine Kinase (IU/L)	118.5	56.5	1.11	2.36	0.40	1.70	0.56	0.88	0.43	1.46										
Days 29-30 (Post Cycle 2)																				
Alanine Aminotransferase (IU/L)	43.5	22.0	1.11	2.07	1.01	1.55	1.17	1.48	0.44	1.34										
Aspartate Aminotransferase (IU/L)	31.5	16.0	0.89	1.56	0.67	1.22	0.78	1.47	0.57	1.13										
Creatinine Kinase (IU/L)	47.5	37.0	0.78	2.81	0.56	1.41	0.94	2.66	1.18	0.95										

[a] Control animals received the vehicle
[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.
[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Clinical Chemistry[c]																				
Days 40-41 (Pre Cycle 3)																				
Alanine Aminotransferase (IU/L)	34.5	19.0	0.94	1.66	0.64	1.37	1.01	1.37	0.83	1.18										
Aspartate Aminotransferase (IU/L)	28.5	20.0	0.86	1.10	0.54	2.10	0.86	1.10	0.67	0.93										
Creatinine Kinase (IU/L)	74.5	56.5	0.95	1.20	0.74	15.50	0.86	1.13	0.69	1.15										
Day 47 (Post Cycle 3)																				
Alanine Aminotransferase (IU/L)	49.5	26.5	0.77	2.53	1.01	1.26	1.16	1.19	0.55	0.92										
Aspartate Aminotransferase (IU/L)	27.0	15.5	0.87	3.13	0.63	1.03	0.83	2.06	0.46	1.10										
Creatinine Kinase (IU/L)	90.5	66.0	0.57	3.14	0.25	0.64	0.57	8.13	0.41	0.68										

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3							Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Clinical Chemistry[c]																				
Days 59-62 (Pre Cycle 4)																				
Alanine Aminotransferase (IU/L)											25.5	19.5	1.12	1.23	0.92	5.31	1.51	1.62	0.75	1.59
Aspartate Aminotransferase (IU/L)											25.5	15.5	0.69	0.94	0.43	6.84	0.86	1.32	0.51	0.97
Creatinine Kinase (IU/L)											88.0	48.0	0.45	1.09	0.32	7.91	0.53	1.16	0.48	1.24
Days 67-68 (Post Cycle 4)																				
Alanine Aminotransferase (IU/L)											30.5	28.0	2.05	3.27	1.77	1.25	x	4.80	0.79	1.38
Aspartate Aminotransferase (IU/L)											23.5	18.5	0.87	6.27	0.81	1.89	x	7.81	0.64	1.16
Creatinine Kinase (IU/L)											69.5	62.0	0.78	26.93	1.34	4.71	x	51.65	0.58	0.62

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Clinical Chemistry[c]																				
Days 70-71 (Post Cycle 4)																				
Alanine Aminotransferase (IU/L)											29.0	22.0	2.22	3.16	1.66	1.36	x	8.05	0.64	1.11
Aspartate Aminotransferase (IU/L)											27.5	16.5	1.87	3.00	1.85	2.48	x	13.36	0.53	1.15
Creatinine Kinase (IU/L)											63.5	38.0	4.68	4.42	17.86	12.66	x	66.34	0.80	0.88
Days 79, 88-89 (Post Cycle 4)																				
Alanine Aminotransferase (IU/L)											27.0	30.0	6.67	1.10	x	x	x	28.33	0.67	x
Aspartate Aminotransferase (IU/L)											23.0	18.0	8.74	1.06	x	x	x	51.67	0.52	x
Creatinine Kinase (IU/L)											54.0	62.0	14.87	2.98	x	x	x	88.23	0.78	x

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (μg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Urinalysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Organ Weight[c]																				
5-7 Day Recovery Period (Post Cycle 4) (N=1)																				
Adrenal (g)											0.73	0.44	0.85	1.32	0.97	1.53	x	1.89	1.41	1.20
Adrenal/body weight (%)											0.03	0.02	0.87	1.22	1.10	1.27	x	1.49	1.64	1.26
Liver (g)											45.70	56.69	1.10	1.03	1.06	1.10	x	1.18	1.45	1.05
Liver/body weight (%)											1.87	2.21	1.13	1.11	1.21	1.06	x	1.09	1.71	1.28
Kidney (g)											11.37	10.48	0.85	1.17	0.85	1.25	x	1.20	2.14	1.64
Kidney/body weight (%)											0.47	0.41	0.88	1.26	0.96	1.21	x	1.09	2.49	2.00
Thymus (g)											4.99	3.78	0.48	0.56	0.49	0.42	x	0.57	0.10	0.19
Thymus/body weight (%)											0.20	0.15	0.51	0.59	0.57	0.40	x	0.51	0.12	0.22

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

x = No data available due to animal death; - = No noteworthy findings

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3							Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle ($\mu g/m^2$)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Organ Weight (Cont)[c]																				
3-Week Recovery Period (Post Cycle 4) (N = 1)																				
Liver (g)											52.29	54.32	x	1.12	x	x	x	x	1.28	x
Liver/body weight (%)											1.84	2.23	x	1.29	x	x	x	x	1.44	x
Kidney (g)											13.35	11.11	x	1.19	x	x	x	x	1.04	x
Kidney/body weight (%)											0.47	0.46	x	1.35	x	x	x	x	1.17	x
Thymus (g)											3.77	2.81	x	0.58	x	x	x	x	0.53	x
Thymus/body weight (%)											0.13	0.12	x	0.64	x	x	x	x	0.61	x

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Gross Pathology[c]																				
5-7 Day Recovery Period (Post Cycle 4)																				
Kidney-enlarged											-	-	-	-	-	-	-	-	1/1	1/1
Kidney-paleness											-	-	-	-	1/2	-	-	-	1/1	1/1
Liver-enlarged											-	-	-	-	1/2	-	-	-	-	-
Liver-accentuated lobular pattern											-	-	-	-	-	1/2	-	-	-	-
Spleen-reduced in size											-	-	-	-	1/2	-	1/2	-	-	-
Thymus-reduced in size											-	-	-	-	-	-	-	-	1/1	1/1

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] For controls, group means are shown. For treated groups, multiples of controls are shown.

- = No noteworthy findings

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Gross Pathology (Cont)[c]										
3-Week Recovery Period (Post Cycle 4)										
Liver-enlarged						- -	- -	- -	- 1/1	- -
Liver-firm consistency						- -	- -	- -	- 1/1	- -
Thymus- reduced in size						- -	- -	- -	- 1/1	- 1/1
Histopathology[d]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Liver										
Number Examined						1 1	1 1	2 2	2 1	1 1
Hepatocellular hypertrophy						0 0	0 0	1 1	0 1	1 0
Score 1						“ “	“ “	0 0	“ 0	1 “
Score 2						“ “	“ “	1 0	“ 1	0 “
Score 3						“ “	“ “	0 1	“ 0	0 “

[a] Control animals received the vehicle
[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.
[c] For controls, group means are shown. For treated groups, multiples of controls are shown.
[d] Number with observation/Number examined

“ = Finding not present score not applicable; - = No noteworthy findings

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (μg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Liver										
Number Examined						1 1	1 1	2 2	2 1	1 1
Mixed cell infiltration						0 0	0 0	0 0	0 0	1 1
Score 2						“ “	“ “	“ “	“ “	0 1
Score 3						“ “	“ “	“ “	“ “	1 0
Hepatocellular degeneration/necrosis						0 0	0 0	0 1	0 0	0 0
Score 4						“ “	“ “	“ 1	“ “	“ “

[a] Control animals received the vehicle
[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.
[c] Number with observation/Number examined

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (μg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Bone marrow-Femur										
Number Examined						1 1	1 1	2 2	2 1	1 1
Myeloid increase erythroid decrease						0 0	0 0	0 0	0 0	1 1
Score 2						“ “	“ “	“ “	“ “	0 1
Score 4						“ “	“ “	“ “	“ “	1 0
Tissue Examined: Bone marrow-Sternum										
Number Examined						1 1	1 1	2 2	2 1	1 1
Myeloid increase erythroid decrease						0 0	0 0	0 0	0 0	1 1
Score 2						“ “	“ “	“ “	“ “	0 1
Score 4						“ “	“ “	“ “	“ “	1 0
Medullary hypoplasia						0 0	1 1	2 2	2 1	0 0
Score 3						“ “	1 1	0 0	2 0	“ “
Score 4						“ “	0 0	2 2	0 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3									
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (μg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Spleen										
Number Examined						1 1	1 1	2 2	2 1	1 1
Lymphoid depletion						0 0	0 0	1 2	2 1	0 0
Score 1						“ “	“ “	0 1	0 0	“ “
Score 2						“ “	“ “	1 1	2 1	“ “
Tissue Examined: Thymus										
Number Examined						1 1	1 1	2 2	2 1	1 1
Lymphoid depletion						0 0	0 1	1 2	2 1	1 1
Score 1						“ “	“ 0	0 1	0 0	0 0
Score 2						“ “	“ 1	0 1	2 1	0 0
Score 3						“ “	“ 0	0 0	0 0	1 1
Score 4						“ “	“ 0	1 0	0 0	0 0

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3										Cycle 4									
Group	**1**		**2**		**3**		**4**		**5**		**1**		**3**		**4**		**2**		**5**	
Dose/infusion or cycle (µg/m²)	**0[a]**		**300**		**600**		**900**		**900**		**0**		**900**		**1200**		**1440**		**1200**	
No. Dosing/Recovery Cycles	3		3		3		3		3		1		1		1		1		1	
No. Doses Administered	3		3		3		3		3		1		1		1		1		1	
Duration of Each Dose Administration	3 hours		3 hours		3 hours		3 hours		24 hours		3 hours		3 hours		3 hours		3 hours		24 hours	
Days of Treatment (Study Day)	1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		1, 22, 43		62		62		62		62		62	
No. Weeks of Recovery (Weeks/Cycle)	3		3		3		3		3		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals[b]	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2
Histopathology (Cont)[c]																				
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)																				
Tissue Examined: Kidney																				
Number Examined											1	1	1	1	2	2	2	1	1	1
Tubular dilatation flat epithelium											0	0	0	0	0	1	0	1	1	1
Score 2											“	“	“	“	“	1	“	1	0	0
Score 4											“	“	“	“	“	0	“	0	1	1
Interstitial fibrosis											0	0	0	0	1	0	0	0	1	1
Score 1											“	“	“	“	1	“	“	“	0	0
Score 2											“	“	“	“	0	“	“	“	0	1
Score 3											“	“	“	“	0	“	“	“	1	0
Tubular epithelial degeneration-necrosis											0	0	0	0	0	0	0	0	0	1
Score 2											“	“	“	“	“	“	“	“	“	1

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (μg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Kidney										
Number Examined						1 1	1 1	2 2	2 1	1 1
Dilated Glomerular Capsule						0 0	0 0	1 0	0 0	1 1
Score 1						“ “	“ “	1 “	“ “	0 0
Score 2						“ “	“ “	0 “	“ “	1 1
Tissue Examined: Infusion Site Cephalic vein[d]										
Number Examined						1 1	1 1	2 2	2 1	1 1
Thrombophlebitis						0 0	0 0	1 0	0 0	0 0
Score 3						“ “	“ “	1 “	“ “	“ “
Necrosis Venous Wall						0 0	0 0	1 0	0 1	0 0
Score 2						“ “	“ “	0 “	1 “	“ “
Score 3						“ “	“ “	1 “	0 “	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present Score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Infusion Site Cephalic vein[d]										
Collagen degeneration venous wall	0 0	1 0	1 1	0 1	0 0					
Score 2	“ “	0 “	0 0	“ 1	“ “					
Score 3	“ “	1 “	1 1	“ 0	“ “					
Perivenous inflammatory cells	1 1	1 0	2 1	2 1	0 0					
Score 1	0 0	0 “	0 0	1 0	“ “					
Score 2	0 0	1 “	1 1	1 1	“ “					
Score 3	1 1	0 “	1 0	0 0	“ “					

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (μg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
5-7 Day Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Infusion Site Cephalic vein[d]										
Perivenous collagen degeneration						1 1	1 1	1 1	0 1	0 0
Score 1						0 0	0 0	0 0	“ 0	“ “
Score 2						0 1	0 0	0 0	“ 0	“ “
Score 3						1 0	0 0	1 1	“ 0	“ “
Score 4						0 0	1 0	0 0	“ 1	“ “
Perivenous hemorrhage						1 1	1 0	2 1	0 1	0 0
Score 2						0 0	0 “	0 0	“ 0	“ “
Score 3						1 1	0 “	2 1	“ 1	“ “
Score 4						0 0	1 “	0 0	“ 0	“ “
Perivenous fibroplasia						0 0	0 0	0 1	0 1	0 0
Score 2						“ “	“ “	“ 1	“ 0	“ “
Score 3						“ “	“ “	“ 0	“ 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present score not applicable

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3							Cycle 4		
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Liver										
Number Examined						1 1	1 1	x x	x 1	1 1
Hepatocellular hypertrophy						0 0	0 0	x x	x 0	1 0
Score 1						“ “	“ “	x x	x “	1 “
Hepatocellular degeneration/necrosis						0 0	1 0	x x	x 1	0 0
Score 3						“ “	1 “	x x	x 0	“ “
Score 4						“ “	0 “	x x	x 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Bone Marrow-Sternum										
Number Examined						1 1	1 1	x x	x 1	1 1
Medullary hypoplasia						0 0	1 1	x x	x 1	0 0
Score 2						“ “	0 1	x x	x 0	“ “
Score 4						“ “	1 0	x x	x 1	“ “
Tissue Examined: Bone Marrow-Femur										
Number Examined						1 1	1 1	x x	x 1	1 1
Medullary hypoplasia						0 0	0 1	x x	x 1	0 0
Score 2						“ “	“ 1	x x	x 0	“ “
Score 4						“ “	“ 0	x x	x 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Spleen										
Number Examined						1 1	1 1	x x	x 1	1 1
Lymphoid depletion						0 0	1 1	x x	x 1	0 1
Score 1						“ “	0 1	x x	x 0	“ 0
Score 2						“ “	1 0	x x	x 1	“ 0
Score 3						“ “	0 0	x x	x 0	“ 1
Tissue Examined: Thymus										
Number Examined						1 1	1 1	x x	x 1	1 1
Lymphoid depletion						0 0	1 1	x x	x 1	1 1
Score 2						“ “	0 0	x x	x 0	1 0
Score 3						“ “	1 1	x x	x 0	0 0
Score 4						“ “	0 0	x x	x 1	0 1

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Kidney										
Number Examined						1 1	1 1	x x	x 1	1 1
Tubular dilatation flat epithelium						0 0	1 0	x x	x 1	0 0
Score 1						“ “	0 “	x x	x 1	“ “
Score 2						“ “	1 “	x x	x 0	“ “
Tubulae epithelial degeneration-necrosis						0 0	0 0	x x	x 1	0 0
Score 2						“ “	“ “	x x	x 1	“ “
Tissue Examined: Infusion Site Cephalic vein[d]										
Number Examined										
Necrosis venous wall						0 0	0 1	x x	x 1	0 0
Score 4						“ “	“ 1	x x	x 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle (µg/m²)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Infusion Site Cephalic vein (Cont)[d]										
Collagen degeneration venous wall						0 0	1 0	x x	x 0	0 0
Score 2						“ “	1 “	x x	x “	“ “
Perivenous inflammatory cells						1 0	0 1	x x	x 1	0 0
Score 2						1 “	“ 0	x x	x 1	“ “
Score 3						0 “	“ 1	x x	x 0	“ “
Perivenous collagen degeneration						1 0	1 1	x x	x 1	0 0
Score 2						1 “	0 0	x x	x 0	“ “
Score 3						0 “	1 1	x x	x 0	“ “
Score 4						0 “	0 0	x x	x 1	“ “

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.1 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Cycles 1, 2 and 3					Cycle 4				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**4**	**2**	**5**
Dose/infusion or cycle ($\mu g/m^2$)	**0[a]**	**300**	**600**	**900**	**900**	**0**	**900**	**1200**	**1440**	**1200**
No. Dosing/Recovery Cycles	3	3	3	3	3	1	1	1	1	1
No. Doses Administered	3	3	3	3	3	1	1	1	1	1
Duration of Each Dose Administration	3 hours	3 hours	3 hours	3 hours	24 hours	3 hours	3 hours	3 hours	3 hours	24 hours
Days of Treatment (Study Day)	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	1, 22, 43	62	62	62	62	62
No. Weeks of Recovery (Weeks/Cycle)	3	3	3	3	3	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)	1 (N = 1) and 3 (N = 1)
Sex: No. of Animals[b]	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2	M: 2 F: 2
Histopathology (Cont)[c]										
3-Week Recovery Period and Found Dead/Moribund (Post Cycle 4)										
Tissue Examined: Infusion Site Cephalic vein (Cont)[d]										
Number Examined	1 1	1 1	1 1	1 1	x x	x 1	1 1	1 1		
Perivenous hemorrhage	1 1	1 1	1 1	1 1	x x	x 1	0 0			
Score 2	0 1	1 0	0 1	1 0	x x	x 0	“ “			
Score 3	1 0	0 0	0 0	0 1	x x	x 0	“ “			
Score 4	0 0	0 0	0 1	0 0	x x	x 1	“ “			
Degeneration/necrosis subcutis muscle	0 0	0 0	0 0	0 0	x x	x 1	0 0			
Score 3	“ “	“ “	“ “	“ “	x x	x 1	“ “			

[a] Control animals received the vehicle

[b] The animals treated during Cycles 1, 2 and 3 were the same animals treated during Cycle 4.

[c] Number with observation/Number examined

[d] Right and Left Cephalic veins were used for injection. The injection site data presented represents the highest score observed in either the right or left vein at any one of three levels examined/vein.

“ = Finding not present score not applicable; x = No data available due to animal death.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は３週間ごと１回（4 サイクル）反復投与試験

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

Species/Strain: Primate/ Cynomolgus

Duration of Dosing: Each cycle consisted of a 3-hour i.v. infusion administered once a week for 3 weeks followed by a one week treatment-free period for 3 cycles (Groups 1-4) or once every 3 weeks for 4 cycles (Group 5). Treatment was administered as follows: Cycle 1 on Test Days 1, 8 and 15; Cycle 2 on Test Days 29, 36 and 43; Cycle 3 on Test Days 57, 64 and 71; Cycle 4 on Test Days 1, 22, 43 and 64.

Study No.: [redacted]

Age at First Dose: At least 24 months

Duration of Treatment-Free/Recovery: Treatment-free periods for Groups 1-4: 1 week per dosing cycle; Group 5: 3 weeks per dosing cycle. At the end of the last cycle for each group, the first surviving animal of each sex/group was kept for a 7- to 8-day recovery period before necropsy. The second animal/sex/group was kept for a 3-week recovery period before necropsy.

Location in CTD: 4.2.3.2.7

Date of First Dose: Males: [redacted], Females: [redacted] **Route:** Intravenous Infusion

Vehicle/Formulation: Water for injection and sterile isotonic saline/ R279741 diluted with water to 50 µg/mL and further diluted as necessary with saline **GLP Compliance:** Yes

Special Features: None

No Observed Adverse Effect Level: <360 µg/m^2 (30 µg/kg)/cycle

DOSING AND TREATMENT-FREE/RECOVERY PERIODS

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)								One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)	
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (µg/kg)	**0**[a]		**10**		**20**		**30**		**70**	
Dose/infusion (µg/m^2)	**0**		**120**		**240**		**360**		**840**	
Dose/cycle (µg/kg)	**0**		**30**		**60**		**90**		**70**	
Dose/cycle (µg/m^2)	**0**		**360**		**720**		**1080**		**840**	
No. Dosing/Recovery Cycles	3		3		3		3		4	
No. Doses Administered	9		9		9		9		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
No. Weeks of Recovery Following Last Infusion Cycle	1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)		1 (N = 1) and 3 (N = 1)	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Toxicokinetics[c]:										
C_{max} (ng/mL) 1st Cycle			0.40	0.40	0.95	0.59	1.48	1.83	2.63	5.29
C_{max} (ng/mL) 3rd Cycle			0.40	0.67	1.10	1.17	1.85	3.41	NA	NA
C_{max} (ng/mL) 4th Cycle			NA	NA	NA	NA	NA	NA	3.95	6.19

[a] Control animals received the vehicle

[b] One Group 5 female died post dosing on test Day 1. This animal was immediately replaced.

[c] Toxicokinetics Report [redacted], samples collected after the first administration of Cycle 1 or after the last administration of Cycle 3 (Cycle 4 in Group 5). N = 1, animals were bled at alternate time points.

Note: Dose conversion to µg/m^2: multiply µg/kg by 12 for monkeys

NA = Sample not collected based on study design

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，３サイクル）又は３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)								One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)	
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Toxicokinetics[c]:										
$T_{1/2}$ (h) 1st Cycle[d]			/	/	60	73	149	/	61	42
$T_{1/2}$ (h) 3rd Cycle[d]			63	85	49	74	/	138	NA	NA
$T_{1/2}$ (h) 4th Cycle[d]			NA	Na	NA	NA	NA	NA	64	45
AUC (ng.h/mL) 1st Cycle[e]			1.63	/	3.96	2.94	5.73	6.72	12.8	15.8
AUC (ng.h/mL) 3rd Cycle[e]			1.88	2.57	5.13	5.25	6.98	10.30	NA	NA
AUC (ng.h/mL) 4th Cycle[e]			NA	Na	NA	NA	NA	NA	15.5	19.0
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	1	2
Day of Death (Found dead/Moribund Sacrifice)									38	1, 66
Number Killed at Terminal Sacrifice (1/sex/group Days 72 or 79 and Days 85 or 92)	2	2	2	2	2	2	2	2	1	1
Body weight (g)	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Electrocardiograms	-	-	-	-	-	-	-	-	-	-
Ophthalmology	-	-	-	-	-	-	-	-	-	-
Rectal Body Temperature >40°C	-	-	-	-	-	-	-	-	40.2°C- moribund animal day prior to sacrifice; surviving animal increased temperature twice during study	40.2°C- moribund animal day prior to sacrifice

[a] Control animals received the vehicle

[b] One Group 5 female died post dosing on test Day 1. This animal was immediately replaced.

[c] Toxicokinetics Report [redacted], Samples collected after the first administration of Cycle 1 or after the last administration of Cycle 3 (Cycle 4 in the high dose). N=1, animals were bled at alternate time points.

[d] Time for calculation: males-10 μg/kg: 24-72 hours; 20 μg/kg: 72-96 hours; 30 μg/kg: 96-144 hours; 70 μg/kg: 144-216 hours (Cycle 1), 24-144 hours (Cycle 4)
Time for calculation: females-10 μg/kg: 24-72 hours; 20 μg/kg: 48-96 hours (Cycle 1), 96-144 hours (Cycle 3); 30 μg/kg: 96-144 hours (Cycle 3); 70 μg/kg: 144-216 hours

[e] Time for calculation: 0-24 hours

NA = Sample not collected based on study design; / = Sample not available or not analyzed, or concentration not reliable, or parameter not calculated; - = No noteworthy findings

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，３サイクル）又は３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m^2)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m^2)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Clinical Observations[c]										
Injection site skin thickening/hardening/ swelling	1/2	-	1/2	1/2	2/2	1/2	1/2	-	-	-
Hypoactivity	-	-	-	-	-	-	-	-	1/2	2/3
Prostration and/or vomiting	-	-	-	-	-	-	-	-	1/2	2/3
Hematology[d]										
Day 3 (Post Cycle 1, first infusion)										
RBC (10^{12}/L)	5.99	6.21	1.00	1.01	0.98	1.06	0.98	1.03	0.91	0.89
Hgb (g/dL)	11.9	12.9	1.08	0.98	0.98	1.08	1.03	0.98	0.93	0.88
PCV (L/L)	0.39	0.42	1.04	0.98	0.95	1.06	1.00	0.95	0.92	0.86
Retics (p. 1000)	5.0	4.0	0.90	1.00	1.00	0.25	0.50	0.75	0.20	0.25
Day 17 (Post Cycle 1, third infusion)										
RBC (10^{12}/L)	6.25	6.38	0.95	0.96	0.86	0.88	0.85	0.82		
Hgb (g/dL)	12.4	13.0	1.03	0.94	0.86	0.91	0.89	0.80		
PCV (L/L)	0.41	0.45	1.01	0.94	0.87	0.88	0.87	0.74		
Retics (p. 1000)	3.5	4.0	0.57	0.50	5.57	0.38	0.43	0.88		

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] Number with observation/Number examined

[d] For controls, group means are shown. For treated groups, multiples of control are shown.

- = No noteworthy findings

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，３サイクル）又は３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m^2)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m^2)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Hematology[c] (Cont)										
Day 16/19 (Post Cycle 1, first infusion)[d]										
RBC (10^{12}/L)									0.74	0.84
Hgb (g/dL)									0.78	0.83
PCV (L/L)									0.81	0.82
Retics (p. 1000)									6.25	0.86
Day 26 (Post Cycle 1, third infusion)										
RBC (10^{12}/L)	6.59	6.23	0.89	0.98	0.86	0.88	0.81	0.80		
Hgb (g/dL)	13.0	12.9	0.96	0.95	0.88	0.93	0.86	0.77		
PCV (L/L)	0.42	0.43	0.94	0.99	0.90	0.93	0.86	0.74		
Retics (p. 1000)	2.0	3.5	1.25	1.14	16.50	1.00	3.50	2.57		
Day 37/38/40 (Post Cycle 2, second infusion) [d]										
RBC (10^{12}/L)									0.46	0.85
Hgb (g/dL)									0.49	0.92
PCV (L/L)									0.50	0.94
Retics (p. 1000)									0.75	4.86
Day 54 (Post Cycle 2, third infusion)										
RBC (10^{12}/L)	6.91	6.52	0.85	0.94	0.83	0.76	0.71	0.52		
Hgb (g/dL)	13.5	13.4	0.94	0.93	0.90	0.88	0.84	0.55		
PCV (L/L)	0.45	0.45	0.92	0.96	0.93	0.87	0.87	0.54		
Retics (p. 1000)	1.50	2.0	2.00	2.00	18.00	2.25	4.33	8.25		

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval, multiple of control was calculated based on control data from the Day 26 interval.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，３サイクル）又は３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m^2)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m^2)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Hematology[c] (Cont)										
Day 58/61 (Post Cycle 3, third infusion)[d]										
RBC (10^{12}/L)									0.76	0.72
Hgb (g/dL)									0.88	0.77
PCV (L/L)									0.97	0.75
Retics (p. 1000)									7.33	3.75
Day 72/85 (Post Cycle 4, fourth infusion)[e]										
RBC (10^{12}/L)									0.79	0.81
Hgb (g/dL)									0.93	0.89
PCV (L/L)									0.95	0.83
Retics (p. 1000)									0.33	2.75
Day 79/82 (Post Cycle 3, third infusion)										
RBC (10^{12}/L)	5.95	6.22	0.87	0.83	0.69	0.40	0.59	0.36		
Hgb (g/dL)	11.4	12.7	0.97	0.86	0.77	0.51	0.69	0.43		
PCV (L/L)	0.40	0.42	0.93	0.74	0.74	0.49	0.68	0.40		
Retics (p. 1000)	3.0	4.0	0.50	2.88	10.17	4.88	2.17	12.50		
Day 92 (Post Cycle 3, third infusion)										
RBC (10^{12}/L)	6.69	6.34	0.80	0.84	0.71	0.44	0.54	0.58		
Hgb (g/dL)	12.8	13.5	0.93	0.85	0.84	0.56	0.70	0.61		
PCV (L/L)	0.41	0.43	0.90	0.86	0.85	0.58	0.71	0.65		
Retics (p. 1000)	1.0	3.0	2.00	0.67	57.00	13.3	74.00	6.00		

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval, multiples of control were calculated based on control data from the Day 54 interval.

[e] For this interval, multiples of control were calculated based on control data from the Day 79/82 interval.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Bone Marrow Differential Cell Counts[c]										
Day 38 (Post Cycle 2, second infusion)[d]										
Total Myeloid Series (%)									0.10	
Neutrophils (%)									0.04	
Total Erythroid Series (%)									0.11	
Normoblasts (%)									0.14	
Myeloid/Erythroid Ratio									0.91	
Day 72 (Post Cycle 4, fourth infusion)[d]										
Total Myeloid Series (%)									0.63	
Neutrophils (%)									1.00	
Total Erythroid Series (%)									0.13	
Normoblasts (%)									0.08	
Myeloid/Erythroid Ratio									4.98	
Day 79/85 (Post Cycle 3, third infusion)										
Total Myeloid Series (%)	45.0	44.5	0.90	0.84	0.67	0.70	0.78	0.53		0.72
Neutrophils (%)	22.5	26.0	0.84	0.62	0.60	0.71	0.89	0.40		0.56
Total Erythroid Series (%)	31.5	31.0	0.89	1.63	1.46	1.82	1.13	1.27		1.66
Normoblasts (%)	18.5	22.0	0.89	1.41	1.51	1.48	1.22	1.05		1.52
Myeloid/Erythroid Ratio	1.43	1.44	1.01	0.52	0.46	0.38	0.69	0.42		0.43

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval, multiple of control was calculated based on control data from the Day 79 interval.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，３サイクル）又は３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)				One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)					
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Bone Marrow Differential Cell Counts[c]										
Day 92 (Post Cycle 3, third infusion)										
Total Myeloid Series (%)	39.5	52.0	0.85	0.86	0.67	0.64	0.96	0.59		
Neutrophils (%)	19.5	28.0	0.74	0.70	0.51	0.52	0.79	0.43		
Total Erythroid Series (%)	31.0	31.5	1.05	1.11	1.26	1.89	1.69	1.83		
Normoblasts (%)	19.0	19.5	1.11	1.18	1.34	1.67	1.76	1.49		
Myeloid/Erythroid Ratio	1.27	1.65	0.81	0.77	0.53	0.34	0.57	0.32		
Clinical Chemistry[c]										
Day 3 (Post Cycle 1, first infusion)										
Aspartate aminotransferase (IU/L)	71.0	233.5	0.68	0.39	8.68	0.31	4.11	0.19	3.55	0.79
Alanine aminotransferase (IU/L)	73.5	187.5	0.71	0.33	3.03	0.46	2.50	0.28	2.18	0.86
Creatine kinase (IU/L)	707.0	3447.5	0.67	0.29	1.97	0.10	6.12	0.05	9.57	0.38
Lactate dehydrogenase (IU/L)	928.0	1808	0.76	0.58	0.82	0.42	2.72	0.30	2.40	0.61
Day 17 (Post Cycle 1, third infusion)										
Aspartate aminotransferase (IU/L)	27.5	38.5	1.15	1.13	1.36	2.09	2.36	0.79		
Alanine aminotransferase (IU/L)	42.5	83.5	0.79	0.47	1.33	1.07	2.32	0.75		
Creatine kinase (IU/L)	121.5	130.0	1.66	4.92	1.31	3.74	4.56	0.55		
Lactate dehydrogenase (IU/L)	569.0	665.0	0.94	0.97	1.16	1.16	1.66	0.80		

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4))			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Clinical Chemistry[c]										
Day 16/19 (Post Cycle 1, first infusion)[d]										
Aspartate aminotransferase (IU/L)									1.53	0.84
Alanine aminotransferase (IU/L)									1.94	0.78
Creatine kinase (IU/L)									2.18	1.11
Lactate dehydrogenase (IU/L)									0.71	0.55
Day 26 (Post Cycle 1, third infusion)										
Aspartate aminotransferase (IU/L)	25.5	27.0	0.88	0.87	1.25	1.33	1.51	1.20		
Alanine aminotransferase (IU/L)	30.5	56.5	0.93	0.49	1.69	1.42	2.48	0.96		
Creatine kinase (IU/L)	59.0	82.0	1.42	1.26	1.55	1.87	2.39	3.24		
Lactate dehydrogenase (IU/L)	385.5	315.0	0.94	1.06	1.08	1.27	1.52	1.24		
Day 38 (Post Cycle 2, second infusion)[e]										
Aspartate aminotransferase (IU/L)									0.86	
Alanine aminotransferase (IU/L)									0.56	
Creatine kinase (IU/L)									3.42	
Lactate dehydrogenase (IU/L)									0.66	

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval multiple of control was calculated based on control data from Day 17 interval.

[e] For this interval multiple of control was calculated based on control data from Day 26 interval.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Clinical Chemistry[c]										
Day 37/40 (Post Cycle 2, second infusion)[d]										
Aspartate aminotransferase (IU/L)									0.38	1.46
Alanine aminotransferase (IU/L)									0.66	1.59
Creatine kinase (IU/L)									0.56	2.48
Lactate dehydrogenase (IU/L)									0.78	1.44
Day 54 (Post Cycle 2, third infusion)										
Aspartate aminotransferase (IU/L)	26.0	27.0	0.83	0.80	1.15	1.50	1.48	1.17		
Alanine aminotransferase (IU/L)	30.5	48.0	0.82	0.50	1.98	1.65	2.36	0.99		
Creatine kinase (IU/L)	87.0	75.0	0.84	1.01	1.69	2.45	2.76	1.64		
Lactate dehydrogenase (IU/L)	324.0	307.0	1.12	0.95	1.28	1.42	1.59	1.18		
Day 58/61 (Post Cycle 3, third infusion)[d]										
Aspartate aminotransferase (IU/L)									1.65	1.46
Alanine aminotransferase (IU/L)									1.93	1.59
Creatine kinase (IU/L)									3.32	2.11
Lactate dehydrogenase (IU/L)									1.51	1.43
Day 66 (Post Cycle 4, fourth infusion)[d]										
Aspartate aminotransferase (IU/L)										14.37
Alanine aminotransferase (IU/L)										2.54
Creatine kinase (IU/L)										/
Lactate dehydrogenase (IU/L)										/

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval multiple of control was calculated based on control data from Day 54 interval.

/ = Insufficient sample

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Clinical Chemistry (Cont)[c]										
Day 72 (Post Cycle 3, third infusion)[d]										
Aspartate aminotransferase (IU/L)									1.05	
Alanine aminotransferase (IU/L)									1.95	
Creatine kinase (IU/L)									1.02	
Lactate dehydrogenase (IU/L)									1.67	
Day 79/82 (Post Cycle 3, third infusion)										
Aspartate aminotransferase (IU/L)	30.5	24.0	0.80	0.88	0.93	1.00	1.82	1.13		
Alanine aminotransferase (IU/L)	39.0	59.5	0.82	0.49	1.45	1.01	1.29	0.85		
Creatine kinase (IU/L)	102.0	102.5	1.05	0.67	1.12	0.84	35.58	1.04		
Lactate dehydrogenase (IU/L)	337.0	368.0	1.15	1.03	1.37	1.33	2.79	1.50		
Day 85 (Post Cycle 4, fourth infusion)[d]										
Aspartate aminotransferase (IU/L)										1.88
Alanine aminotransferase (IU/L)										1.38
Creatine kinase (IU/L)										2.07
Lactate dehydrogenase (IU/L)										1.03

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

[d] For this interval multiple of control was calculated based on control data from Day 79 interval.

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Clinical Chemistry (Cont)[c]										
Day 92 (Post Cycle 3, third infusion)										
Aspartate aminotransferase (IU/L)	26.0	22.0	1.15	0.86	1.15	3.09	1.27	1.32		
Alanine aminotransferase (IU/L)	27.0	47.0	1.41	0.40	2.81	2.02	2.07	0.81		
Creatine kinase (IU/L)	95.0	106.0	1.29	0.44	1.58	3.42	1.32	1.26		
Lactate dehydrogenase (IU/L)	402.0	289.0	1.17	1.14	1.04	1.74	1.45	1.04		
Urinalysis	-	-	-	-	-	-	-	-	-	-
Organ Weight	-	-	-	-	-	-	-	-	-	-
Organ/Body Weight	-	-	-	-	-	-	-	-	-	-
Organ/Brain Weight	-	-	-	-	-	-	-	-	-	-

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

[c] For controls, group means are shown. For treated groups, multiples of control are shown.

- = No noteworthy findings

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Gross Necropsy[c]										
Number of Animals Examined	2	2	2	2	2	2	2	2	2	3
Injection Sites[d]										
Hematoma	2/2	1/2	2/2	1/2	1/2	2/2	2/2	1/2	1/2	2/3
Edema	1/2	0/2	1/2	1/2	1/2	1/2	1/2	1/2	0/2	0/3
Thickening of subcutaneous/muscular tissue	1/2	0/2	1/2	1/2	1/2	2/2	1/2	1/2	0/2	0/3
Induration of subcutaneous/muscular tissue	0/2	0/2	1/2	0/2	1/2	2/2	1/2	1/2	0/2	0/3
Histopathology										
7-8 Day Recovery Period and Found Dead/Moribund										
Tissue Examined: Cecum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Granulocyte infiltration	0	1	0	0	0	0	0	0	0	1
Score 1	“	1	“	“	“	“	“	“	“	1
Necrotic typhlitis	0	0	0	0	0	0	0	0	0	1
Score 5	“	“	“	“	“	“	“	“	“	1
Tissue Examined: Colon										
Number Examined	1	1	1	1	1	1	1	1	2	2
Ulceration	0	0	0	0	0	0	0	0	1	0
Score 1	“	“	“	“	“	“	“	“	1	“

[a] Control animals received the vehicle
[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.
[c] Number with observation/Number Examined
[d] Data presented represents the most severe finding of all dosing sites.
“ = Finding not present score not applicable

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
7-8 Day Recovery Period and Found Dead/Moribund										
Histopathology (Cont)										
Tissue Examined: Duodenum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Duodenitis	0	0	0	0	0	0	0	0	1	1
Score 1	“	“	“	“	“	“	“	“	1	0
Score 2	“	“	“	“	“	“	“	“	0	1
Dilated glands	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Subacute peritonitis	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Tissue Examined: Ileum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Epithelial cell necrosis	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Acute ileitis	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Subacute peritonitis	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

“ = Finding not present score not applicable

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Histopathology (Cont)										
7-8 Day Recovery Period and Found Dead/Moribund										
Tissue Examined: Jejunum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Granulocyte infiltration	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Capillary ectasia	0	0	0	0	0	0	0	0	0	1
Score 2	“	“	“	“	“	“	“	“	“	1
Subacute peritonitis	0	0	0	0	0	0	0	0	0	1
Score 1	“	“	“	“	“	“	“	“	“	1
Tissue Examined: Rectum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Ulceration	0	0	0	1	0	0	0	0	1	0
Score 2	“	“	“	1	“	“	“	“	1	“
Tissue Examined: Kidney										
Number Examined	1	1	1	1	1	1	1	1	2	2
Interstitial mononuclear cell aggregation	1	1	1	1	1	1	1	1	1	1
Score 1	0	0	0	0	0	1	1	0	1	1
Score 2	1	1	1	1	1	0	0	1	0	0
Tubular basophilia	0	0	0	1	0	1	1	0	0	0
Score 1	“	“	“	1	“	1	1	“	“	“

[a] Control animals received the vehicle
[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.
“ = Finding not present score not applicable

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Histopathology (Cont)										
7-8 Day Recovery Period and Found Dead/Moribund										
Tissue Examined: Kidney (cont)										
Number Examined	1	1	1	1	1	1	1	1	2	2
Tubular cyst dilation	0	0	1	0	0	0	0	0	0	0
Score 2	“	“	1	“	“	“	“	“	“	“
Mononuclear cell aggregation in pelvis	0	0	0	0	0	1	0	0	0	0
Score 1	“	“	“	“	“	1	“	“	“	“
Brownish pigment-laden tubular cells	0	0	0	0	0	0	1	0	0	0
Score 1	“	“	“	“	“	“	1	“	“	“
Tubular dilatation with flattened epithelium	0	0	0	0	0	0	0	0	1	2
Score 1	“	“	“	“	“	“	“	“	0	2
Score 3	“	“	“	“	“	“	“	“	1	0
Tissue Examined: Thymus										
Number Examined	1	1	1	1	1	1	1	1	2	2
Lymphoid depletion	0	0	0	0	0	1	1	1	1	1
Score 1	“	“	“	“	“	1	1	0	0	1
Score 2	“	“	“	“	“	0	0	0	1	0
Score 4	“	“	“	“	“	0	0	1	0	0

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

“ = Finding not present score not applicable

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0[a]**		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Histopathology (Cont)										
7-8 Day Recovery Period and Found Dead/Moribund										
Tissue Examined: Lymph Node-Axillary										
Number Examined	1	1	1	1	1	1	1	1	2	2
Lymphoid depletion	0	0	0	0	0	0	0	0	2	1
Score 1	“	“	“	“	“	“	“	“	1	1
Score 2	“	“	“	“	“	“	“	“	1	0
Tissue Examined: Lymph Node-Mandibular										
Number Examined	1	1	1	1	1	1	1	1	2	2
Lymphoid depletion	0	0	0	0	0	0	0	0	1	1
Score 2	“	“	“	“	“	“	“	“	0	1
Score 3	“	“	“	“	“	“	“	“	1	0
Tissue Examined: Lymph Node-Mesenteric										
Number Examined	1	1	1	1	1	1	1	1	2	2
Lymphoid depletion	0	0	0	0	0	0	0	0	1	1
Score 2	“	“	“	“	“	“	“	“	1	1
Tissue Examined: Lymph Node-Retropharyngeal										
Number Examined	1	1	1	1	1	1	1	1	2	2
Lymphoid depletion	0	0	0	0	0	0	0	0	2	1
Score 1	“	“	“	“	“	“	“	“	1	1
Score 3	“	“	“	“	“	“	“	“	1	0

[a] Control animals received the vehicle

[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.

“ = Finding not present score not applicable

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Histopathology (Cont)										
7-8 Day Recovery Period and Found Dead/Moribund										
Tissue Examined: Bone Marrow-Sternum										
Number Examined	1	1	1	1	1	1	1	1	2	2
Medullary hypocellularity	0	0	0	0	0	0	0	0	2	1
Score 3	“	“	“	“	“	“	“	“	2	1
Tissue Examined: Injection Site[c]										
Number Examined	1	1	1	1	1	1	1	1	2	2
Necrosis-venous wall	0	0	1	1	1	1	1	1	0	0
Score 2	“	“	1	0	0	0	0	0	“	“
Score 3	“	“	0	0	1	0	0	0	“	“
Score 4	“	“	0	1	0	1	1	1	“	“
Histopathology 3-Week Recovery Period										
Tissue Examined: Thymus										
Number Examined	1	1	1	1	1	1	1	1	0	1
Lymphoid depletion	0	0	0	0	0	1	0	1	“	0
Score 1	“	“	“	“	“	0	“	1	“	“
Score 4	“	“	“	“	“	1	“	0	“	“
Tissue Examined: Bone Marrow-Sternum	-	-	-	-	-	-	-	-	x	-
Number Examined	1	1	1	1	1	1	1	1	0	1

[a] Control animals received the vehicle
[b] One Group 5 female died post-dosing on test Day 1. This animal was immediately replaced.
[c] Data presented represents the most severe finding of all dosing sites.
“ = Finding not present score not applicable; - = No noteworthy findings; x = No survivors

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Noteworthy Findings										
Histopathology (Cont)										
Tissue Examined: Lymph Nodes - Axillary, Mandibular, Mesenteric, Retropharyngeal	-	-	-	-	-	-	-	-	x	-
Number Examined	1	1	1	1	1	1	1	1	0	1
Tissue Examined: Skin										
Number Examined	1	1	1	1	1	1	1	1	0	1
Ulceration	0	0	0	0	0	1	0	0	“	0
Score 4	“	“	“	“	“	1	“	“	“	“
Tissue Examined: Injection Site[c]										
Number Examined	1	1	1	1	1	1	1	1	0	1
Necrosis-venous wall	0	0	1	1	1	1	1	1	“	1
Score 3	“	“	0	0	1	0	1	0	“	1
Score 4	“	“	1	1	0	0	0	1	“	0
Score 5	“	“	0	0	0	1	0	0	“	0
Tissue Examined: Kidney										
Number Examined	1	1	1	1	1	1	1	1	0	1
Glomerular Fibrosis	0	0	0	0	0	1	0	0	“	1
Score 1	“	“	“	“	“	1	“	“	“	1

[a] Control animals received the vehicle
[b] One Group 5 female died post dosing on test Day 1. This animal was immediately replaced.
[c] Data presented represents the most severe finding of all dosing sites

“ = Finding not present score not applicable; - = No noteworthy findings; x = No survivors

2.6.7.7.2.2 サル１週間ごと１回投与（3 回投与，3 サイクル）又は 3 週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Dose Range-Finding Toxicity Study Following 3 or 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

	Weekly 3-Hour Infusion 3 Weeks on, 1 Week off/ Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2 and 3)						One 3-Hour Infusion Treatment Once Every 3 Weeks/Cycle Followed by 1- and 3-Week Recovery Periods (Cycles 1, 2, 3 and 4)			
Group	**1**		**2**		**3**		**4**		**5**	
Dose/infusion (μg/m²)	**0**[a]		**120**		**240**		**360**		**840**	
Dose/cycle (μg/m²)	**0**		**360**		**720**		**1080**		**840**	
Number of Dosing/Recovery Cycles	3		3		3		3		4	
Days of Treatment (Study Day)	1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 8, 15, 29, 36, 43, 57, 64, 71		1, 22, 43, 64	
Sex: No. of Animals	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 2	M: 2	F: 3[b]
Histopathology (Cont)										
3-Week Recovery Period										
Tissue Examined: Kidney (cont)										
Number Examined	1	1	1	1	1	1	1	1	0	1
Interstitial mononuclear cell aggregation	1	1	1	1	1	1	1	1	0	1
Score 1	1	1	1	1	1	0	1	1	“	0
Score 2	0	0	0	0	0	1	0	0	“	0
Score 3	0	0	0	0	0	0	0	0	“	1
Mononuclear cell aggregation in pelvis	0	0	0	0	0	0	0	0	0	1
Score 1	“	“	“	“	“	“	“	“	“	1
Peritubular fibrosis	1	0	0	0	0	0	1	1	0	1
Score 1	1	“	“	“	“	“	1	1	“	1
Proteinaceous casts	0	0	1	0	0	1	1	0	0	1
Score 1	“	“	1	“	“	1	1	“	“	1
Tubular basophilia	1	0	0	0	1	0	0	0	0	0
Score 1	1	“	“	“	1	“	“	“	“	“
Tubular dilatation with flattened epithelium	0	0	0	0	1	1	0	0	0	1
Score 1	“	“	“	“	1	1	“	“	“	1

[a] Control animals received the vehicle

[b] One Group 5 female died post dosing on test Day 1. This animal was immediately replaced.

“ = Finding not present score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験

Report Title: **Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys**

Test Article: R279741（Trabectedin）

Species/Strain: Primate/Cynomolgus

Duration of Dosing: Each cycle consisted of a 24-hour intravenous infusion followed by 3 treatment-free weeks. The study was initially planned for 8 cycles; dosing was terminated after 4 cycle.

Study No.: [redacted]

Age at First Dose: At least 24 months of age

Duration of Treatment-Free Period: 3 Weeks/Cycle

Location in CTD: 4.2.3.2.9

Date of First Dose: Males: [redacted]; Females: [redacted]

Route: Intravenous Infusion (24-hours/dosing cycle, via vascular access port)

Vehicle/Formulation: Sterile normal saline/ R279741 plus vehicle

GLP Compliance: No

Special Features: None

No Observed Adverse Effect Level: <300 μg/m^2

DOSING AND TREATMENT-FREE PERIODS

Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Dose Volume (mL/kg/cycle) (Cycles 1-3/Cycle 4)	60/10		60/10		60/10		60/10	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Recovery Days Following Last Dose (Males/Females)	20/19		20/19		20/19		20/19	
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Toxicokinetics[a]								
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	2	0	3	2
Day of Death	-	-	-	-	65, 73 (1 and 9 days post 4th infusion)	-	73, 73, 75 (9, 9 and 11 days post 4th infusion)	58, 71 (15 days post 3rd infusion, 7 days post 4th infusion)
Body Weight (kg)	-	-	-	-	-	-	-	-
Food Consumption (Qualitative Evaluation)	-	-	-	-	-	Decreased during week following third infusion	-	Decreased during week following third infusion
Ophthalmology	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-

[a] Toxicokinetic samples were collected, but were not analyzed, due to the early termination of the study.

- No noteworthy findings

Note: Dose conversion to μg/m^2: multiply μg/kg by 12.

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose µg/m² (µg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last Dose (Males/Females)	20/19		20/19		20/19		20/19	
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Rectal Body Temperature	-	-	-	-	-	-	-	-
Clinical Observations[a]								
Liquid feces	3/5	3/5	3/3	1/3	3/3	2/3	1/5	2/5
Vomiting	0/5	0/5	0/3	0/3	1/3	0/3	2/5	3/5
Dehydration	0/5	0/5	1/3	0/3	1/3	0/3	1/5	2/5
Problems with infusion systems and/or intolerance at infusion sites	4/5	2/5	3/3	3/3	1/3	3/3	2/5	3/5
Hematology[b]								
Day 6 (5 Days Post Cycle 1 Dosing)								
Fibrinogen (g/L)	3.52	2.87	1.22	1.48	1.28	1.66*	1.20	1.66*
Day 20 (19 Days Post Cycle 1 Dosing)	-	-	-	-	-	-	-	-
Day 27 (5 Days Post Cycle 2 Dosing)								
RBC (10^{12}/L)	5.78	6.16	1.08	0.93	1.04	0.81	0.91	0.80*
Platelets (10^{9}/L)	472	339	0.81	1.70	1.00	1.51	1.26	2.09*
Fibrinogen (g/L)	3.01	3.19	1.45	1.92*	2.22*	1.65	1.67	1.84*
Day 41 (19 Days Post Cycle 2 Dosing)	-	-	-	-	-	-	-	-
Day 48 (5 Days Post Cycle 3 Dosing)								
WBC (10^{9}/L)	10.74	11.74	1.44	1.21	1.10	1.09	0.63	1.03
RBC (10^{12}/L)	6.07	6.14	0.97	0.98	0.92	0.83	0.81	0.70*
MCV								
MCV (10^{-15}/L)	67.9	66.7	0.93	0.89	0.98	0.96	1.01	1.06
Platelets (10^{9}/L)	420	393	1.05	1.33	1.24	1.21	1.41	1.63
Fibrinogen (g/L)	2.88	3.78	2.03*	1.17	1.95	1.80*	2.17*	1.74

[a] Number with observation/Number observed

[b] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p<0.05, ** = p<0.01 (Dunn test)

- No noteworthy findings

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Hematology[a] (Cont)								
Day 62 (19 Days Post Cycle 3 Dosing)								
WBC (10^9/L)	9.97	10.05	1.82	1.29	0.92	1.20	0.69	0.86
RBC (10^{12}/L)	6.51	6.36	0.92	1.00	0.86	0.82	0.72**	0.66**
Platelets (10^9/L)	369	413	1.36	1.30	0.96	1.14	2.01	1.34
Fibrinogen (g/L)	2.83	2.44	1.34	1.90	1.34	1.72	1.27	1.71
Day 69 (5 Days Post Cycle 4 Dosing)								
RBC (10^{12}/L)	6.25	6.05	1.00	1.05	0.77	0.87	0.67*	0.69*
MCV (10^{-15}/L)	66.8	67.5	0.93	0.91	1.01	0.97	1.04	1.11
Platelets (10^9/L)	377	388	0.99	1.57	1.32	1.13	1.44	1.59
Fibrinogen (g/L)	3.58	3.63	1.20	1.26	1.78	1.23	1.66*	1.49
Day 83/84 (19/20 Days Post Cycle 4, Study Termination)								
RBC (10^{12}/L)	6.46	5.98	1.00	0.97	0.83	1.02	0.78	0.74
MCV (10^{-15}/L)	67.7	67.7	0.92	0.95	1.00	0.99	1.07	1.10
Platelets (10^9/L)	379	356	1.03	1.56	1.01	0.99	1.36	1.32
Fibrinogen (g/L)	2.86	2.34	1.44	2.05*	1.14	1.55	1.34	1.76

[a] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p<0.05, ** = p<0.01 (Dunn test)

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Clinical Chemistry[a]								
Day 6 (5 Days Post Cycle 1 Dosing)								
Inorganic Phosphorous (mmol/L)	1.79	1.92	0.97	0.92	0.91	0.95	1.03	0.84
Day 20/22 (19/21 Days Post Cycle 1 Dosing)								
Inorganic Phosphorous (mmol/L)	2.14	2.29	1.02	0.85	1.00	0.87	1.08	0.89
Day 27 (5 Days Post Cycle 2 Dosing)								
Inorganic Phosphorous (mmol/L)	2.31	2.18	0.83	0.82	0.87	0.83	0.84	0.73**
Day 41 (19 Days Post Cycle 2 Dosing)								
Inorganic Phosphorous (mmol/L)	2.18	2.12	0.90	0.86	0.97	0.79	0.99	0.97
Day 48 (5 Days Post Cycle 3 Dosing)								
Inorganic Phosphorous (mmol/L)	2.33	2.05	0.64*	0.91	0.70*	0.69	0.76	0.69*
Urea (mmol/L)	8.6	7.9	0.78	0.85	0.77	0.90	0.86	1.10
Creatinine (mmol/L)	79	73	0.91	1.01	0.95	1.15	1.16	1.10
Day 62 (19 Days Post Cycle 3 Dosing)								
Inorganic Phosphorous (mmol/L)	2.36	2.15	0.84	0.87	0.83	0.86	0.81	0.80
Urea (mmol/L)	7.6	6.5	0.88	1.05	0.96	1.32	1.09	1.43*
Creatinine (mmol/L)	78	64	0.86	1.13	0.94	1.22	1.08	1.09

[a] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = $p<0.05$, ** = $p<0.01$ (Dunn test)

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Clinical Chemistry[a] (Cont)								
Day 69 (5 days Post Cycle 4 Dosing)								
Inorganic Phosphorous (mmol/L)	2.03	1.94	0.92	0.97	0.66	0.87	0.69*	0.91
Urea (mmol/L)	8.6	8.3	0.86	0.92	0.79	1.10	0.79	2.01*
Creatinine (mmol/L)	77	70	0.88	1.03	1.12	1.14	1.01	1.27
Day 83/84 (19/20 Days Post Cycle 4, Study Termination)								
Inorganic Phosphorous (mmol/L)	2.04	2.24	0.94	0.82	0.75	1.06	0.92	0.74
Urea (mmol/L)	9.8	9.8	0.87	0.81	1.09	0.88	1.17	1.73
Creatinine (mmol/L)	80	72	0.90*	1.06	1.18	1.11	1.30	1.40*
Organ Weights [a]								
Kidney (g)	13.25	14.72	1.08	0.94	1.71	1.05	1.51	1.31
Kidney/body weight (%)	0.48	0.53	1.06	0.92	1.60	1.11	1.52	1.58
Thymus (g)	4.76	3.71	0.88	1.05	0.41	0.85	0.54	0.23
Thymus/body weight (%)	0.17	0.13	0.88	1.08	0.41	0.92	0.53	0.31

[a] For controls, group means are shown. For treated groups, multiples of control are shown. Statistical significance is based on actual data (not on the multiples of control).

* = p<0.05, ** = p<0.01, (Mann-Whitney U test-clinical chemistry; Dunn test-organ weight data)

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Gross Pathology[a]								
Infusion Site								
Induration of Adjacent Tissue	-	-	3/3	2/3	3/3	3/3	5/5	5/5
Kidneys-dilated pelvis	-	-	-	-	1/3	-	1/5	3/5
Kidneys-pale	1/5	-	-	-	1/3	2/3	3/5	4/5
Kidneys-enlarged	-	-	-	-	1/3	-	2/5	5/5
Spleen-enlarged	1/5	-	-	1/3	1/3	1/3	2/5	1/5
Thymus-reduced in size	-	-	-	-	-	-	2/5	4/5
Lymph Nodes								
Axillary-enlarged	1/5	-	-	-	-	-	-	-
Iliac-enlarged	1/5	-	2/3	-	2/3	1/3	2/5	2/5
Inguinal-enlarged	1/5	-	-	1/3	-	-	-	2/5
Popliteal-enlarged	-	-	-	1/3	-	-	-	-

[a] Number with observation/number observed

- No noteworthy findings

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology								
Tissue Examined: Infusion Site 1, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Thrombophlebitis	0	1	1	0	3	0	2	5
Score 3	“	1	1	“	1	“	0	0
Score 4	“	0	0	“	2	“	0	0
Score 5	“	0	0	“	0	“	2	5
Phlebetis	3	0	0	0	0	2	1	0
Score 1	3	“	“	“	“	0	0	“
Score 2	0	“	“	“	“	1	0	“
Score 4	0	“	“	“	“	1	1	“
Collagen degeneration	3	2	1	2	0	1	3	0
Score 1	1	0	0	1	“	0	0	“
Score 2	0	2	1	0	“	0	1	“
Score 3	2	0	0	1	“	1	1	“
Score 4	0	0	0	0	“	0	1	“
Intimal endothelial cell necrosis	3	3	1	1	0	0	2	0
Score 1	2	1	1	0	“	“	0	“
Score 2	1	2	0	1	“	“	1	“
Score 3	0	0	0	0	“	“	1	0

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 1, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Intimal endothelial cell proliferation	1	0	1	1	0	0	1	0
Score 1	1	“	1	0	“	“	0	“
Score 2	0	“	0	1	“	“	1	“
Perivenous hemorrhage	0	1	1	1	1	0	2	2
Score 1	“	1	0	1	1	“	1	0
Score 2	“	0	1	0	0	“	1	0
Score 3	“	0	0	0	0	“	0	2
Perivenous inflammatory cells	3	3	2	1	3	3	5	5
Score 1	2	1	1	0	0	1	1	0
Score 2	0	1	0	1	0	2	1	0
Score 3	0	0	1	0	1	0	2	2
Score 4	1	1	0	0	1	0	1	3
Score 5	0	0	0	0	1	0	0	0
Perivenous collagen degeneration	1	2	1	1	3	2	4	5
Score 1	0	1	0	0	0	0	0	0
Score 3	0	0	0	1	0	2	0	0
Score 4	1	1	1	0	2	0	3	0
Score 5	0	0	0	0	1	0	1	5
Perivenous granulation tissue	0	0	0	0	1	0	0	0
Score 4	“	“	“	“	1	“	“	“

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 1, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Degenerative/necrotic myopathy of subcutaneous muscle	0	0	1	1	3	1	3	4
Score 1	“	“	0	0	0	1	0	0
Score 2	“	“	1	0	0	0	0	0
Score 3	“	“	0	1	1	0	2	0
Score 4	“	“	0	0	2	0	0	0
Score 5	“	“	0	0	0	0	1	4
Tissue Examined: Infusion Site 2, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Thrombophlebitis	0	2	2	0	3	0	4	3
Score 3	“	2	1	“	0	“	0	0
Score 4	“	0	1	“	3	“	1	1
Score 5	“	0	0	“	0	“	3	2
Phlebetis	1	0	0	0	0	1	0	0
Score 1	0	“	“	“	“	0	“	“
Score 2	1	“	“	“	“	1	“	“
Collagen degeneration	5	2	0	2	1	2	0	0
Score 1	1	0	“	1	0	0	“	“
Score 2	1	1	“	1	1	0	“	“
Score 3	3	1	“	0	0	2	“	“

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

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DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 2, Left Femoral[a]								
Intimal endothelial cell necrosis	5	3	0	0	1	0	0	0
Score 1	4	2	“	“	0	“	“	“
Score 2	1	1	“	“	1	“	“	“
Perivenous inflammatory cells	1	3	3	1	3	3	5	4
Score 1	1	3	0	0	0	1	0	0
Score 2	0	0	2	0	0	2	2	2
Score 3	0	0	1	1	2	0	2	1
Score 4	0	0	0	0	1	0	1	1
Perivenous hemorrhage	0	0	1	0	2	2	2	0
Score 1	“	“	0	“	0	0	1	“
Score 2	“	“	1	“	1	1	1	“
Score 3	“	“	0	“	1	1	0	“
Perivenous collagen degeneration	0	0	3	1	3	2	5	4
Score 3	“	“	1	0	0	1	1	0
Score 4	“	“	2	1	3	1	0	0
Score 5	“	“	0	0	0	0	4	4
Perivenous granulation tissue	0	0	1	0	1	0	0	1
Score 2	“	“	0	“	1	“	“	0
Score 3	“	“	1	“	0	“	“	1

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS

Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last Dose (Males/Females)	20/19		20/19		20/19		20/19	
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 2, Left Femoral[a]								
Intimal endothelial cell proliferation	2	3	1	0	1	1	1	0
Score 1	2	2	1	0	1	0	1	“
Score 2	0	1	0	0	0	1	0	“
Degenerative/necrotic myopathy of subcutaneous muscle	0	0	2	0	1	0	4	4
Score 1	“	“	1	“	0	“	0	0
Score 2	“	“	0	“	0	“	1	0
Score 3	“	“	0	“	0	“	1	0
Score 4	“	“	1	“	1	“	1	1
Score 5	“	“	0	“	0	“	1	3
Tissue Examined: Infusion Site 3, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Thrombophlebitis	0	1	0	0	1	0	1	1
Score 3	“	1	“	“	0	“	0	0
Score 4	“	0	“	“	1	“	0	0
Score 5	“	0	“	“	0	“	1	1
Phlebetis	0	0	0	0	0	0	1	0
Score 4	“	“	“	“	“	“	1	“
Collagen degeneration	3	2	1	2	2	1	1	2
Score 1	1	0	0	1	1	1	0	1
Score 2	1	0	1	1	1	0	0	1
Score 3	1	2	0	0	0	0	1	0

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 3, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Intimal endothelial cell necrosis	3	3	2	0	2	0	3	0
Score 1	3	2	1	“	1	“	0	“
Score 2	0	1	1	“	1	“	2	“
Score 3	0	0	0	“	0	“	1	“
Perivenous inflammatory cells	0	2	2	0	1	2	5	2
Score 1	“	1	0	“	0	1	1	0
Score 2	“	1	1	“	0	1	1	1
Score 3	“	0	0	“	0	0	1	1
Score 4	“	0	1	“	1	0	2	0
Perivenous collagen degeneration	0	2	2	0	1	1	5	2
Score 1	“	1	0	“	0	0	0	0
Score 2	“	1	0	“	0	0	0	0
Score 3	“	0	0	“	0	1	0	0
Score 4	“	0	2	“	1	0	2	0
Score 5	“	0	0	“	0	0	3	2
Perivenous fibroplasia	0	0	2	0	1	3	0	1
Score 2	“	“	1	“	1	0	“	1
Score 3	“	“	1	“	0	3	“	0

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m² (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tissue Examined: Infusion Site 3, Left Femoral[a]								
Number Examined	5	5	3	3	3	3	5	5
Degenerative/necrotic myopathy of subcutaneous muscle	0	0	1	0	1	0	4	2
Score 2	“	“	0	“	0	“	1	0
Score 3	“	“	0	“	1	“	1	0
Score 4	“	“	1	“	0	“	0	1
Score 5	“	“	0	“	0	“	2	1
Kidney								
Number Examined	5	5	3	3	3	3	5	5
Peritubular fibrosis	0	0	0	0	1	2	3	5
Score 3	“	“	“	“	1	1	2	1
Score 4	“	“	“	“	0	1	1	4
Tubular dilatation with flattened epithelium	0	0	0	0	1	2	3	5
Score 2	“	“	“	“	1	0	0	0
Score 3	“	“	“	“	0	2	2	1
Score 4	“	“	“	“	0	0	1	4
Tubular epithelial cell degeneration and necrosis	0	0	0	0	1	2	3	5
Score 2	“	“	“	“	1	2	2	1
Score 3	“	“	“	“	0	0	1	4

[a] Infusions were administered at three sites in each of the left and right femoral. Data are presented from each site for the left femoral and are representative of findings for the right femoral.

“ = finding not present, score not applicable

2.6.7.7.2.3 サル３週間ごと１回（4 サイクル）反復投与試験（続き）

Report Title: Chronic Toxicity Study Following 4-Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys **Test Article: R279741（Trabectedin）**

DOSING AND TREATMENT-FREE PERIODS								
Group	**1**		**2**		**3**		**4**	
Dose μg/m^2 (μg/kg)	**0**		300 (25)		600 (50)		840 (70)	
Number of Days of Dosing	4		4		4		4	
Days of Treatment (Study Days)	1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64		1, 22, 43, 64	
Number of Treatment Free Days Following Last	20/19		20/19		20/19		20/19	
Dose (Males/Females)								
Sex: No. of Animals	M:5	F:5	M:3	F:3	M:3	F:3	M:5	F:5
Noteworthy Findings								
Histopathology (Cont)								
Tubular Basophilia	0	0	1	0	1	2	3	5
Score 1	“	“	1	“	0	0	0	0
Score 2	“	“	0	“	0	0	1	0
Score 3	“	“	0	“	1	1	2	4
Score 4	“	“	0	“	0	1	0	1
Spleen								
Number Examined	5	5	3	3	3	3	5	5
Lymphoid depletion	0	0	0	0	0	0	1	0
Score 3	“	“	“	“	“	“	1	“
Thymus								
Number Examined	5	5	3	3	3	3	5	5
Lymphoid depletion	0	0	0	0	3	0	5	5
Score 1	“	“	“	“	1	“	2	0
Score 2	“	“	“	“	“	“	“	1
Score 3	“	“	“	“	2	“	1	3
Score 4	“	“	“	“	0	“	2	1
Sternum								
Number Examined	5	5	3	3	3	3	5	5
Medullary hypocellularity	0	0	2	1	2	2	4	4
Score 1	“	“	2	1	2	2	2	2
Score 2	“	“	0	0	0	0	2	2

“ = finding not present, score not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験

Report Title: **Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery** **Test Article: R279741（Trabectedin）**

Species/Strain: Primate/Cynomolgus
Duration of Dosing: Up to 24 weeks
Study No.: [redacted]
Age at First Dose: 2 to 3 years
Duration of Postdose Recovery: Up to 8 weeks
Location in CTD: 4.2.3.2.10
Date of First Dose: [redacted]
Route: Intravenous Infusion - 3 hour period
Vehicle/Formulation: 0.9% Sodium Chloride, USP
GLP Compliance: Yes

Special Features: The study was initiated with three-hour infusions of 25, 50, or 65 μg/kg/infusion trabectedin administered once every three weeks (i.e. a cycle). Due to mortality in the 50 and 65 μg/kg/infusion groups, a 35-μg/kg/infusion group was added to the study.

No Observed Adverse Effect Level: not established

DOSING PERIOD

Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
$AUC_{0-\infty}$ (h.ng/mL)								
Day 1	-	-	12.3	12.9	23.3	25.0	28.8	31.5
Last occasion	-	-	--	--	--	--	--	--
C_{max} (ng/mL)								
Day 1	-	-	1.70	2.09	2.96	3.76	3.71	5.23
Last occasion	-	-	0.09[c,d]	0.99[c]	--	--	--	--
Noteworthy Findings								
Died	-	-	-	-	1	-	1	-
Day of Death	-	-	-	-	37	-	71	-
Unscheduled Euthanasia	-	-	-	-	1	1	4	3
Day of Unscheduled Euthanasia	-	-	-	-	42	74	12, 64, 74, 74	73, 79, 79
Bodyweights (kg)	-	-	-	-	-	-	-	-
No notable mean changes	-	-	-	-	-	-	-	-
Bodyweight gain								
No notable mean changes	-	-	-	-	-	-	-	-

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] Repeated dose data may have been confounded by the inflammatory reaction at the site of injection and resulting secondary pathology
[d] One animal had trabectedin levels which were below the lower limit of quantification at all time points; these data were not included in the calculation of mean values
- No noteworthy findings; -- Parameter could not be accurately estimated
Note: Dose conversion to μg/m^2: multiply μg/kg by 12.

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Food Consumption	-	-	Decreased during the 2 weeks following 5th infusion with recovery within approximately 2 weeks.	Decreased during the 2 weeks following 5th infusion with recovery within approximately 2 weeks.	-	Decreased during the 3 weeks following 4th infusion	Decreased during the 1 weeks following 1st infusion and from the 3rd infusion to necropsy	Decreased during the 1 weeks following 1st infusion and from the 3rd infusion to necropsy
Clinical Observations[c]								
Abdominal distension	1/5	0/5	1/3	1/3	1/3	2/3	1/5	5/5
Cold to touch	0/5	0/5	0/3	1/3	2/3	1/3	3/5	1/4
Dehydrated	0/5	0/5	2/3	0/3	2/3	1/3	4/5	2/5
Feces absent	0/5	0/5	1/3	1/3	0/3	0/3	4/5	1/5
Feces black	0/5	0/5	3/3	2/3	0/3	3/3	5/5	5/5
Hunched posture	0/5	0/5	3/3	1/3	1/3	3/3	5/5	4/5
Limited usage	0/5	0/5	3/3	1/3	0/3	1/3	3/5	5/5
Prominent backbone	0/5	2/5	3/3	2/3	1/3	3/3	3/5	5/5
Reduced activity	0/5	0/5	3/3	2/3	2/3	3/3	5/5	5/5
Reduced appetite	0/5	1/5	3/3	1/3	2/3	3/3	5/5	5/5
Reduced muscle tone	0/5	1/5	3/3	0/3	1/3	2/3	4/5	5/5
Reduced feces output	0/5	0/5	3/3	1/3	1/3	3/3	5/5	5/5
Swollen	1/5	1/5	3/3	1/3	2/3	3/3	4/5	5/5
Thin	1/5	3/5	3/3	2/3	2/3	3/3	5/5	5/5
Urine absent	0/5	0/5	0/3	0/3	0/3	1/3	4/5	0/5
Vomitus	0/5	1/5	1/3	0/3	1/3	2/3	1/5	1/5
Weak	0/5	0/5	1/3	0/3	2/3	1/3	5/5	5/5

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] Number with observation/number observed
- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Body Temprature								
No notable mean changes	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Day 149 – following cycle 8								
focal area of retinal edema	-	-	1/3	-	N/A	N/A	N/A	N/A
Hematology[c]								
Day 5 (4 Days Post Cycle 1 Dosing)								
Neutrophil (10^3/μL)	4.674	3.718	1.095	0.964	0.869	0.978	1.060	1.720*
Hemoglobin (g/dL)	10.98	10.80	1.002	1.031	0.990	0.889**	0.920	1.013
Hematocrit (%)	36.00	34.38	0.992	1.048	0.958	0.903*	0.914	1.048
Day 20 (19 Days Post Cycle 1 Dosing)								
WBC (10^3/μL)	-	9.456	-	0.820	-	0.673	-	0.578
Neutrophil (10^3/μL)	-	5.360	-	0.651	-	0.310	-	0.225
Monocytes (10^3/μL)	-	0.258	-	1.252	-	0.337*	-	0.295**
RBC (10^6/μL)	4.942	4.946	0.927	0.962	0.835	0.711***	0.791	0.815**
Hemoglobin (g/dL)	11.94	11.98	0.915	0.946	0.810*	0.710***	0.779**	0.806**
Hematocrit (%)	39.14	38.36	0.896	0.969	0.788	0.714**	0.789*	0.815*
Day 26 (4 Days Post Cycle 2 Dosing)								
WBC (10^3/μL)	7.836	7.634	1.159	1.307	0.482	0.878	1.431	0.580
Neutrophil (10^3/μL)	3.268	3.204	1.311	1.707	0.275	1.182	2.105	0.416
Monocytes (10^3/μL)	0.212	0.338	1.840	1.547	0.283	0.601	2.632*	0.426
RBC (10^6/μL)	4.952	5.006	0.932	0.918	0.765*	0.695***	0.767*	0.740***
Hemoglobin (g/dL)	11.98	12.08	0.916	0.913	0.754*	0.706*	0.739**	0.745**
Hematocrit (%)	39.48	38.84	0.914	0.921	0.720**	0.720*	0.756**	0.746**

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable
* = p<0.05, ** = p<0.01, *** = p<0.001

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Hematology (con't)[c]								
Day 41 (19 Days Post Cycle 2 Dosing)								
WBC (10^3/μL)	7.524	7.472	1.400	1.440	0.281	0.623	1.614	0.575*
Neutrophil (10^3/μL)	3.614	2.916	1.185	2.109*	0.054	0.479	2.521	0.196
Monocytes (10^3/μL)	0.252	0.274	1.905	1.449	0.060	0.339	1.421	0.474
RBC (10^6/μL)	4.754	4.714	1.034	0.991	0.591**	0.622*	0.918	0.663*
Hemoglobin (g/dL)	11.40	11.26	1.006	0.977	0.596**	0.642*	0.895	0.673*
Hematocrit (%)	36.86	35.92	1.049	1.010	0.575**	0.671	0.926	0.689*
RDW (%)	12.56	12.98	1.075	1.084	1.170	1.404***	1.162	1.291**
Day 47 (4 Days Post Cycle 3 Dosing)								
WBC (10^3/μL)	8.180	9.170	1.551	1.011	N/A	1.247	1.697	1.502
Neutrophil (10^3/μL)	2.752	4.398	2.667	1.120	N/A	1.653	3.805*	2.160
Monocytes (10^3/μL)	0.204	0.358	2.123	1.081	N/A	1.620	3.309	1.587
RBC (106/μL)	4.726	4.696	1.040	0.988	N/A	0.642***	0.933	0.649***
Hemoglobin (g/dL)	11.34	11.30	1.020	0.971	N/A	0.637***	0.884	0.655***
Hematocrit (%)	37.28	36.06	1.024	1.013	N/A	0.698**	0.938	0.687***
Day 62 (19 Days Post Cycle 3 Dosing)								
WBC (10^3/μL)	6.896	11.454	2.112	0.846	N/A	0.898	1.939	1.151
Neutrophil (10^3/μL)	2.822	7.166	3.448	0.607	N/A	1.060	3.725	1.314
Monocytes (10^3/μL)	0.198	0.342	2.005	1.120	N/A	1.073	2.389*	1.643
RBC (10^6/μL)	4.974	4.906	1.007	0.990	N/A	0.756*	0.889	0.740**
Hemoglobin (g/dL)	11.86	11.56	0.972	0.989	N/A	0.718**	0.835*	0.701**
Hematocrit (%)	38.66	37.82	0.998	1.023	N/A	0.788*	0.893	0.766**

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings
* = p<0.05, ** = p<0.01, *** = p<0.001

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Hematology (con't) [c]								
Day 68 (4 Days Post Cycle 4 Dosing)								
WBC (10^3/μL)	6.598	10.868	1.594	0.976	N/A	1.281	3.054*	1.669
Neutrophil (10^3/μL)	2.194	4.756	2.273	1.284	N/A	2.294	7.515	3.171
Monocytes (10^3/μL)	0.188	0.374	2.713	1.230	N/A	1.444	3.601*	1.428
Hemoglobin (g/dL)	12.22	11.52	1.110	1.098	N/A	0.744	0.813	0.944
Hematocrit (%)	39.80	37.14	1.134	1.130	N/A	0.814	0.869	1.077
Day 83 (19 Days Post Cycle 4 Dosing)								
WBC (10^3/μL)	8.346	9.614	1.777	1.263	N/A	1.544	N/A	2.182**
Neutrophil (10^3/μL)	3.100	4.173	3.127	1.382	N/A	2.647*	N/A	3.846**
Monocytes (10^3/μL)	0.258	0.356	2.558	1.424	N/A	2.416***	N/A	2.935***
RBC (10^6/μL)	5.288	5.026	0.951	1.029	N/A	0.807*	N/A	0.827*
Hemoglobin (g/dL)	12.66	11.90	0.890*	1.017	N/A	0.769**	N/A	0.718**
Hematocrit (%)	41.02	38.44	0.914	1.050	N/A	0.832*	N/A	0.816*
Day 89 (4 Days Post Cycle 5 Dosing)								
Monocytes (10^3/μL)	0.236	0.362	3.136**	1.740	N/A	N/A	N/A	N/A
Hematocrit (%)	39.60	-	0.871**	-	N/A	N/A	N/A	N/A
Day 104 (19 Days Post Cycle 5 Dosing)								
Hemoglobin (g/dL)	11.86	-	0.835**	-	N/A	N/A	N/A	N/A
Hematocrit (%)	38.30	-	0.872*	-	N/A	N/A	N/A	N/A

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable
* = p<0.05, ** = p<0.01, *** = p<0.001

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Hematology (con't)[c]								
Day 110 (4 Days Post Cycle 6 Dosing)								
WBC (10^3/μL)	7.890	7.280	2.022	2.391	N/A	N/A	N/A	N/A
Neutrophil (10^3/μL)	4.685	2.705	2.682	5.160	N/A	N/A	N/A	N/A
Day 120 (Terminal Samples - Recovery Phase)	N/A	-	N/A	-	N/A	-	N/A	-
No notable mean changes								
Day 125 (19 Days Post Cycle 6 Dosing)	-	-	-	-	-	-	-	-
No notable mean changes					N/A	N/A	N/A	N/A
Day 131 (4 Days Post Cycle 7 Dosing)								
WBC (10^3/μL)	7.800	7.425	2.646	1.852	N/A	N/A	N/A	N/A
Neutrophil (10^3/μL)	2.880	1.935	5.339	4.190	N/A	N/A	N/A	N/A
Day 146 (19 Days Post Cycle 7 Dosing)								
WBC (10^3/μL)	8.620	9.575	1.707	1.432	N/A	N/A	N/A	N/A
Neutrophil (10^3/μL)	2.725	3.700	3.611	2.432	N/A	N/A	N/A	N/A
Day 152 (5 Days Post Cycle 8 Dosing)								
WBC (10^3/μL)	9.025	8.415	1.839	1.951	N/A	N/A	N/A	N/A
Neutrophil (10^3/μL)	3.335	2.725	3.625	4.218	N/A	N/A	N/A	N/A
Monocytes (10^3/μL)	0.200	0.335	2.835	2.239	N/A	N/A	N/A	N/A

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Hematology (con't)[c]								
Day 154 (Terminal Samples after 8 cycles)								
WBC (10^3/μL)	7.405	7.805	1.408	1.800	N/A	N/A	N/A	N/A
Neutrophil (10^3/μL)	3.005	2.240	2.220	3.536	N/A	N/A	N/A	N/A
Monocytes (10^3/μL)	0.160	0.245	3.375	2.163	N/A	N/A	N/A	N/A
Hematocrit (%)	36.70	-	0.865	-	N/A	N/A	N/A	N/A
Serum Chemistry[c]								
Day 5 (4 Days Post Cycle 1 Dosing)								
No notable mean changes								
Day 20 (19 Days Post Cycle 1 Dosing)								
Alkaline Phosphatase (U/L)	432.2	-	1.158	-	1.289	-	1.975**	-
Day 26 (4 Days Post Cycle 2 Dosing)								
Alkaline Phosphatase (U/L)	398.0	-	1.302	-	1.113	-	1.965**	-
Albumin (g/dL)	4.40	4.48	0.939	0.908	0.977	0.848*	0.773**	0.884
Day 41 (19 Days Post Cycle 2 Dosing)								
Alkaline Phosphatase (U/L)	516.0	-	1.148	-	1.214	-	2.039*	-
Albumin (g/dL)	-	4.32	-	0.956	-	0.771	-	0.907
Day 47 (4 Days Post Cycle 3 Dosing)								
Creatinine (mg/dL)	0.54	-	1.167	-	N/A	-	1.796**	-
Albumin (g/dL)	4.32	4.42	0.949	0.957	N/A	0.814*	0.787**	0.760**

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable
* = $p<0.05$, ** = $p<0.01$

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Serum Chemistry (Con't)[c]								
Day 62 (19 Days Post Cycle 3 Dosing)								
Albumin (g/dL)	4.40	4.16	0.880	1.010	N/A	0.738	0.784*	0.750*
Globulin (g/dL)	2.66	3.10	1.316	1.097	N/A	1.494	1.842***	1.497
Albumin/Globulin Ratio	1.688	1.478	0.689	0.902	N/A	0.476	0.427**	0.471*
Day 68 (4 Days Post Cycle 4 Dosing)								
Alkaline Phosphatase (U/L)	504.8	-	1.692*	-	N/A	-	1.778**	-
Urea (mg/dL)	18.80	16.40	0.948	0.821	N/A	2.705	2.461	1.159
Albumin (g/dL)	4.60	4.24	0.804	0.920	N/A	0.700*	0.652	0.684*
Globulin (g/dL)	2.72	3.34	1.360	1.147	N/A	1.347	1.765	1.401
Day 83 (19 Days Post Cycle 4 Dosing)								
Alkaline Phosphatase (U/L)	523.2	494.4	1.811*	1.011	N/A	1.794**	N/A	1.286
Albumin (g/dL)	4.60	4.27	0.761*	0.953	N/A	0.749	N/A	0.679*
Globulin (g/dL)	2.86	3.06	1.503*	1.232	N/A	1.585	N/A	1.520
Albumin/Globulin Ratio	1.610	1.496	0.528*	0.809	N/A	0.445	N/A	0.428
Day 89 (4 Days Post Cycle 5 Dosing)								
Alkaline Phosphatase (U/L)	524.4	548.4	1.955**	1.125	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.42	-	0.663***	-	N/A	N/A	N/A	N/A
Globulin (g/dL)	2.86	-	1.584***	-	N/A	N/A	N/A	N/A
Albumin/Globulin Ratio	1.554	-	0.418***	-	N/A	N/A	N/A	N/A
Day 104 (19 Days Post Cycle 5 Dosing)								
Alkaline Phosphatase (U/L)	592.2	-	1.980**	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.50	-	0.682***	-	N/A	N/A	N/A	N/A

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable
* = p<0.05, ** = p<0.01, *** = p<0.001

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Serum Chemistry (Con't) [c]								
Globulin (g/dL)	2.96	-	1.723***	-	N/A	N/A	N/A	N/A
Albumin/Globulin Ratio	1.550	-	0.389**	-	N/A	N/A	N/A	N/A
Day 110 (4 Days Post Cycle 6 Dosing)								
Alkaline Phosphatase (U/L)	491.5	-	2.183	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.20	-	0.667	-	N/A	N/A	N/A	N/A
Day 120 (Terminal Samples - Recovery Phase)								
Alkaline Phosphatase (U/L)	N/A	441.0	N/A	N/A	N/A	1.625	N/A	1.262
Albumin (g/dL)	N/A	4.50	N/A	N/A	N/A	0.800	N/A	0.756
Day 125 (19 Days Post Cycle 6 Dosing)								
Alkaline Phosphatase (U/L)	601.5	-	1.712	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	3.80	-	0.692	-	N/A	N/A	N/A	N/A
Day 131 (4 Days Post Cycle 7 Dosing)								
Alkaline Phosphatase (U/L)	583.0	-	1.759	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	3.85	-	0.688	-	N/A	N/A	N/A	N/A
Day 146 (19 Days Post Cycle 7 Dosing)								
Alkaline Phosphatase (U/L)	572.0	-	2.056	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.00	-	0.758	-	N/A	N/A	N/A	N/A
Day 152 (4 Days Post Cycle 8 Dosing)								
Alkaline Phosphatase (U/L)	518.5	-	1.998	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.20	-	0.714	-	N/A	N/A	N/A	N/A

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
- No noteworthy findings; N/A not applicable
** = $p<0.01$, *** = $p<0.001$

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Serum Chemistry[a] (Con't)[c]								
Day 154 (Terminal Samples after 8 cycles)								
Alkaline Phosphatase (U/L)	504.5	-	1.909	-	N/A	N/A	N/A	N/A
Albumin (g/dL)	4.20	-	0.690	-	N/A	N/A	N/A	N/A
Urinalysis[b]								
No notable mean changes	-	-	-	-	-	-	-	-
Organ Weights								
Kidney (g)	12.9715	9.3450	1.17398[d]	1.43642[d]	N/A	N/A	N/A	N/A
Kidney/body weight (%)	0.49890	0.38191	1.40912	1.57707	N/A	N/A	N/A	N/A
Liver (g)	49.4915	45.1820	1.14752[d]	1.27542[d]	N/A	N/A	N/A	N/A
Liver/body weight (%)	1.90352	1.84427	1.41042	1.39011	N/A	N/A	N/A	N/A
Gross Pathology								
Number Examined- Main	2	2	3	3	2	1	5	3
INFUSION SITE								
- Mass	1	-	3	2	-	1	4	3
- Swelling	-	-	-	-	1	-	-	-
- Thickening	1	2	-	1	1	-	1	-
ADHESION								
- kidney	-	-	-	-	-	-	-	1
- Liver	-	-	1	-	-	-	-	1
- lung	-	-	-	-	-	-	1	2
KIDNEY								
- pelvic dilatation	-	-	2	1	-	-	3	3

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
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[c] For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline).
[d] Number indicates multiple of control for the absolute organ weights.
- No noteworthy findings; N/A not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Gross Pathology (con't)								
- pale discoloration	-	-	2	1	1	1	5	3
- enlargement	-	-	-	-	-	1	3	2
Number Examined- Recovery	N/A	2	N/A	N/A	1	2	N/A	2
INFUSION SITE-Mass	N/A	-	N/A	N/A	1	2	N/A	2
KIDNEY								
- pelvic dilatation	N/A-	-	N/A	N/A	-	2	N/A	2
- pale discoloration	N/A	-	N/A	N/A	-	2	N/A	2
Histopathology								
Number Examined-Main	2	2	3	3	2	1	5	3
BONE –hypocellularity Grade 4	-	-	-	-	2	-	1	-
CECUM								
- hemorrhage Grade 1	-	-	-	-	1	-	-	-
- inflammation Grade 2	-	-	-	-	1	-	-	-
- bacterial colonies Grade 3	-	-	-	-	1	-	-	-
- erosion Grade 1	-	-	-	-	-	-	-	1
- congestion Grade 1	-	-	-	-	-	1	-	-
COLON								
- necrosis Grade 4	-	-	-	-	1	-	-	-
- hemorrhage Grade 3	-	-	-	-	1	-	-	-
INFUSION SITE								
- thrombosis Grade 3	1	1	3	2	-	-	-	-
- thrombosis Grade 4	1	-	-	-	-	-	-	-
- perivascular inflammation Grade 1	-	-	-	1	-	-	-	-
- perivascular inflammation Grade 3	2	1	3	2	-	-	-	-

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[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology – Main (con't)								
-fibrosis Grade 2	-	1	-	-	-	-	-	-
-fibrosis Grade 3	2	1	-	-	-	-	-	-
-fibrosis Grade 4	-	-	3	2	-	-	-	-
- necrosis Grade 2	-	1	-	-	-	-	-	-
- necrosis Grade 4	-	-	3	2	-	-	-	-
- hemorrhage Grade 1	-	-	-	1	-	-	-	-
- mineralization Grade 3	1	-	-	1	-	-	-	-
- exostosis from adjacent bone Grade 3	1	-	-	-	-	-	-	-
INFUSION SITE -1cm above catheter tip								
- hyperplasia: intima Grade 1	-	-	-	-	1	-	-	-
- necrosis: perivascular Grade 3	-	-	-	-	-	1	-	1
- necrosis: perivascular Grade 4	-	-	-	-	-	-	3	1
- inflammation: perivascular Grade 3	-	-	-	-	-	1	2	2
- inflammation: perivascular Grade 4	-	-	-	-	-	-	-	1
- hemorrhage Grade 1	-	-	-	-	1	-	-	-
- hemorrhage Grade 2	-	-	-	-	-	-	-	1
INFUSION SITE -1cm below catheter tip								
- thrombosis Grade 1	-	-	-	-	1	-	-	-
- thrombosis Grade 3	-	-	-	-	1	-	2	-
- thrombosis Grade 4	-	-	-	-	-	-	1	1
- hypertrophy Grade 1	-	-	-	-	1	-	-	-
- bacterial colonites Grade 1	-	-	-	-	-	-	1	-
- bacterial colonies Grade 2	-	-	-	-	1	-	-	-

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- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology – Main (con't)								
- necrosis: vascular Grade 4	-	-	-	-	-	-	1	1
- necrosis: perivascular Grade 1	-	-	-	-	-	-	1	-
- necrosis: perivascular Grade 4	-	-	-	-	-	1	3	3
- inflammation: perivascular Grade 2	-	-	-	-	-	1	1	-
- inflammation: perivascular Grade 3	-	-	-	-	-	-	2	1
- inflammation: perivascular Grade 4	-	-	-	-	-	-	-	2
- mineralization Grade 2	-	-	-	-	-	-	1	-
- hemorrhage Grade 3	-	-	-	-	1	-	-	-
INFUSION SITE – at the catheter tip								
- thrombosis Grade 3	-	-	-	-	1	-	-	-
- hypertrophy Grade 2	-	-	-	-	2	-	-	-
- inflammation: perivascular Grade 2	-	-	-	-	-	-	2	-
- inflammation: perivascular Grade 3	-	-	-	-	-	1	1	1
- inflammation: perivascular Grade 4	-	-	-	-	-	-	-	2
- necrosis: perivascular Grade 4	-	-	-	-	-	1	2	3
- mineralization Grade 2	-	-	-	-	-	-	1	-
JEJUNUM								
- ulceration Grade 3	-	-	-	-	-	-	1	-
- inflammation Grade 2	-	-	-	-	1	-	1	-
- inflammation Grade 3	-	-	-	-	1	-	-	-
- bacterial colonies Grade 2	-	-	-	-	2	-	1	-
KIDNEY						-		-
- inflammation: interstitial Grade 3	-	-	-	1	-	-	1	1
- inflammation: interstitial Grade 4	-	-	2	-	-	1	3	2
- infiltration: mononuclear cell Grade 1	-	1	-	-	-	-	-	-

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[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology – Main (con't)								
- basophilia: tubular Grade 3	-	-	-	1	-	1	4	1
- dilatation : tubular Grade 1	-	-	-	-	-	1	-	-
- dilatation : tubular Grade 2	-	-	-	-	-	-	4	1
- dilatation : pelvis Grade 1	-	-	-	-	-	1	-	-
- dilatation : pelvis Grade 2	-	-	-	1	-	-	2	3
- dilatation : pelvis Grade 3	-	-	2	-	-	-	1	-
- necrosis : papilla Grade 3	-	-	-	-	-	-	-	1
- necrosis : hilus Grade 3	-	-	-	-	-	-	-	1
- inflammation : capsule Grade 3	-	-	-	-	-	1	-	-
LIVER								
- inflammation Grade 1	1	-	-	2	-	-	1	-
- inflammation Grade 2	-	-	2	-	-	-	-	-
- reactive sinusoidal lining cells Grade 1	-	-	-	1	-	1	1	-
- reactive sinusoidal lining cells Grade 2	-	-	2	1	-	-	-	-
- reactive sinusoidal lining cells Grade 3	-	-	-	-	1	-	1	-
- involvement with infusion site mass Grade 4	-	-	-	-	-	-	-	1
- necrosis Grade 1	-	-	-	-	1	-	-	-
- necrosis Grade 2	-	-	-	-	1	-	-	-
-bacterial colonies Grade 1	-	-	-	-	2	-	-	-
-hemorrhage Grade 2	-	-	-	-	1	-	-	-
- fibrosis: capsular Grade 1	-	-	1	-	-	-	-	-
- inflammation: biliary Grade 1	-	1	-	-	-	-	-	-
- inflammation: biliary Grade 3	-	-	-	-	-	-	-	1

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- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

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DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology – Main (con't)								
LUNG								
- necrosis Grade 3	-	-	-	-	1	-	-	-
- inflammation Grade 2	-	-	-	-	1	-	-	-
- bacterial colonies Grade 2	-	-	-	-	1	-	-	-
- hemorrhage Grade 2	-	-	-	-	1	-	-	-
- adhesion Grade 1	-	-	-	-	-	-	1	1
- adhesion Grade 2	-	-	-	-	-	-	-	1
PANCREAS								
- degranulation Grade 1	-	-	-	1	-	-	1	-
- degranulation Grade 2	-	-	-	-	1	1	-	2
- degranulation Grade 3	-	-	1	-	-	-	4	1
- inflammation Grade 1	-	-	-	-	-	1	-	-
RECTUM								
- ulceration Grade 3	-	-	-	-	-	-	1	-
- inflammation Grade 2	-	-	-	-	1	-	-	-
- necrosis Grade 3	-	-	-	-	1	-	-	-
- bacterial colonies Grade 3	-	-	-	-	1	-	-	-
- hemorrhage Grade 2	-	-	-	-	1	-	-	-
SPLEEN								
- Atrophy/necrosis: lymphoid Grade 1	-	-	-	-	1	-	-	-
- hyperplasia: lymphoid Grade 2	-	1	1	1	-	-	-	-
- congestion	-	-	-	-	-	-	1	-
STOMACH								
- hemorrhage Grade 1	-	-	-	-	-	-	1	-
- hemorrhage Grade 2	-	-	-	-	2	-	-	-
- ulceration Grade 3	-	-	-	-	-	-	1	-

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology - Main (con't)								
- inflammation Grade 2	-	-	-	-	2	-	1	1
- involvement with infusion site: mass Grade 3	-	-	-	-	-	-	-	1
- infiltration: mononuclear cell Grade 2	1	-	-	-	-	-	-	-
- infiltration: mixed cell Grade 1	-	-	-	-	-	-	1	-
- bacterial colonies Grade 3	-	-	-	-	-	-	1	-
- dilatation: glandular Grade 2	-	-	-	-	1	-	-	-
- atrophy: mucosa Grade 2	-	-	-	-	1	-	-	-
-hypertrophy Grade 2	-	-	-	1	-	-	-	-
SURGICAL SITE								
- inflammation Grade 1	-	-	-	-	-	-	1	1
- inflammation Grade 2	-	-	-	-	-	-	1	-
- inflammation Grade 3	-	-	-	-	-	1	-	2
- necrosis Grade 2	-	-	-	-	-	-	1	-
- necrosis Grade 3	-	-	-	-	-	-	-	2
- necrosis Grade 4	-	-	-	-	-	-	1	-
- edema Grade 3	-	-	-	-	-	1	2	1
- hemorrhage Grade 1	-	-	-	-	-	-	1	-
- ulceration: epidermal Grade 3	-	-	-	-	-	-	-	1
THYMUS								
- atrophy/necrosis: lymphoid Grade 1	-	-	-	2	-	-	-	-
- atrophy/necrosis: lymphoid Grade 2	-	-	2	-	2	-	-	-
- atrophy/necrosis: lymphoid Grade 3	-	-	-	-	-	1	4	2
- atrophy/necrosis: lymphoid Grade 4	-	-	-	-	-	-	1	1
- hemorrhage Grade 1	-	-	-	-	1	-	-	-

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology- Main (con't)								
URETER								
- dilatation Grade 2	-	-	-	-	-	-	1	-
- dilatation Grade 3	-	-	-	1	-	1	3	2
- dilatation Grade 4	-	-	2	-	-	-	-	-
- inflammation Grade 1	-	-	-	1	-	-	-	-
- inflammation Grade 2	-	-	1	-	-	-	1	1
- inflammation Grade 3	-	-	1	-	-	-	-	-
- necrosis Grade 2	-	-	-	-	-	-	-	1
- necrosis Grade 3	1	-	-	-	-	-	-	1
Histopathology- Recovery								
INFUSION SITE								
- thrombosis Grade 1	N/A	2	N/A	N/A	-	-	N/A	-
- thrombosis Grade 3	N/A	-	N/A	N/A	-	1	N/A	-
- thrombosis Grade 4	N/A	-	N/A	N/A	1	-	N/A	1
-fibrosis Grade 3	N/A	-	N/A	N/A	-	1	N/A	-
-fibrosis Grade 4	N/A	-	N/A	N/A	1	1	N/A	1
-fibrosis Grade 5	N/A	-	N/A	N/A	-	-	N/A	1
- necrosis Grade 3	N/A	-	N/A	N/A	1	1	N/A	-
- necrosis Grade 4	N/A	-	N/A	N/A	-	1	N/A	1
- necrosis Grade 5	N/A	-	N/A	N/A	-	-	N/A	1
- hyperplasia Grade 1	N/A	1	N/A	N/A	-	-	N/A	-
- hyperplasia Grade 2	N/A	1	N/A	N/A	-	-	N/A	-
KIDNEY								
- inflammation: interstitial Grade 4	N/A	-	N/A	N/A	-	2	N/A	2
- infiltration: mononuclear cell Grade 1	N/A	-	N/A	N/A	-	-	N/A	1

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings, N/A not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD								
Dose μg/m^2 (μg/kg)	**0 (Control)**		**300 (25)**		**600 (50)**		**780 (65)**	
No. of Animals	M:5 (2)[a]	F:5 (2)[a]	M:3	F:3	M:3	F:3	M:5	F:5
Recovery:								
No. of Animals	-	F:2[b]	-	-	M:1	F:2	-	F:2
Histopathology- Recovery (con't)								
- dilatation: pelvis Grade 2	N/A	-	N/A	N/A	-	-	N/A	1
- dilatation: pelvis Grade 3	N/A	-	N/A	N/A	-	2	N/A	1
LIVER								
- Inflammation Grade 1	N/A	-	N/A	N/A	-	1	N/A	1
- reactive sinusoidal lining cells Grade 1	N/A	-	N/A	N/A	-	-	N/A	1
- reactive sinusoidal lining cells Grade 2	N/A	-	N/A	N/A	-	2	N/A	-
-hemorrhage Grade 2	N/A	-	N/A	N/A	-	-	N/A	1
- vacuolation: hepatocellular Grade 2	N/A	1	N/A	N/A	1	-	N/A	-

[a] Three/sex animals from the Control Group were re-allocated to Group 5 (35μg/kg).
[b] Two spare female animals were assigned to Group 1 and underwent an 8-week recovery period.
- No noteworthy findings, N/A not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
$AUC_{0-\infty}$ (h.ng/mL)		
Day 1	12.5[c,d]	11.5
Last occasion	--	--
C_{max} (ng/mL)		
Day 1	2.50[c]	1.99
Last occasion	1.94[c,e]	1.85[e]
Noteworthy Findings		
Unscheduled Euthanasia	-	1
Day of Unscheduled Euthanasia		87
Bodyweights (kg)	-	-
Bodyweight gain	-	-
Food Consumption[a]	Decreased following 4th infusion to necropsy	Decreased following 4th infusion to necropsy
Rectal Body Temprature	-	-
Ophthalmoscopy	-	-
focal retinal edema after 4th cycle (Day 65) and after 6th cycle (Day 107)	-	1
Clinical Observations[b]		
Abdominal distension	2/3	3/3
Dehydrated	1/3	1/3
Feces absent	1/3	3/3
Feces black	3/3	3/3
Hunched posture	2/3	3/3
Limited usage	0/3	3/3

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
[b] Number with observation/number observed
[c] One animal had trabectedin levels which were below the lower limit of quantification at all time points; these data were not included in the calculation of mean values
[d] AUC_{0-144}
[e] Repeated dose data may have been confounded by the inflammatory reaction at the site of injection and resulting secondary pathology
- No noteworthy findings; -- Parameter could not be accurately estimated

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
Clinical Observations[b] (con't)		
Prominent backbone	2/3	3/3
Reduced activity	3/3	3/3
Reduced muscle tone	2/3	3/3
Swollen	0/3	3/3
Thin	2/3	3/3
Vomitus	1/3	2/3
Weak	1/3	2/3
Hematology[c]		
Day 5 (4 Days Post Cycle 1 Dosing)		
No notable mean changes	-	-
Day 20 (19 Days Post Cycle 1 Dosing)		
RBC (10^6/μL)	-	4.353
Hemoglobin (g/dL)	-	9.77
Hematocrit (%)	-	32.37
Day 26 (4 Days Post Cycle 2 Dosing)		
RBC (10^6/μL)	-	4.283
Hemoglobin (g/dL)	-	9.53
Hematocrit (%)	-	31.77
Day 41 (19 Days Post Cycle 2 Dosing)		
RBC (10^6/μL)	4.273	4.470
Hemoglobin (g/dL)	10.40	9.80
Hematocrit (%)	33.20	32.85
Day 47 (4 Days Post Cycle 3 Dosing)		
RBC (106/μL)	4.223	4.455

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
[b] Number with observation/number observed
[c] Group means are presented

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD			
Dose μg/m^2 (μg/kg)		**420 (35)**	
No. of Animals	M:3[a]		F:3[a]
Hematology (con't)[b]			
Hemoglobin (g/dL)	10.27		9.80
Hematocrit (%)	32.83		33.55
Day 62 (19 Days Post Cycle 3 Dosing)			
RBC (10^6/μL)	4.003		-
Hemoglobin (g/dL)	9.63		10.07
Hematocrit (%)	31.40		34.57
Day 68 (4 Days Post Cycle 4 Dosing)			
RBC (10^6/μL)	3.927		-
Hemoglobin (g/dL)	9.33		10.20
Hematocrit (%)	31.23		-
Day 83 (19 Days Post Cycle 4 Dosing)			
RBC (10^6/μL)	4.210		-
Hemoglobin (g/dL)	9.93		10.97
Hematocrit (%)	33.00		-
Day 89 (4 Days Post Cycle 5 Dosing)			
RBC (10^6/μL)	4.290		N/A
Hemoglobin (g/dL)	10.13		N/A
Hematocrit (%)	33.87		N/A
Day 104 (19 Days Post Cycle 5 Dosing)			
RBC (10^6/μL)	4.467		-
Hemoglobin (g/dL)	10.13		10.30

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
[b] Group means are presented

2.6.7.7.2.4 サル３週間ごと１回（4～8サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
Hematology (con't) [b]		
Day 110 (4 Days Post Cycle 6 Dosing)		
RBC (10^6/μL)	4.020	N/A
Hemoglobin (g/dL)	9.40	N/A
Hematocrit (%)	30.47	N/A
Day 112 (terminal sample)		
RBC (10^6/μL)	4.040	4.375
Hemoglobin (g/dL)	9.40	9.60
Hematocrit (%)	29.73	30.95
Serum Chemistry[b]		
Day 5 (4 Days Post Cycle 1 Dosing)		
No notable mean changes	-	-
Day 20 (19 Days Post Cycle 1 Dosing)		
No notable mean changes	-	-
Day 26 (4 Days Post Cycle 2 Dosing)		
Albumin (g/dL)	-	2.97
Day 41 (19 Days Post Cycle 2 Dosing)		
Albumin (g/dL)	-	3.03
Day 47 (4 Days Post Cycle 3 Dosing)		
No notable mean changes	-	-
Day 62 (19 Days Post Cycle 3 Dosing)		
Albumin (g/dL)	-	3.30

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
[b] Group means are presented

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
Serum Chemistry (Con't)[b]		
Day 68 (4 Days Post Cycle 4 Dosing)		
Albumin (g/dL)	-	3.30
Day 83 (19 Days Post Cycle 4 Dosing)		
Albumin (g/dL)	-	3.20
Urea (mg/dL)	-	42.43
Day 89 (4 Days Post Cycle 5 Dosing)		
Albumin (g/dL)	3.53	N/A
Day 104 (19 Days Post Cycle 5 Dosing)		
Albumin (g/dL)	3.43	3.25
Day 110 (4 Days Post Cycle 6 Dosing)		
Albumin (g/dL)	3.50	-
Day 112 (terminal sample)		
Albumin (g/dL)	3.47	3.40
Urinalysis		
No notable mean changes	-	-
Organ Weights		
Kidney (g)	17.2013[b]	22.6450[b]
Kidney/body weight (%)	0.63186	0.91087
Liver (g)	66.3910[b]	71.1170[b]
Liver/body weight (%)	2.40867	2.79607

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
[b] Group means are presented

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
Gross Pathology	N/A	N/A
Number Examined		
INFUSION SITE		
- Mass	2	2
- Thickening	1	-
ADHESION		
- kidney	-	1
- lung	1	1
KIDNEY		
- pelvic dilatation	1	2
- pale discoloration	1	2
- enlargement	-	1
- mass	-	1
Histopathology		
CECUM		
- inflammation Grade 2	1	-
- Adhesion/involvement in infusion site Grade 3	1	-
COLON		
- adherent to mass Grade 4	-	1
INFUSION SITE		
- thrombosis Grade 3	3	2
- perivascular inflammation Grade 2	1	-
- fibrosis Grade 4	1	1
- fibrosis Grade 5	1	1
- necrosis Grade 4	2	1
- necrosis Grade 5	-	1
- necrosis: mural Grade 4	2	2

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
N/A not applicable

2.6.7.7.2.4 サル３週間ごと１回（4～8 サイクル）反復投与試験（続き）

Report Title: Trabectedin (ET-743): Chronic Toxicity Study Following 8 Cycles of Administration by Intravenous Infusion to Cynomolgus Monkeys With 8 Weeks of Recovery **Test Article: R279741（Trabectedin）**

DOSING PERIOD		
Dose μg/m^2 (μg/kg)	**420 (35)**	
No. of Animals	M:3[a]	F:3[a]
Histopathology (con't)		
KIDNEY		
- inflammation: interstitial Grade 2	-	1
- inflammation: interstitial Grade 3	1	-
- inflammation: interstitial Grade 4	-	1
- inflammation: interstitial Grade 5	1	1
- infiltration: mononuclear cell Grade 1	1	-
- hyperplasia : transitional cell Grade 3	-	1
- dilatation : pelvis Grade 2	-	1
- dilatation : pelvis Grade 3	1	1
LIVER		
- Inflammation Grade 1	2	-
- Inflammation Grade 2	-	1
- reactive sinusoidal lining cells Grade 2	2	1
- thromboembolism Grade 1	-	1
- cytoplasmic rarefaction Grade 3	-	1
LUNG		
- inflammation Grade 1	1	-
- inflammation Grade 3	-	1
- adhesion Grade 1	1	1
- thromboembolism Grade 1	-	1
THYMUS		1
- atrophy/necrosis: lymphoid Grade 1	1	1
- atrophy/necrosis: lymphoid Grade 4	-	1
URETER		
- dilatation Grade 2	1	1
- dilatation Grade 3	-	1
- inflammation Grade 2	1	-
- hyperplasia: transitional cell Grade 2	-	1

[a] Three/sex animals from the Control Group were re-allocated to Group 5(35μg/kg).
N/A not applicable

2.6.7.8 *In vitro*遺伝毒性試験

2.6.7.8.1 復帰突然変異試験

Report Title: Salmonella/Escherichia Coli Plate Incorporation Mutagenicity Assay **Test Article: R279741（Trabectedin）**

Test for Induction of: Reverse point mutations
Strains: *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. Coli* strain WP2 *urv*A
Metabolizing System: Arochlor 1254-induced rat liver S9 (50 µL)
Vehicles: Ethanol
Treatment: *In vitro*
Cytotoxic Effects: Yes
Genotoxic Effects: Yes (TA100 with activation)

No. of Independent Assays: 1
No. of Replicates: 3
Approximate No. of Bacteria Assayed/Dose: $10E^8$

Study No: [redacted]
Location in CTD: 4.2.3.3.1.1
GLP Compliance: Yes
Date of Treatment: [redacted]

			(Plate Incorporation) Revertant Colony Counts (Mean ± SD)				
Metabolic Activation	**Test Article**	**Concentration Level (µg/plate)**	**TA98**	**TA100**	**TA1535**	**TA1537**	**WP2 *uvr*A**
Without Activation	Ethanol	100 µL Ethanol/2.0 mL medium	12 ± 5	105 ± 18	12 ± 5	4 ± 4	11 ± 3
	R279741	0.010	16 ± 2	130 ± 3	8 ± 3	5 ± 3	---
		0.033	14 ± 3	127 ± 10	8 ± 1	5 ± 2	---
		0.10	10 ± 3	167 ± 18	8 ± 3	8 ± 1	---
		0.33	23 ± 6	178 ± 32	9 ± 3	10 ± 3	---
		0.5	---	---	---	---	14 ± 6
		1.0	12 ± 4[a]	2 ± 2[a]	0 ± 0[a]	2 ± 2[a]	19 ± 2
		3.3	---	---	---	---	20 ± 5
		10	---	---	---	---	22 ± 1
		20	---	---	---	---	12 ± 3
	2-Nitrofluorene	1	151 ± 7	---	---	---	---
	Sodium Azide	1	---	943 ± 145	624 ± 73	---	---
	9-Aminoacridine	75	---	---	---	248 ± 172	---
	Methyl methanesulfonate	1000	---	---	---	---	150 ± 1

[a] Toxicity observed

--- = not applicable

2.6.7.8.1. 復帰突然変異試験（続き）

Report Title: Salmonella/Escherichia Coli Plate Incorporation Mutagenicity Assay **Test Article: R279741（Trabectedin）**

			(Plate Incorporation) Revertant Colony Counts (Mean ± SD)				
Metabolic Activation	**Test Article**	**Concentration Level (µg/plate)**	**TA98**	**TA100**	**TA1535**	**TA1537**	**WP2 *uvr*A**
With Activation	Ethanol	100 µL Ethanol/2.0 mL medium	32 ± 8	112 ± 2	11 ± 5	5 ± 1	13 ± 1
	R279741	0.10	24 ± 6	123 ± 11	9 ± 3	6 ± 1	---
		0.20	32 ± 6	170 ± 18	10 ± 2	8 ± 5	---
		0.33	29 ± 3	268 ± 74	10 ± 3	7 ± 3	---
		0.5	40 ± 4	213 ± 22	11 ± 5	9 ± 2	11 ± 6
		1.0	41 ± 10[a]	50 ± 8[a]	9 ± 2[a]	10 ± 2[a]	16 ± 4
		3.3	5 ± 3[a]	0 ± 0[a]	6 ± 1[a]	0 ± 0[a]	13 ± 2
		10	---	---	---	---	26 ± 6
		20	---	---	---	---	18 ± 5
	2-Aminoanthracene	1	297 ± 64	438 ± 6	57 ± 9	145 ± 198	---
	2-Aminoanthracene	10	---	---	---	---	103 ± 12

[a] Toxicity observed

--- = not applicable

2.6.7.8.2 染色体異常試験

Report Title: In Vitro Mammalian Chromosome Aberration Test **Test Article: R279741（Trabectedin）**

Test for Induction of: Chromosome aberrations
Test System: Chinese hamster ovary (CHO) cells
Metabolizing System: Arochlor 1254-induced rat liver S9
Vehicles: DMSO
Treatment: In vitro
No. of Independent Assays: 1
No. of Replicates: 2
Approximate No. of Cells Seeded/25 cm^2 Flask: 10E^5/mL
Study No: [redacted]
Location in CTD: 4.2.3.3.1.2
GLP Compliance: Yes
Date of Treatment: [redacted]
Genotoxic Effects: Positive for structural aberrations with and without activation. Negative for numerical aberrations with and without activation.

Test Article	Concentration	S9 Activation Status	Treatment Time (Hours)[a]	Mean Mitotic Index	Cells Scored	Aberrations/Cell (Mean ± SD)	% Cells with Numerical Aberrations	% Cells with Structural Aberrations
DMSO	10 µL/mL	Negative	4	10.8	200	0.000 ± 0.000	0.5	0.0
R279741	0.001 µmol/L	Negative	4	11.3	200	0.040 ± 0.242	3.0	3.0*
	0.005 µmol/L	Negative	4	11.2	200	0.195 ± 0.855	0.5	11.0**
	0.01 µmol/L	Negative	4	7.6	200	1.055 ± 2.452	3.0	30.5**
	0.05 µmol/L	Negative	4	4.6	200	1.535 ± 2.872	6.0**[b]	40.5**
Mitomycin C[c]	0.2 µg/mL	Negative	4	8.9	200	0.220 ± 0.881	4.0*	12.0**
DMSO	10 µL/mL	Negative	20	12.4	200	0.065 ± 0.716	2.0	2.0
R279741	0.001 µmol/L	Negative	20	10.4	200	0.245 ± 1.262	2.5	9.0**
	0.005 µmol/L	Negative	20	9.8	100	0.940 ± 1.549	4.0	45.0**
	0.01 µmol/L	Negative	20	5.5	100	1.080 ± 1.662	3.0	52.0**
Mitomycin C[c]	0.1 µg/mL	Negative	20	11.9	200	0.245 ± 0.544	1.5	19.5**
DMSO	10 µL/mL	Positive	4	12.8	200	0.030 ± 0.171	1.5	3.0
R279741	0.031 µmol/L	Positive	4	12.6	200	0.035 ± 0.184	2.0	3.5
	0.0625 µmol/L	Positive	4	13.3	200	0.110 ± 0.329	1.0	10.5**
	0.125 µmol/L	Positive	4	6.0	200	0.180 ± 0.489	1.5	14.0**
Cyclophosphamide[c]	10 µg/mL	Positive	4	7.8	200	0.280 ± 0.635	0.0	20.5**

[a] All cells were harvested at 20 hours post initiation of treatment.
[b] Not considered biologically significant, within range of historical solvent control (0-8%).
[c] Positive control

* = p≤0.05, ** = p≤0.01 (Fisher's exact test)

2.6.7.9 In vivo遺伝毒性試験

2.6.7.9.1 マウス小核試験

Report Title: **Mammalian Erythrocyte Micronucleus Test** **Test Article: R279741（Trabectedin）**

Test for Induction of: Micronuclei in bone marrow
Treatment Schedule: Single iv injection
Study No: [redacted]
Species/Strain: Mouse/ICR
Sample Time: 24 and 48 hours
Location in CTD: 4.2.3.3.2.1
Age/Weight: 6 to 8 Weeks at initiation/Males 27.9 to 34.1 grams; Females 24.5 to 29.4 grams
Method of Administration: Intravenous injection
GLP Compliance: Yes
Cells Evaluated: Bone marrow erythrocytes
Vehicle/Formulation: Sterile water/R279741 plus vehicle (initial assay) Sterile 0.9% Sodium Chloride/R279741 plus vehicle (repeat assay)
Date of Dosing: [redacted]
No. of Cells Analyzed/Animal: 2000 polychromatic erythrocytes/animal
Positive Control: Cyclophosphamide
Toxic/Cytotoxic Effects: At 48 hours excessive reduction in PCE:NCE ratio at dose levels ≥225 µg/m^2 (75 µg/kg).
Genotoxic Effects: Yes ≥225 µg/m^2 (75 µg/kg)
Evidence of Exposure: Mortality in one male at ≥225 µg/m^2 (75 µg/kg). Prostration observed in males at 225 µg/m^2 (75 µg/kg) immediately post dosing, at 48 hours excessive reduction in PCE:NCE ratio at dose levels ≥225 µg/m^2 (75 µg/kg)

Test Article	Dose	No./Sex of Animals/	Mean PCE:NCE Ratio Sampling Time				Mean % MNPCEs Sampling Time			
			24 h		48 h		24 h		48 h	
			Males	Females	Males	Females	Males	Females	Males	Females
Vehicle Control[a]	10 mL/kg	5	0.407	0.415	0.467	0.452	0.03	0.07	0.05	0.06
Vehicle Control[b]	10 mL/kg	5	--	--	0.446	0.452	--	--	0.09	0.08
R279741	4.5 µg/m^2 (1.5 µg/kg)[b]	5	--	--	0.464	0.467	--	--	0.04	0.06
	15 µg/m^2 (5 µg/kg)[b]	5	--	--	0.437	0.480	--	--	0.04	0.10
	45 µg/m^2 (15 µg/kg)[b]	5	--	--	0.435	0.450	--	--	0.05	0.10
	150 µg/m^2 (50 µg/kg)[b]	5	--	--	0.391	0.409	--	--	0.09	0.09
	225 µg/m^2 (75 µg/kg)[a]	5[c]	0.414	0.425	0.055	0.081	0.10	0.13	/	/
	450 µg/m^2 (150 µg/kg)[a]	5	0.413	0.401	0.018	0.027	0.27*	0.20*	/	/
	900 µg/m^2 (300 µg/kg)[a]	5	0.352	0.362	0.007	0.015	0.67*	0.56*	/	/
Cyclophosphamide[a]	50 mg/kg	5	0.370	0.402	--	--	2.21*	2.25*	--	--
Cyclophosphamide[b]	50 mg/kg	5	0.426	0.443	--	--	2.26*	2.42*	--	--

[a] This study consisted of an initial assay (75 to 300 µg/kg) and a repeat assay (1.5 to 50 µg/kg). Each assay included a vehicle control and a positive control.
[b] Repeat assay
[c] N = 4 for males, at 24 hours, due to mortality.

-- = This time interval not evaluated based on study design; / = Due to excessive reduction in the number of PCEs, mean % MNPCEs was not determined.
Note: Dose conversion to µg/m^2: multiply µg/kg by 3 for mice.
* - p≤0.05 (Kastenbaum-Bowman Tables); Statistical comparisons based on the actual number PCEs scored/10000 cells.

2.6.7.10 がん原性試験

トラベクテジンのがん原性については，本薬の対象疾患が進行軟部肉腫であり，ICH ガイドライン S1A「医薬品におけるがん原性試験の必要性に関するガイダンス」では，「対象の患者集団で長期の延命が望めないような場合，例えば，進行がんの治療を目的とした抗悪性腫瘍剤などでは，通常，がん原性試験を必要としない.」とされていることから，試験の実施は必要ないと判断した.

2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

2.6.7.11.1 胚・胎児発生に関する試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Dosing Period	Doses μg/m^2 (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat, CD®, Female, 5/group	Intravenous, bolus (Sterile water, sterile 0.9% sodium chloride / R279741 plus vehicle)	Gestation Days 6-17	0 1.8 (0.3) 6 (1) 18 (3) 60 (10) 180 (30)	All Groups: Dose related ↓ maternal body weight, ↓ maternal body weight gain. 18 μg/m^2: ↓ food consumption; 2 of 5 animals exhibited swollen tails. 60 μg/m^2: 5 of 5 animals sacrificed early or found dead after exhibiting: ↓ food consumption, dark shedding, material around eyes/nose, hunched posture, emaciation, piloerection, rough coat and orange colored urine. 180 μg/m^2: 5 of 5 animals sacrificed early or found dead after exhibiting: ↓ food consumption, slight dehydration, shedding, ↓ activity, ataxia, dark material around eyes/nose, hunched posture, jaundice, labored breathing, piloerection and rough coat. No affects on c-section parameters and no fetotoxicity observed at any dose level. No Observed Effect Level: <1.8 μg/m^2	[redacted] 4.2.3.5.2.1
Rabbit, New Zealand White, Female, 5/group	Intravenous, bolus (Sterile water, sterile 0.9% sodium chloride/ R279741 plus vehicle)	Gestation Days 7-20	0 3.6 (0.3) 12 (1) 36 (3) 120 (10) 300 (25)	3.6 μg/m^2: No observed effects 12 μg/m^2: Dark spots on lung of one animal. 36 μg/m^2: 1 of 5 animals found dead, this animal exhibited mottled lungs, mottled/discolored liver, enlarged small intestine; all animals exhibited swollen, irritated and/or necrotic ears as local effects of drug administration. One fetus –intestines erupting from umbilicus, one fetus (different litter) pale mottled kideneys. 120 μg/m^2: 5 of 5 animals sacrificed early after exhibiting ↓ activity/lethargy, ↓ appetite, ↓ maternal body weight, ↓ maternal body weight gain, ↓ food consumption; all animals exhibited swollen, irritated and/or necrotic ears as local effects of drug administration, one animal exhibited red areas on the lung and thickened uterine tissue. 300 μg/m^2: 5 of 5 animals sacrificed early or found dead after exhibiting ↓ activity, labored breathing, ↓ maternal body weight, ↓ maternal body weight gain, ↓ food consumption; all animals exhibited swollen, irritated and/or necrotic ears as local effects of drug administration. Discolored lungs noted at necropsy. No maternal toxicity, embryotoxicity, fetotoxicity or treatment related fetal gross abnormalities at 3.6 and 12 μg/m^2 No Observed Adverse Effect Level: 12 μg/m^2	[redacted] 4.2.3.5.2.3

Note: Dose conversion to μg/m^2: multiply μg/kg by 6 for rats, or 12 for rabbits.

2.6.7.12 受胎能

トラベクテジンは，臨床で抗悪性腫瘍剤として使用されることから，ICH ガイドライン S9「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，トラベクテジンの受胎能又は着床までの初期胚発生に関する試験は実施しなかった.

2.6.7.13 胚・胎児発生に関する試験

2.6.7.13.1 ラット胚・胎児発生に関する試験

Report Title: **Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rats** **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Design Similar to ICH 4.1.3 **Yes** **No**
Species/Strain: Rat/CD®
Age at First Dose: 9 – 10 weeks
Date of First Dose: [redacted], Dosing stagger-started over two days in order to match the staggered mating.
Special Features: None

Duration of Dosing: 12 days (GD[a] 6-17)
Day of Mating: GD 0 (Mating staggered over two days)
Day of C-Section: GD 20
Route: Intravenous (bolus)

Vehicle/Formulation: Sterile water, sterile 0.9% sodium chloride/R279741 plus vehicle

Study No.: [redacted]
Location in CTD: 4.2.3.5.2.2
GLP Compliance: No

No Observed Adverse-Effect Level:
F_0 Females: 3.0 µg/m^2 (0.5 µg/kg)
F_1 Litters: 0.6 µg/m^2 (0.1 µg/kg)

Dose µg/m^2 (µg/kg)	**0 (Control)**	**0.6 (0.1)**	**3.0 (0.5)**	**15 (2.5)**
No. of Animals	25	25	25	25
Toxicokinetics:	Not Evaluated	Not Evaluated	Not Evaluated	Not Evaluated
Noteworthy Findings				
No. Pregnant[b]	25/25	25/25	24/25	24/25
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted or with Total Resorption of Litter	0	0	0	0

[a] GD = Gestation Day
[b] Number of positive animals/total number of animals

Note: Dose conversion to µg/m^2: multiply µg/kg by 6 for rats.

2.6.7.13.1 ラット胚・胎児発生に関する試験（続き）

Report Title: Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rats **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Dose µg/m^2 (µg/kg)	**0 (Control)**	**0.6 (0.1)**	**3.0 (0.5)**	**15 (2.5)**
Noteworthy Findings (Continued)				
Clinical Observations	-[d]	-	-	-
Body Weight[a] (g)				
Gestation Day 0	214	1.00	1.00	1.00
Gestation Day 6	250	0.99	0.98	0.97
Gestation Day 10	268	0.99	0.99	0.96*
Gestation Day 17	322	1.00	0.98	0.95*
Gestation Day 20	371	1.00	1.00	0.95*
Body Weight Gain[a] (g)				
Gestation Day 6-17	72	1.03	1.00	0.85*
Gestation Day 0-20	157	0.99	0.99	0.87*
Adjusted Body Weight[a,b] (g)	301	0.99	0.99	0.93*
Corrected Mean Maternal Weight Gain[a,c] (g)	87	0.94	0.94	0.75*
Food Consumption[a] (g)				
Gestation Day 12	21.7	0.98	1.00	0.89*
Gestation Day 17	23.9	1.00	1.04	0.90*
Gestation Day 20	24.4	0.97	0.94	0.88*
Mean No. Corpora Lutea	13.4	14.5	14.8	14.8
Mean No. Implantations	11.6	12.8	12.6	12.8
Mean % Preimplantation Loss	13.0	11.2	13.3	13.4
Necropsy Observations	-	-	-	-
Litters: No. of Litters Evaluated	25	25	24	24
No. Live Fetuses	283	305	297	288
Mean No. Live Fetuses	11.3	12.2	12.4	12.0
Mean No. Early Resorptions	0.3	0.6	0.2	0.8
Mean No. Late Resorptions	0.00	0.00	0.04	0.00
Mean No. Total Resorptions	0.3	0.6	0.2	0.8

[a] For controls, group means are shown. For treated groups, noteworthy findings are expressed as multiples of control. Statistical significance is based on actual data (not on the multiples of control).
[b] Adjusted body weight = body weight on day of cesarean sectioning minus gravid uterine weight.
[c] Corrected Mean Maternal Weight Gain = Total body weight gain (GD 0-20) minus gravid uterine weight.
[d] - = no noteworthy findings

* $p < 0.05$ (Analysis of Variance and Dunnett's Procedure)

2.6.7.13.1 ラット胚・胎児発生に関する試験（続き）

Report Title: Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rats **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Dose µg/m^2 (µg/kg)	0 (Control)	0.6 (0.1)	3.0 (0.5)	15 (2.5)
No. Dead Fetuses	0	0	0	0
Mean No. of Dead Fetuses	0.0	0.0	0.0	0.0
Mean % Postimplantation Loss	2.7	4.4	1.6	6.3
Mean Fetal Body Weight (g)				
Males	4.13	4.01	3.98	3.96*
Females	3.94	3.84	3.73*	3.69*
Fetal Sex Ratios (% males fetuses)	49	54	56	52
Fetal Anomalies:				
Gross External	-	-	-	-
Visceral Anomalies	-	-	-	-
Skeletal Anomalies	-	-	-	-
Total Affected Fetuses (Litters)	-	-	-	-

- = no noteworthy findings

* - p <0.05 (Analysis of Variance and Dunnett’s Procedure for fetal body weights; Chi Square/Fisher’s Exact Test for fetal sex ratio)

2.6.7.13.2 ウサギ胚・胎児発生に関する試験

Report Title: Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rabbits **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Design Similar to ICH 4.1.3 **Yes** **No**
Species/Strain: Rabbit/New Zealand White
Age at First Dose: 6 months
Date of First Dose: [redacted], Dosing stagger-started over three days in order to match the staggered mating.
Special Features: None

Duration of Dosing: 14 days (GD[a] 7-20)
Day of Mating: GD 0 (Mating staggered over three days)
Day of C-Section: GD 29
Route: Intravenous (bolus)
Vehicle/Formulation: Sterile water, sterile 0.9% sodium chloride/R279741 plus vehicle

Study No.: [redacted]
Location in CTD: 4.2.3.5.2.4
GLP Compliance: No

No Observed Effect Level:
F_0 Females: 3.5 µg/m^2 (0.3 µg/kg)
F_1 Litters: 23.6 µg/m^2 (2.0 µg/kg)

Dose µg/m^2 (µg/kg)	**0 (Control)**	**3.6 (0.3)**	**9 (0.75)**	**24 (2.0)**
No. of Animals	20	20	20	20
Toxicokinetics:	Not Evaluated	Not Evaluated	Not Evaluated	Not Evaluated
Noteworthy Findings				
No. Pregnant[b]	18/20	19/20	19/20	19/20
No. Died or Sacrificed Moribund	0/20	0/20	0/20	0/20
No. Aborted or with Total Resorption of Litter	0	0	0	0

[a] GD = Gestation Day
[b] Number of positive animals/total number of animals

Note: Dose conversion to µg/m^2: multiply µg/kg by 12 for rabbits.

2.6.7.13.2 ウサギ胚・胎児発生に関する試験（続き）

Report Title: Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rabbits **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Dose µg/m^2 (µg/kg)	**0 (Control)**	**3.6 (0.3)**	**9 (0.75)**	**24 (2.0)**
Noteworthy Findings (Continued)				
Clinical Observations[a]				
Tissue damage to ear/limp ear (Dose site)	0/20	0/20	3/20	20/20
Body Weight[b] (kg)				
Gestation Day 7	3.33	1.01	1.00	0.99
Gestation Day 20	3.59	0.99	0.99	0.99
Gestation Day 29	3.71	1.00	0.99	1.00
Adjusted Body Weight[b,c] (kg)	3.22	1.00	1.00	0.99
Corrected Mean Maternal Weight Gain[b,d] (kg)	-0.24	1.08	0.96	1.17
Food Consumption[b] (g)				
Gestation Day 15	130	0.99	0.99	0.88*
Gestation Day 18	130	1.00	1.00	0.94*
Gestation Day 21	128	1.02	1.02	0.77*
Gestation Day 24	130	1.00	1.00	0.94*
Gestation Day 29	127	1.02	1.02	1.00
Mean No. Corpora Lutea	11.6	11.9	11.2	10.9
Mean No. Implantations	9.7	9.3	9.1	9.3
Mean % Preimplantation Loss	16.4	19.6	18.0	14.4
Necropsy Observations	-	-	-	-

[a] Number with observation/Number observed
[b] For controls, group means are shown. For treated groups, noteworthy findings are expressed as multiples of control. Statistical significance is based on actual data (not on the multiples of control).
[c] Adjusted body weight = body weight on day of cesarean sectioning minus gravid uterine weight.
[d] Corrected Mean Maternal Weight Gain = Total body weight gain (GD 0-29) minus gravid uterine weight.

- = no noteworthy findings
* $p < 0.05$ (Kruskal-Wallis and Mann-Whitney U test)

2.6.7.13.2 ウサギ胚・胎児発生に関する試験（続き）

Report Title: Intravenous Developmental Toxicity Study of Ecteinascidin 743 (ET-743) in Rabbits **Test Article: R279741（Trabectedin）**

Effects on Embryo-Fetal Development

Dose μg/m^2 (μg/kg)		0 (Control)	3.6 (0.3)	9 (0.75)	24 (2.0)
Litters:	No. of Litters Evaluated	18	19	19	19
	No. Live Fetuses	166	164	157	167
	Mean No. Live Fetuses	9.2	8.6	8.3	8.8
	Mean No. Early Resorptions	0.2	0.5	0.7	0.2
	Mean No. Late Resorptions	0.2	0.2	0.1	0.2
	Mean No. Total Resorptions	0.4	0.7	0.8	0.4
	No. Dead Fetuses	0	0	0	1
	Mean No. of Dead Fetuses	0	0	0	0.1
	Mean % Postimplantation Loss	4.1	8.6	8.8	5.1
	Mean Fetal Body Weight (g)				
	Males	37.2	38.5	39.7	37.2
	Females	37.4	38.3	38.4	37.2
	Fetal Sex Ratio (% male fetuses)	51	41	52	46
	Fetal Anomalies:				
	Gross External	-	-	-	-
	Visceral Anomalies	-	-	-	-
	Skeletal Anomalies	-	-	-	-
	Total Affected Fetuses (Litters)	-	-	-	-

- = no noteworthy findings

2.6.7.14 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

トラベクテジンは，臨床で抗悪性腫瘍剤として使用されることから，ICH ガイドライン S9「抗悪性腫瘍薬の非臨床評価に関するガイドライン」に従い，トラベクテジンの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を実施しなかった.

2.6.7.15 新生児を用いた試験

トラベクテジンは，新生児を用いた試験を実施しなかった.

2.6.7.16 局所刺激性試験

2.6.7.16.1 血管刺激性に関する試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Doses (µg/mL)/Dose Volume (mL)	Noteworthy Findings	Study No./ Location in CTD
Rabbit, New Zealand White, Male, 4/Group	Bolus intravenous (Groups 1 and 2) Paravenous (Groups 3 and 4) (Sterile water, sterile 0.9% sodium chloride/R279741 plus vehicle) (Test article formulation; right ear all animals)	Group 1: 2.5/1.0 Group 2: 25/1.0 Group 3: 2.5/0.3 Group 4: 25/0.3 (Vehicle Control: saline, left ear all animals)	Intravenous Administration/2.5 µg/mL: Single intravenous injection resulted in slight injection site swelling and minimal erythema. Histologic lesions included minimal epithelial necrosis, minimal subacute inflammation and minimal to mild edema. No ulceration was observed. Intravenous Administration/25 µg/mL: Single intravenous injection resulted in more pronounced injection site swelling and minimal to moderate erythema. Histologic lesions included focal fibrinoid necrosis, epithelial necrosis, subacute inflammation and edema. No ulceration was observed. Paravenous Administration/2.5 and 25 µg/mL: Single paravenous injection resulted in injection site swelling, mild to moderate erythema, hematoma and vessel dilation. Histologic lesions included ulceration, focal fibrinoid necrosis, epithelial necrosis, subacute inflammation and edema.	[redacted] 4.2.3.6.1

2.6.7.16.1 血管刺激性に関する試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Doses (µg/mL)/Dose Volume (mL/kg)	Noteworthy Findings	Study No./ Location in CTD
Rabbit, New Zealand White, Female, 10/Group	Groups I and II: Bolus intravenous injection in the left ear of the first 5 animals/group on day 0. Bolus intravenous injection in the left ear of the second 5 animals/group on day 0, 7, 14, and 21. (Group I: pyrogen free water, saline / [redacted] R279741plus [redacted] and vehicle) (Group II: pyrogen free water, saline/[redacted] R279741plus [redacted] and vehicle)	Group I: [redacted] R279741 7.0 µg/mL/0.3 mL/kg Group II: [redacted] R279741 7.0 µg/mL/0.3 mL/kg Vehicle Control: saline (0.3 mL/kg) right ear all animals	The right ear served as the saline control, the left ear received the test article. Necropsies were performed on the Group I and II single dose animals 3 days after administration of the test article. Necropsies were also performed on the Group I and II multiple (4×) dose animals 3 days after the fourth administration of the test article. Group I: 7.0 µg/mL ([redacted] R279741 Single Dose): Within normal limits. Group I: 7.0 µg/mL ([redacted] R279741 Multiple Dose): Slight erythema noted at the region of the marginal auricular vein (dose site) was noted in 1 of 5 rabbits following four repeated intravenous administrations. Histopathologically, slight irritation (vasculopathy) was noted in 3 of 5 rabbits. Group II: 7.0 µg/mL ([redacted] R279741 Single Dose): Within normal limits. Group II: 7.0 µg/mL ([redacted] R279741 Multiple Dose): Slight erythema noted at the region of the marginal auricular vein (dose site) was noted in 3 of 5 rabbits following four repeated intravenous administrations. At necropsy slight red focal discoloration was noted at the injection sites of 3 of 5 animals. This gross necropsy finding correlated to histopasthological changes indicative of irritation. Histopathologically, minimal to slight irritation (vasculopathy) was noted in 4 of 5 rabbits. It was concluded, that there were no relevant differences in the local tolerability of [redacted] and [redacted] R279741 based on clinical observations and histopathological findings.	[redacted] 4.2.3.6.2

2.6.7.17 その他の試験

2.6.7.17.1 肝毒性に対する試験（*in vitro*試験）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses	Noteworthy Findings	Study No./ Location in CTD
Mouse, rat, monkey and human primary cultured hepatocytes. Cytotoxicity assessed spectrophotometricaly by ability of mitochondrial succinate dehydrogenase to transform MTT substrate into an insoluble blue formazan.	Culture incorporation, R279741 and radioactively labelled ^{14}C-R279741 (mouse/rat: supplemented Ham's F-12 /Lebovitz L-15 medium; monkey/human: supplemented Ham's F-12 /Williams Medium)	8 and 24-hour exposure periods.	0.03, 0.3, 1, 3, 10, 30, 100, and 300 nmol/L and 2 µmol/L	R279741 concentration of 10 nmol/L was cytotoxic in mouse and human hepatocytes after a 24-hour incubation period. In contrast, rat and monkey hepatocytes presented signs of cytotoxicity when incubated with trabectedin at a concentration of 100 nmol/L after a 24-hour incubation period.	[redacted] 4.2.3.7.3.1
Mouse, rat, monkey and human primary cultured hepatocytes. Human hepatoma cell line (HepG2)	Culture incorporation, R279741 and ET-729 in appropriate culture medium	24-hour exposure periods.	0.03, 0.3, 1, 3, 10, 30, 100, and 300 nmol/L and 2 µmol/L	Mouse hepatocytes and female rat hepatocytes were the most sensitive cells to trabectedin and ET-729. The toxicity of ET-729 did not meaningfully differ from that of trabectedin. Female rats are somewhat more sensitive to both compounds than male rats.	[redacted] 4.2.3.7.3.2

2.6.7.17.2 肝毒性に対する試験（*in vivo*試験）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat, Wistar, Female 5/group	Intravenous R279741 (Water/ R279741 -plus vehicle) Oral (Glycerol formal/ dexamethasone -plus vehicle)	Single Dose Tumor Models Once, Twice or Three Times	R279741: 0, 240 (40) DEX: 0, 5-20 mg/kg	This study was conducted in order to determine if dexamethasone could ameliorate manifestations of R279741-induced hepatotoxicity R279741 (240 $\mu g/m^2$ i.v): dramatic ↑ of plasma ALP, AST, and bilirubin levels, and degeneration and patchy focal necrosis of bile duct epithelial cells. Pretreatment of rats with dexamethasone 24 hours prior to R279741 administration: ameliorated or abrogated the biochemical and histopathological manifestations of R279741 associated liver toxicity. Dexamethasone administered simultaneously with R279741: R279741 toxicity was not reduced. Dexamethasone (10 mg/kg) administered 24 hours before R279741: decreased hepatic levels of R279741 compared with those obtained after administration of R279741 alone, whereas R279741 plasma levels after the drug combination were not markedly different from those in rats on R279741 alone. Pretreatment with dexamethasone (10 mg/kg, p.o.) reversed the gene expression changes induced by R279741 in rat liver. Tumor Models: Dexamethasone pretreatment did not interfere with the antitumor efficacy of R279741 in rats bearing the 13762 mammary carcinoma or in four murine models. These results suggest that pretreatment with high-dose dexamethasone effectively protects rats against R279741 mediated hepatic damage by decreasing hepatic exposure to trabectedin.	4.3.44
Tumor Models: Rat, Fischerm Female: 13762 tumor Mice,C57B1/6J, Female: B16F1 melanomaM5076 reticulum cell sarcoma Mice, MCr-ν / ν , Female Igrov/1 ovarian carcinoma Mice, CDI ν/ν, Male TE-671 rhabdomyosarcoma	Tumor Models i.p. DEX Intravenous R279741		Tumor Models Rat: DEX: 10 mg/kg followed 24 hrs by R279741: 180 (30) or 240 (40) Mice: DEX: 20 or 40 mg/kg daily for 3 or 4 days, R279741: 450 (150) or 600 (200)		

↑ = increase, ↓ = decrease, ALP = alkaline phosphatase, AST = aspartate aminotransferase, DEX = dexamethasone

2.6.7.17.3 代謝物の毒性試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	**Route (Vehicle/ Formulation)**	**Duration of Dosing**	**Doses µg/m² (µg/kg)**	**Noteworthy Findings**	**Study No./ Location in CTD**
Mouse, CD-1, Male and Female, 5/sex/group	Intravenous (Vehicle not specified)	Single Dose (14 day observation period)	R279741: 600 (200) 675 (225) 750 (250) 900 (300) ET-729: 225 (75) 300 (100) 375 (125) 450 (150)	Mortality (Number died/Number treated [Day of Death]) Dose (µg/m²) / R279741 Males / R279741 Females / ET-729 Males / ET-729 Females 225: Not tested / Not tested / 0/5 / 0/5 300: Not tested / Not tested / 0/5 / 0/5 375: Not tested / Not tested / 4/5 (3, 5, 8, 8) / 1/5 (5) 450: Not tested / Not tested / 5/5 (3, 4, 4, 5, 7) / 4/5 (3, 4, 6, 8) 600: 0/5 / 0/5 / Not tested / Not tested 675: 0/5 / 0/5 / Not tested / Not tested 750: 1/5 (13) / 0/5 / Not tested / Not tested 900: 4/5 (10, 11, 12, 13) / 1/5 (8) / Not tested / Not tested Maximum Tolerated Dose: 675 µg/m² / 750 µg/m² / 300 µg/m² / 300 µg/m² In conclusion, based on maximum tolerated dose levels, ET-729 was considered more toxic than R279741	[redacted] 4.2.3.7.5.1

2.6.7.17.4　不純物の毒性試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat, Sprague-Dawley, Male and Female, 10/sex/group	Intravenous Infusion (Sterile water - saline/ R279741-plus vehicle or Sterile water - saline/R279741 and 不純物 B* (impurity) plus vehicle)	Group 1: 3 hrs Group 2: 24 hrs Group 3: 3 hrs Group 4: 24 hrs Group 5: 3 hrs 5/sex/group sacrificed 3 days postdosing; 5/sex/group were allowed a three-week recovery period postdosing.	Group 1: 0 (vehicle control) Group 2: 0 (vehicle control) Group 3: 300 (50) R279741 Group 4: 300 (50) R279741 Group 5: 291 (48.5)/9 (1.5) R279741/ 不純物 B* (impurity)	*Summary* Single dose intravenous administration of R279741 by 3-hour infusion might be more toxic than by 24-hour infusion as suggested by the depletion of bone marrow cellularity. No clear differences in toxicity were observed between R279741 and R279741 plus the impurity 不純物 B* when administered as a three-hour infusion. 0 $\mu g/m^2$/cycle - 3 hour infusion: Males: No noteworthy findings. Females: No noteworthy findings. <u>0 $\mu g/m^2$/cycle - 24 hour infusion</u>: Males: No noteworthy findings. Females: No noteworthy findings. <u>300 $\mu g/m^2$/cycle R279741 – 3-hour infusion</u>: Males: Slight ↓ body weight, body weight gain and food consumption during week 1. *Postdosing Hematology*: Slight ↓ HCT, moderate ↓ WBC, pronounced ↓ RETICS, slight ↓ BASO, moderate ↓ LYMPH, marginal ↓ EOSIN, moderate ↓ MONO. *End of Recovery Hematology:* marginal ↓ RBC, slight ↓ WBC, slight ↑ RETICS, MCV, slight ↓ BASO and LYMPH. *Postdosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate, total protein and creatinine. *End of Recovery Clinical Chemistry:* No noteworthy findings. No noteworthy macroscopic findings. Females: Dark urine noted in 5 of 10 prior to interim kill and in 3 of 5 recovery animals. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week postdosing, by end of second week ↓ was slight. *Postdosing Hematology*: Slight ↓ THROMBO, slight ↓ LYMPH, BASO and EOSIN, pronounced ↓ in RETICS. *End of Recovery Hematology*: Moderate ↓ HCT, HGB, RBC, moderate ↑ THROMBO, MCV, MCH, slight ↓ MCHC, pronounced ↑ RETICS, slight ↑ MONO. *Postdosing Clinical Chemistry*: Slight ↑ calcium, moderate ↓ chloride, albumin, pronounced ↑ GGT, ALP, AST, ALT, TBI, CHOL, TRIGL. *End of Recovery Clinical Chemistry*: Slight ↑ calcium, marginal ↑ BUN, pronounced ↑ GGT, TBI, CHOL, TRIGLY, moderate ↑ ALT, ALP, AST. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen and thymus weight observed 3 days postdosing. Following 3 weeks recovery liver weight increase more pronounced and spleen weight slightly increased. Slight ↑ in absolute and relative weight of the pancreas and kidneys observed at end of recovery only.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				Postdosing Macroscopic Pathology: General anemia, yellow abdominal mesothelium, yellow subcutis, pale liver, swollen liver, hemorrhagic stomach content, dark focus on the stomach, yellow urinary bladder content. *End of Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale/yellow-stippled liver, swollen liver and pancreas, yellow tissue mass at dose site and swollen spleen. 300 µg/m^2/cycle R279741- 24 hour infusion: Males: Slight ↓ body weight gain and food consumption during week 1. *Postdosing Hematology:* Marginal ↓ RBC, slight ↓ HCT, WBC, BASO, Lymph, pronounced ↓ RETICS. *End of Recovery Hematology:* Slight ↓ RBC, slight ↑ RETICS and MCV. *Postdosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate, TP, ALB. *End of Recovery Clinical Chemistry:* Slight ↑ calcium, inorganic phosphate. *End of Recovery Macroscopic Pathology:* White tissue mass at dose site Females: Dark urine noted in 5 of 10 prior to interim kill and in 2 of 5 recovery animals. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week postdosing, by end of second week ↓ was slight. *Postdosing Hematology:* Pronounced ↓ RETICS, slight ↓ BASO. *End of Recovery Hematology:* Pronounced ↑ RETICS, moderate ↓ HCT, HGB and RBC. Moderate ↑ THROMBO, MCV, MCH, slight ↑ MONO. *Postdosing Clinical Chemistry:* Moderate↓ chloride, ALB, slight ↑ calcium, pronounced ↑ CHOL, TRIGLY, TBI, GGT, ALT, moderate ↑ ALP, AST, marginal ↓ BUN. *End of Recovery Clinical Chemistry:* Slight ↑ calcium, potassium, pronounced ↑ CHOL, TRIGLY, GGT, moderate ↑ ALT, ALP, AST, TBI, marginal ↑ BUN. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen weight observed 3 days postdosing. Following 3 weeks recovery liver weight increase more pronounced and spleen weight slightly increased, slight ↑ in absolute and relative weight of the pancreas and kidney. *Postdosing Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, pronounced liver lobulation, and swollen liver. *Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale liver, swollen liver, swollen pancreas and swollen spleen.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TP = total protein, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4　不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses $\mu g/m^2$ ($\mu g/kg$)	Noteworthy Findings	Study No./ Location in CTD
				291/9 $\mu g/m^2$/cycle R279741/ 不純物 B* (impurity) - 3 hour infusion: Males: Slight ↓ body weight, body weight gain and food consumption during week 1. *Postdosing Hematology:* Moderate ↓ WBC, pronounced ↓ RETICS, slight ↓ LYMPH, MONO, marginal ↓ BASO and EOSIN. *End of Recovery Hematology:* Marginal ↓ RBC, slight ↓ WBC, slight ↑ RETICS and MCV. *Postdosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate, TP, creatinine. *End of Recovery Clinical Chemistry:* No significant findings. No noteworthy macroscopic findings. Females: Dark urine noted in 6 of 10 prior to interim kill and in 3 of 5 recovery animals. Feed wastage noted in 2 of 5 during recovery. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first week postdosing, by end of second week ↓ was slight. *Postdosing Hematology:* Slight ↓ LYMPH, BASO and EOSIN. Pronounced ↓ RETICS. End of Recovery Hematology: Slight ↓ MCHC, moderate ↓ HCT, HGB, RBC, moderate ↑ THROMBO, RETICS, MCV, MCH. *Postdosing Clinical Chemistry:* Moderate↓ chloride, ALB, slight ↑ calcium, pronounced ↑ CHOL, TRIGLY, TBI, GGT, ALT, moderate ↑ ALP, AST, marginal ↓ BUN. *End of Recovery Clinical Chemistry:* Slight ↑ calcium, pronounced ↑ GGT, CHOL, moderate ↑ TRIGLY, TBI, ALP, AST, ALT, marginal ↑ BUN. Moderate ↑ absolute and relative liver weights and slight ↓ in spleen and thymus weight observed 3 days postdosing. Following 3 weeks recovery liver weight increase more pronounced and spleen weight slightly increased. Slight ↑ in absolute and relative weight of the pancreas and kidneys observed at end of recovery only. *Postdosing Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, pronounced liver lobulation, swollen liver, dilated stomach, yellow urinary bladder content. *Recovery Macroscopic Pathology:* Yellow abdominal mesothelium, yellow subcutis, dark kidneys, pale liver, swollen liver, swollen pancreas, swollen spleen. *Histopathology Findings (All Treated Groups):* *Administration Sites*: Irritation, some with necrosis of the vessel wall, especially in animals killed after dosing. *Bone Marrow:* Decreased cellularity, especially after 3 hour infusion. Recovery almost complete after the recovery period.	[redacted] 4.2.3.1.4

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TP = total protein, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/ Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
				Gastrointestinal Tract: Single cell necrosis of epithelial crypt cells of the rectum, glandular stomach, small and/or large intestine present in most males and females killed after dosing. No gastrointestinal effects observed following recovery. *Pancreas:* Male groups after dosing exhibited increased minimal pancreatic acinar single cell necrosis. In female recovery groups the presence of intracytoplasmatic zymogen in the pancreatic acinar cells was minimally augmented. *Histopathology Findings (All Treated Female Groups)*: *Liver*: Moderate hepatotoxicity in females killed after dosing characterized by: swelling of hepatocytes hepatocellular necrosis, proliferative/inflammatory and epithelial changes of bile ducts and Kupffer cell proliferation. Following recovery, a moderate diffuse chronic hepatotoxicity characterized by diffuse chronic inflammation, pigmentation of sinusoidal lining cells, proliferative and epithelial changes of bile ducts and hepatocellular necrosis. *Kidney:* In female recovery groups, clear vacuolization with pigmentation of the renal corticotubular cytoplasm. *Spleen:* In female recovery groups, splenic hyperplastic changes increased with more prominent erythropoiesis and granulopoiesis, probably related to the primary hepatotoxic inflammatory changes and as a regenerative hematopoietic impulse during the recovery period.	[redacted] 4.2.3.1.4

2.6.7.17.4　不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat, Sprague-Dawley, Male and Female, 10/sex/group (4/sex/group-Groups 2 and 3 for Toxicokinetics)	Intravenous Infusion (Sterile water - saline/[redacted] R279741-plus vehicle or (Sterile water - saline/[redacted] R279741-plus vehicle) or (Sterile water - saline/[redacted] R279741 containing [redacted]% 不純物 C* (impurity) plus [redacted]% 不純物 F* -plus vehicle)	3 hr infusion 5/sex/group sacrificed 3 days postdosing; 5/sex/group were allowed a three-week recovery period postdosing	Group 1: 0 (vehicle control) Group 2: 300 (50) [redacted] R279741 Group 3: 300 (50) [redacted] R279741 Group 4: 290 (48.3) [redacted] R279741/6.6 (1.1) 不純物 C* (impurity)/3.6 (0.6) 不純物 F*	*Summary* No relevant differences were observed between the groups dosed with [redacted] or [redacted] R279741 nor between the group dosed with [redacted] R279741 and the group dosed with [redacted] R279741 spiked with 不純物 F* and 不純物 C* administered intravenously at 50 µg/kg over 3 hours. 0 $\mu g/m^2$/cycle - 3 hour infusion: Males: No noteworthy findings. Females: No noteworthy findings. 300 $\mu g/m^2$/cycle [redacted] R279741 - 3 hour infusion: Males: Dark urine noted in 1 of 10 prior to interim kill. Slight-moderate ↓ body weight, body weight gain and food consumption during week 1. *Postdosing Hematology*: Slight ↓ HCT, BASO, EOSIN, LYMPH, moderate ↓ WBC, MONO, pronounced ↓ RETICS. *End of Recovery Hematology:* Marginal↑ RETICS, marginal ↓ RBC, EOSIN, slight ↓ WBC, and LYMPH. *Post-Dosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate.	[redacted] 4.2.3.7.6.1

↑ = increase, ↓ = decrease, BASO = basophils, EOSIN = eosinophils, HCT = hematocrit, LYMPH = lymphocytes, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, = WBC = white blood cells

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				End of Recovery Clinical Chemistry: No noteworthy findings. Slight ↓ absolute and relative spleen weight. Spleen weights exhibited recovery. *Postdosing and Recovery Macroscopic Pathology*: No noteworthy findings. Females: Dark urine noted in 5 of 10 prior to interim kill and in most recovery animals. Slight-moderate ↓ body weight and body weight gain during week 1. Moderate-pronounced ↓ food consumption during first and second weeks postdosing, at the end of second week ↓ was slight. *Postdosing Hematology*: Moderate ↓ WBC, slight ↓ LYMPH, BASO and EOSIN pronounced ↓ RETICS. *End of Recovery Hematology:* Moderate ↓ HCT, HGB, RBC, moderate ↑ THROMBO, MCV, MCH, slight ↓ MCHC, pronounced ↑ RETICS, slight ↑ MONO, marginal ↓ in fibrinogen. *Postdosing Clinical Chemistry:* Slight ↑ calcium, slight ↓ chloride, pronounced ↑ GGT, ALP, AST, ALT, TBI, CHOL, TRIGLY. *End of Recovery Clinical Chemistry:* Marginal ↑ calcium, pronounced ↑ GGT, CHOL, TRIGLY, ALP, slight ↓ ALB, moderate↑ ALT, AST, TBI. *Postdosing Organ Weights:* Moderate ↑ absolute and relative liver weight, slight ↓ absolute and relative spleen and thymus weight. *End of Recovery Organ Weights:* Slight ↑ absolute and relative spleen weight, moderate to pronounced ↑ absolute and relative liver weight, slight ↑ absolute and relative pancreas and kidney weight, marginal ↓ absolute and relative thymus weight. *Postdosing Macroscopic Pathology*: yellow abdominal mesothelium in 3 rats, pale liver in 4 rats, swollen liver in 5 rats, small spleen in 3 rats, yellow subcutis in 4 rats. *Recovery Macroscopic Pathology*: yellow abdominal mesothelium in 1 rat, yellow subcutis in 3 rats, swollen spleen in 3 rats, pale and swollen pancreas in 1 rat, dark kidneys in 2 rats, swollen liver in 5 rats, pale liver in 2 rats.	[redacted] 4.2.3.7.6.1

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m²/cycle [redacted] R279741 – 3 hour infusion: Males: Marginal-slight- ↓ body weight, body weight gain and food consumption during week 1. *Postdosing Hematology*: Marginal ↓ RBC, Slight ↓ HCT, BASO, EOSIN, LYMPH, moderate ↓ WBC, MONO, pronounced ↓ RETICS. *End of Recovery Hematology:* Slight↑ RETICS, MCV, marginal ↓ EOSIN, slight ↓ HCT, RBC, *Post-Dosing Clinical Chemistry:* Slight ↓ calcium, inorganic phosphate and TP. *End of Recovery Clinical Chemistry:* No noteworthy findings. Slight ↓ absolute and relative spleen weight. Spleen weights exhibited recovery. *Postdosing Macroscopic Pathology*: Small spleen in 1 rat. *Recovery Macroscopic Pathology*: Yellow tissue mass at dosing site and swollen spleen noted in 1 animal. Females: Dark urine noted in 5 of 10 prior to interim kill and in 3 of 5 at end of recovery. Slight-moderate ↓ body weight and body weight gain during weeks 1and 2. Moderate-pronounced ↓ food consumption during first and second weeks postdosing, at the end of second week ↓ was slight. *Postdosing Hematology*: Moderate ↓ WBC, slight ↓ LYMPH, MONO and BASO pronounced ↓ RETICS. *End of Recovery Hematology:* Moderate ↓ HCT, HGB, RBC, moderate ↑ RETICS, THROMBO, MCV, MCH, slight ↓ MCHC and fibrinogen, marginal ↑ MONO. *Postdosing Clinical Chemistry:* Slight ↑ calcium, slight ↓ chloride, moderate ↑ALP, AST, pronounced ↑ GGT, ALT, CHOL, TRIGLY, TBI. *End of Recovery Clinical Chemistry:* Marginal ↑ calcium, pronounced ↑ GGT, CHOL, TRIGLY, ALP, slight ↓ ALB, moderate↑ ALT, AST, TBI.	[redacted] 4.2.3.7.6.1

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TP = total protein, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4　不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				Moderate ↑ absolute and relative liver weight, slight ↓ absolute and relative spleen and thymus weight. At the end of the recovery period moderate to pronounced ↑ absolute and relative liver weight, slight ↑ absolute and relative pancreas and kidney weight, marginal ↓ absolute and relative thymus weight. *Postdosing Macroscopic Pathology*: Yellow abdominal mesothelium in 3 rat, small spleen in 2 rats, pale liver in 2 rats, swollen liver in 4 rats, yellow subcutis in 2 rats. *Recovery Macroscopic Pathology*: Yellow subcutis in 3 rats, swollen spleen in 3 rats, pale pancreas in 1 rat and swollen pancreas in 2 rat, dark kidneys in 3 rats, swollen liver in 5 rats, pale liver in 2 rats. 290µg/m²/cycle [redacted] R279741 - 6.6 µg/m²/cycle 不純物 C* (impurity) - 3.6 µg/m²/cycle 不純物 F* – 3 hour infusion: Males: Marginal to slight ↓ body weight, body weight gain and food consumption during week 1. *Postdosing Hematology*: Slight ↓ HCT, BASO, EOSIN, moderate ↓ WBC LYMPH, MONO, pronounced ↓ RETICS. *End of Recovery Hematology:* Marginal↑ RETICS, Slight↑ MCV, marginal ↓ EOSIN, slight ↓ WBC, RBC, LYMPH, *Post-Dosing Clinical Chemistry:* Slight ↓ calcium and inorganic phosphate. *End of Recovery Clinical Chemistry:* No noteworthy findings. Slight ↓ absolute and relative spleen weight. Spleen weights exhibited recovery. *Post-Dosing Macroscopic Pathology*: adhesions at abdominal mesothelium in one rat. *Recovery Macroscopic Pathology*: No treatment-related findings. Females: Dark urine noted in 4 of 10 prior to interim kill and in 5 of 5 at end of recovery. Slight to moderate ↓ body weight, body weight gain during weeks 1and 2, Moderate-pronounced ↓ food consumption during first and second weeks postdosing, at the end of second week ↓ was slight. *Postdosing Hematology*: Moderate ↓ WBC, slight ↓ EOSIN, LYMPH, MONO and BASO pronounced ↓ RETICS. *End of Recovery Hematology*: Moderate ↓ HCT, HGB, RBC, pronounced ↑ RETICS, moderate ↑ MCV, MCH, slight ↑ THROMBO, slight ↓ MCHC and fibrinogen, marginal ↑ MONO, *Postdosing Clinical Chemistry*: Slight ↑ calcium, slight ↓ chloride, ALB, BUN, pronounced ↑ GGT, ALT, CHOL, TRIGLY, TBI, moderate↑ ALP, AST.	[redacted] 4.2.3.7.6.1

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BASO = basophils, BUN = blood urea nitrogen, CHOL = cholesterol, EOSIN = eosinophils, GGT = gamma-glutamyl transferase, HCT = hematocrit, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MONO = monocytes, RBC = red blood cells, RETICS = reticulocytes, TBI = total bilirubin, THROMBO = thrombocytes, TRIGLY = triglycerides, WBC = white blood cells

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
				End of Recovery Clinical Chemistry: Marginal ↑ calcium, pronounced ↑ GGT, CHOL, TRIGLY, ALP, slight ↓ ALB, moderate↑ ALT, AST, TBI. Moderate ↑ absolute and relative liver weight, slight ↓ absolute and relative spleen and thymus weight. At the end of the recovery period moderate to pronounced ↑ absolute and relative liver weight, slight ↑ absolute and relative spleen, pancreas and kidney weights, slight ↓ absolute and relative thymus weight. *Postdosing Macroscopic Pathology*: Yellow abdominal mesothelium in 3 rats, small spleen in 2 rats, pale liver in 3 rats, swollen liver in 3 rats, yellow subcutis in 3 rats, swollen pancreas in 1 rat. *Recovery Macroscopic Pathology:* Yellow subcutis in 3 rats, swollen spleen in 4 rats, pale pancreas in 1 rat, swollen pancreas in 5 rats, swollen liver in 5 rats, pale liver in 2 rats, dark kidneys in 4 rats. *Histopathology Findings (All Treated Groups)*: Administration Sites: Irritation, some with necrosis of the vessel wall, observed in all treated groups and was less pronounced following recovery. Bone Marrow: Decreased Cellularity following treatment. Recovery almost complete after the recovery period. Focal hyperosteosteosis noted in 1 female treated with [redacted] R279741 and in 4 animals treated with [redacted] R279741 plus the impurity. *Gastrointestinal Tract:* Single cell necrosis of epithelial crypt cells of the rectum, glandular stomach, small and/or large intestine present in several treated males and females killed after dosing. Almost complete recovery of gastrointestinal effects occurred during recovery. One female in the [redacted] R279741 group had ulceration of the forestomach when sacrificed 3 days postdosing. *Pancreas:* All treated groups exhibited an increase in minimal pancreatic acinar single cell necrosis when killed 3 days postdosing. In male recovery groups the presence of acinar cell necrosis was nearly completely recovered. In treated female recovery groups the presence of zymogen in the pancreatic acinar cells was minimally to slightly augmented. The more prominent presence of acinar cell necrosis was less pronounced following recovery.	[redacted] 4.2.3.7.6.1

↑ = increase, ↓ = decrease, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHOL = cholesterol, GGT = gamma-glutamyl transferase, TBI = total bilirubin, TRIGLY = triglycerides

2.6.7.17.4 不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				Parotid Salivary Gland: All treated groups exhibited an increase in minimal acinar single cell necrosis when killed 3 days postdosing. This finding was more prominent in the females. In the male and female recovery groups complete recovery was observed. *Spleen:* Atrophy slightly elevated in treated males and females. In treated female recovery animals minimal atrophy of splenic white pulp noted in some animals, splenic hyperplastic changes increased, probably as a regenerative hematopoietic change during recovery, possibly related to the primary hepatotoxic inflammatory changes. *Histopathology Findings (All Treated Female Groups)*: Thymus: Atrophy slightly elevated and an increased presence of single cell necrosis in treated females only. Following recovery period minimal atrophy still noted. *Mesenteric Lymph Node*: Slightly elevated presence of single cell necrosis noted in the cortex, recovery was complete. *Liver*: Moderate hepatotoxicity in females killed after dosing characterized by: swelling of hepatocytes, hepatocellular necrosis, proliferative/inflammatory changes of bile ducts and Kupffer cell proliferation. Following recovery, a moderate diffuse more chronic hepatotoxicity characterized by diffuse chronic inflammation, changes of the bile ducts and hepatocellular necrosis. *Kidney*: In treated female recovery groups, clear vacuolization with pigmentation of the renal corticotubular cytoplasm. *Toxicokinetics*: Exposure maximum plasma concentration and area under the plasma concentration-time curve following a 3-hour infusion of R279741 at 300 µg/m^2, were similar in the [redacted] and [redacted] groups and in males and females.	[redacted] 4.2.3.7.6.1

2.6.7.17.4　不純物の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses $\mu g/m^2$ (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat/Sprague-Dawley Male and Female, 10/sex/group 3 hr infusion 5/sex/group sacrificed 3 days postdosing; 5/sex/group were allowed a three-week recovery period postdosing	Intravenous Infusion (sterile water for injection, control = 0.9% saline	Single (3 hr)	Group 1: 0 (vehicle control) Group 2: 300 (50) R279741/ [redacted] Formulation Group 3: 300 (50) R279741/ Spiked with [redacted]% 不純物 D* and [redacted]% 不純物 E* Group 4: 300 (50) R279741/ Spiked with [redacted]% 不純物 A*	Main toxic effects of R279741 were identified as: signs of localized intolerability (fibrin deposit, fibrosis, periphlebitis, cellulitis) at the infusion site (Day 4) which progressed to a more fibrosing nature on Day 22; early cytoxicity (Day 4) to tissues or organs with high cell proliferative activity (including bone marrow, lymphoid organs and gastro-intestinal tract), which was at least partially reversed on Day 22; early hepatotoxic effects (Day 4) on hepatocytes and bile ducts, which were still evident on Day 22. There were no toxicologically relevant differences between Group 2 ("pure" R749741) and Group 3 (R279741 spiked with [redacted]% 不純物 D* and [redacted]% 不純物 E*). For Group 4 (R279741 spiked with [redacted]% 不純物 A*), the following observations suggest a slightly greater toxicity: death of one female (due to more pronounced myelosuppression); staggering gait in one male and all females (found only in Group 4); higher incidence and/or severity of lesions associated to the localized intolerability at macroscopic examination (no differences were seen at histopathological examination).	[redacted] 4.2.3.7.6.2

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses μg/m^2 (μg/kg)	Noteworthy Findings	Study No./ Location in CTD
Rat/Sprague-Dawley Male and Female, 10/sex/group 3 hr infusion 5/sex/group sacrificed 3 days postdosing; 5/sex/group were allowed a three-week recovery period postdosing.	Intravenous Infusion (Sterile water - saline/ Group 2: R279741 [redacted] Formulation-plus vehicle Group 3: R279741 [redacted] Formulation-plus vehicle Group 4: R279741/ [redacted] Formulation -stressed plus vehicle[a]	Single (3hr)	Group 1: 0 (vehicle control) Group 2: 300 (50) R279741/ [redacted] Formulation Group 3: 300 (50) R279741/ [redacted] Formulation Group 4: 300 (50) R279741/ [redacted] Formulation - stressed	In summary there no major differences between the three formulations tested. 0 μg/m^2 Vehicle Control – 3 hour infusion: Males: No noteworthy findings. Females: No noteworthy findings. 300 μg/m^2 R279741/ [redacted] Formulation – 3 hour infusion: Males: Left hindlimb wound, swelling and locomotor difficulties possibly related to administration device in 1 of 10 males; ↓ body weight (Days 1-8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* slight ↓ MCV , marked ↓ RETIC associated with ↓HGB, PCV, and MCH, moderate ↓ WBC associated with ↓ EOSIN, BASO, LYMPH and MONO; *after 3 weeks of recovery* RBC, HGB and PCV ↓, PLAT, NEUT, MCV and MCH ↑; *Day 4* ↓ calcium and phosphorous, slight ↑ CHOL; *after 3 weeks of recovery* ↑ CHOL; *Day 4* absolute and relative (to body weight) spleen weights ↓ (32 and 27%), thymus weights ↓ (31 and 25%), iliac lymph nodes weights ↓ (26 and 19%), heart weights ↓ (9 and 2%); *after 3 weeks of recovery* partial reversibility noted in the weights of the thymus, heart and spleen; At necropsy, there was a sign of irritation at infusion sites, thickening. Other necropsy findings, included enlarged lymph nodes and edematous ureter, were noted. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

[a] The Group 4 animals were treated with the R279741 [redacted] formulation that was subjected to temperatures of 25-30 °C for 54 hours prior to evaluation. In this table this formulation is referred to as "R279741/ [redacted] Formulation – Stressed".

↑ = increase, ↓ = decrease, BASO = basophils, CHOL = cholesterol, EOSIN = eosinophils, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, WBC = white blood cells

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m² R279741/[redacted] Formulation – 3 hour infusion: Females: Hunched posture and piloerection Days 9 or 10 to 20 in 4 of 5 females, pallor of extremities and/or eyes, emaciation Days 9 or 10 to 20 in 2 or 3 of 5 females, staggered gait Days 10 to 20 in 2 of 5 females; ↓ body weight (Days 1-8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* slight ↓ MCV, marked ↓ RETIC associated with ↓RBC, HGB, PCV, and MCH (these changes more pronounced in females than in males), slight ↓ WBC associated with ↓ EOSIN, LYMPH and MONO, ↑ PLAT, ↑ NEUT; *after 3 weeks of recovery* RBC, HGB and PCV ↓, PLAT, NEUT, RETIC, MCV and MCH ↑; *Day 4* ↓ chloride and phosphorous, marked ↑ TBI, AST, ALT, moderately ↑CHOL, TRI; *after 3 weeks of recovery* TBI, AST, ALT exhibited partial recovery; *Day 4* urine bilirubin in 4 of 10 females; *after 3 weeks of recovery* urine bilirubin in 2 of 5 females; *Day 4* absolute and relative (to body weight) liver weights ↑ (17 and 27%), thymus weights ↓ (50 and 47%), iliac lymph nodes weights ↑ (64 and 81%), adrenal weights ↑ (3 and 12%), heart weights ↓ (13 and 6%), kidney weights ↑ (10 and 19%); *after 3 weeks of recovery* partial reversibility noted in the weights of the thymus, heart and spleen; At necropsy there was a sign of irritation at infusion sites, edema. Other necropsy findings included enlarged livers and spleen, enlarged and/or edematous lymph nodes, adipose tissue and ureter, and reduced thymus size were noted. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

↑ = increase, ↓ = decrease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHOL = cholesterol, EOSIN = eosinophils, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, TRI = triglyceride, WBC = white blood cells

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m² R279741/[redacted] Formulation – 3 hour infusion: Males: 2 of 10 males emaciated from Day 3; ↓ body weight (Days 1-8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* marked ↓ RETIC associated with ↓RBC, HGB, PCV, and MCH, moderate ↓ WBC associated with ↓ EOSIN, BASO, LYMPH and MONO; *after 3 weeks of recovery* RBC, HGB and PCV ↓, RETIC, PLAT, NEUT, MCV and MCH ↑; *Day 4* ↓ calcium and phosphorous, slight ↑ CHOL; *after 3 weeks of recovery* ↑ CHOL; *Day 4* absolute and relative (to body weight) spleen weights ↓ (26 and 22%), thymus weights ↓ (23 and 17%), iliac lymph nodes weights ↑ (103 and 116%), heart weights ↓ (20 and 14%), pancreas weights ↑ (5 and 12%); *after 3 weeks of recovery* partial reversibility noted in the weights of the thymus, iliac lymph nodes, heart and spleen; At necropsy there was a sign of irritation at infusion sites, induration. Other necropsy findings, included enlarged lymph nodes, edematous adipose tissue and reduced thymus size, were noted. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

↑ = increase, ↓ = decrease, BASO = basophils, CHOL = cholesterol, EOSIN = eosinophils, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MONO = monocytes, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, WBC = white blood cells

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m^2 (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m^2 R279741/[redacted] Formulation – 3 hour infusion: Females: 4 of 5 females hunched posture and piloerection from Days 10 to 13 or 20, 3 of 5 females pallor of extremities and staggering gait, 1 of 5 emaciated (Days 10 to 14) and increased abdomen size (from Day 13), thickening along catheter (from Day 15) in 1 of 5 females; ↓ body weight (Days 1-8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* marked ↓ RETIC associated with ↓RBC, HGB, PCV, and MCH (these changes more pronounced in females than in males), slight to moderate ↓ WBC associated with ↓ EOSIN, LYMPH and MONO, ↑PLAT, ↑ NEUT; *after 3 weeks of recovery* RBC, HGB and PCV ↓, PLAT, NEUT, RETIC, MCV and MCH ↑; *Day 4* ↓ chloride and phosphorous, marked ↑ TBI, AST, ALT, moderate ↑CHOL, TRI; *after 3 weeks of recovery* ↑ chloride, TBI, AST, ALT exhibited partial recovery; *Day 4* hematuria in 2 of 10 females urine bilirubin in 3 of 10 females; *Day 4* absolute and relative (to body weight) liver weights ↑ (24 and 33%), spleen weights ↓ (14 and 7%), iliac lymph nodes weights ↑ (15 and 26%), adrenal weights ↑ (10 and 19%), heart weights ↓ (10 and 4%), kidney weights ↑ (10 and 17%), pancreas weights ↓ (13 and 8%); thymus weights ↓ (38 and 34%); *after 3 weeks of recovery* partial reversibility noted in the weights of the liver, kidneys, adrenals, thymus and spleen; At necropsy there were signs of irritation at infusion sites included thickening, edema adhesion and induration. Other necropsy findings, included enlarged kidneys and lymph nodes, and reduced thymus size were noted. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

↑ = increase, ↓ = decrease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHOL = cholesterol, EOSIN = eosinophils, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, TRI = triglyceride, WBC = white blood cells

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m² R279741/[redacted] Formulation STRESSED – 3 hour infusion: Males: ↓ body weight (Days 1 and 8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* marked ↓ RETIC associated with ↓RBC,HGB and PCV, moderate ↓ WBC associated with ↓ EOSIN, BASO, LYMPH and MONO; *after 3 weeks of recovery* RBC, HGB and PCV ↓, PLAT, NEUT, MCV and MCH ↑; *Day 4* ↓ calcium and phosphorous, slight ↑ CHOL; *after 3 weeks of recovery* ↑ CHOL; *Day 4* hematuria in 3 of 10; *after 3 weeks of recovery*, hematuria in 1 of 5 males; *Day 4* absolute and relative (to body weight) spleen weights ↓ (17 and 14%), thymus weights ↓ (21 and 17%), iliac lymph nodes weights ↑ (84 and 92%), heart weights ↓ (20 and 17%); *after 3 weeks of recovery* partial reversibility noted in the weights of the thymus, iliac lymph nodes, heart and spleen; At necropsy there were signs of irritation at infusion sites included thickening, edema and induration. Other necropsy findings included enlarged and/or edematous lymph nodes, edematous adipose tissue, adhesion of colon and enlarged kidneys were noted. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

↑ = increase, ↓ = decrease, BASO = basophils, CHOL = cholesterol, EOSIN = eosinophils, RETIC = reticulocytes, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MONO = monocytes, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, WBC = white blood cells

2.6.7.17.5 不純物の毒性試験及び製剤の毒性試験（続き）

Test Article: R279741（Trabectedin）

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Duration of Dosing	Doses µg/m² (µg/kg)	Noteworthy Findings	Study No./ Location in CTD
				300 µg/m² R279741/[redacted] Formulation STRESSED – 3 hour infusion: Females: Piloerection in 5 of 5 females from Days 9, 10, or 11 to Day 20, hunched posture in 4 of 5 females and pallor extremities and/or eyes in 3 of 5 females from Days 10 or 11 to 20, staggering gait in 2 of 5 females (Days 10 or 11 to 13, and 15 to 20), emaciated appearance in 1 of 5 females from Days 9 to 11, thickening along catheter (from Day 15) in 1 of 5 females; ↓ body weight (Days 1-8), partial recovery observed Days 8 to 22; ↓ food consumption observed during first days of study, full recovery occurred by study termination; *Day 4* marked ↓ RETIC associated with ↓RBC, HGB, PCV and MCH (these changes more pronounced in females than in males), slight to moderate ↓ WBC associated with ↓ EOSIN, and LYMPH, ↑PLAT, ↑ NEUT; *after 3 weeks of recovery* RBC, HGB and PCV ↓, PLAT, NEUT, RETIC, MCV and MCH ↑; *Day 4* ↓ chloride and phosphorous, marked ↑ TBI, AST, ALT, moderate ↑CHOL, TRI; *after 3 weeks of recovery* TBI, AST, ALT exhibited partial recovery; *Day4* urine bilirubin in 5 of 10 females; *Day 4* absolute and relative (to body weight) liver weights ↑ (17 and 25%), thymus weights ↓ (27 and 22%), spleen weights ↓ (9 and 2%), iliac lymph nodes weights ↑ (44 and 57%), adrenal weights ↑ (8 and 17%), heart weights ↓ (10 and 3%), kidney weights ↑ (7 and 15%), pancreas weights ↓ (29 and 24%); *after 3 weeks of recovery* partial reversibility noted in the weights of the liver, thymus, heart, adrenals and spleen; At necropsy there was a sign of irritation at infusion sites, thickening. Other necropsy finding was enlarged lymph nodes. Complete recovery was not evident. After 3 days and 3 weeks of recovery microscopic findings included a higher incidence and/or severity of venous thrombus, phlebitis, thrombophlebitis, venous wall necrosis and perivenous lesions at the infusion sites were noted. Other tissues were not examined microscopically.	[redacted] 4.2.3.7.6.3

↑ = increase, ↓ = decrease, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHOL = cholesterol, EOSIN = eosinophils, HGB = hemoglobin, LYMPH = lymphocytes, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, NEUT = neutrophils, PCV = packed cell volume, PLAT = platelets, RBC = red blood cells, RETIC = reticulocytes, TBI = total bilirubin, TRI = triglyceride, WBC = white blood cells

2.6.7.17.6 光毒性試験

トラベクテジンの吸収スペクトルでは，290 nm～700 nm の波長に吸収極大はなく，大部分の光吸収は 290 nm 以下で認められたため，光毒性試験は実施しなかった.