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2.6.7　毒性試験概要表

2.6.7.1　毒性試験：一覧表

被験物質：ベルズチファン

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Repeat-Dose Toxicity	Mouse/CByB6F1/Tg rasH2 Hemizygous	Oral (gavage)	28 days	0, 30, 60, 150, 600[b]	Yes	[redacted]	TT #[redacted]-9012	[4.2.3.2.1: TT[redacted]9012]
	Rat / SD	Oral (gavage)	28 days	0, 3, 10, 30, 100 BID (0, 6, 20, 60, 200)	No	[redacted]	TT #[redacted]-7823	[4.2.3.2.2: TT[redacted]7823]
	Rat/ Crl:WI(Han)	Oral (gavage)	28 days	0, 100, 300[c]	No	MRL (WP)	TT #[redacted]-1032	[4.2.3.2.3: TT[redacted]1032]
	Rat / Crl:CD(SD)IGS	Oral (gavage)	28 days	0, 3, 10, 100 BID (0, 6, 20, 200)	Yes	[redacted]	TT #[redacted]-7820	[4.2.3.2.4: TT[redacted]7820]
	Rat / Crl:CD(SD)IGS	Oral (gavage)	91 days	1, 3, 10, 100 BID (2, 6, 20, 200)	Yes	[redacted]	TT #[redacted]-7809	[4.2.3.2.5: TT[redacted]7809]
	Rat/ Crl:WI(Han)	Oral (gavage)	91 days	0, 30, 100, 300[d]	Yes	[redacted]	TT #[redacted]-9011	[4.2.3.2.6: TT[redacted]9011]
	Dog / Beagle	Oral (gavage)	28 days	0, 1, 5, 30	Yes	[redacted]	TT #[redacted]-7821	[4.2.3.2.7: TT[redacted]7821]
	Dog / Beagle	Oral (gavage)	91 days	0, 1, 5, 30	Yes	[redacted]	TT #[redacted]-7808	[4.2.3.2.8: TT[redacted]7808]

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2.6.7.1　毒性試験：一覧表（続き）

被験物質：ベルズチファン

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Genotoxicity	*Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* (WP2 *uvrA)*	In vitro	48-72 hr ±S9	1.5 to 5000 µg/plate ±S9	No	[redacted]	TT #[redacted]-7842	[4.2.3.3.1.1: TT [redacted]7842]
		In vitro	48-72 hr ±S9	50 to 5000 µg/plate ±S9	Yes	[redacted]	TT #[redacted]-7825	[4.2.3.3.1.2: TT [redacted]7825]
	TK6 human lymphoblastoid cells	In vitro	27 hr (-S9); 4 hr (+S9)	92 to 383 µg/mL (4 hr +S9); 31.5 to 383 µg/mL (27 hr -S9)	No	[redacted]	TT #[redacted]-7843	[4.2.3.3.1.3: TT [redacted]7843]
	HPBL	In vitro	4 hr (±S9); 24 hr (-S9)	100 to 383 µg/mL (4 hr ±S9); 10 to 80 µg/mL (24 hr -S9)	Yes	[redacted]	TT #[redacted]-7826	[4.2.3.3.1.4: TT [redacted]7826]
	Rat / Crl:CD(SD)	Oral (gavage)	2 days	10, 30, 100 BID (20, 60, 200)	Yes	[redacted]	TT #[redacted]-9018	[4.2.3.3.2.1: TT [redacted]9018]
Reproductive and Developmental Toxicity	Rat / Crl:CD(SD)	Oral (gavage)	GD 6 through 17	0, 3, 30, 100 BID (0, 6, 60, 200)	No	MRL (WP)	TT #[redacted]-7004	[4.2.3.5.2.1: TT [redacted]7004]
	Rabbit / Dutch Belted	Oral (gavage)	8 days	3, 30, 100 and 0, 100 BID (0, 200)	No	MRL (WP)	TT #[redacted]-7003	[4.2.3.5.2.2: TT [redacted]7003]
Local Tolerance	Isolated bovine corneas	In vitro	4 hr	0.75 mL of a 20% MK-6482 formulation	Yes	[redacted]	TT #[redacted]-7811	[4.2.3.6.1: TT [redacted]7811]
	MatTek EpiDerm™ tissue samples	In vitro	1, 4 and 24 hr	100 mg	Yes	[redacted]	TT #[redacted]-7812	[4.2.3.6.2: TT [redacted]7812]

2.6.7.1　毒性試験：一覧表（続き）

被験物質：ベルズチファン

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Other Toxicity Studies								
Immunotoxicity	Mouse / CBA/J	Topical, ear	3 days	25% (w/v) MK-6482 in DMF	Yes	[redacted]	TT #[redacted]-7813	[4.2.3.7.2.1: TT[redacted]7813]
Phototoxicity	Rat / Crl:LE (Long-Evans)	Oral (gavage)	3 days	0, 100 BID (0, 200)	Yes	[redacted]	TT #[redacted]-9011	[4.2.3.7.7.1: TT[redacted]9011]
Impurity	Rat/ Crl:CD(SD)	Oral (gavage)	13 weeks	0, 0.4, 1 BID (0, 0.8, 2)	Yes	[redacted]	TT #[redacted]-9010	[4.2.3.7.6.1: TT[redacted]9010]
Exploratory TK Study	Mouse / Crl:CD1(ICR) [e]	Oral (gavage)	1 day	60, 200, 600	No	MRL (WP)	TT #[redacted]-1033	[4.2.3.7.7.2: TT[redacted]1033]
	Rat/ Crl:CD(SD) and Crl:WI(Han) [e]	Oral (gavage)	1 day	100, 300	No	MRL (WP)	TT #[redacted]-1023	[4.2.3.7.7.3: TT[redacted]1023]

BID = Twice daily; DMF＝N,N-Dimethylformamide; GD = Gestation day; GLP = Good Laboratory Practice; HPBL = Human peripheral blood lymphocytes; TK = Toxicokinetics

Testing Facilities: [redacted] = [redacted], USA; [redacted] = [redacted], China; [redacted] = [redacted], Canada; [redacted] = [redacted], USA; [redacted] = [redacted], Canada; [redacted] = [redacted], USA; [redacted] = [redacted], USA; **MRL (WP)** = Merck Research Laboratories, West Point, Pennsylvania, USA

a Doses are mg/kg/day unless otherwise specified. For Repeat-Dose Toxicity, the NOAEL is underlined. When the study NOAEL was different for males and females, the NOAEL for females is underlined and the NOAEL for males is double underlined.

b NOAEL: Females: ≥600 mg/kg/day, Males:60 mg/kg/day

c NOAEL: Females: ≥300 mg/kg/day, Males: <100 mg/kg/day

d NOAEL: Females: ≥300 mg/kg/day, Males: <30 mg/kg/day

e Males only.

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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

被験物質：ベルズチファン

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Study Number	Location Vol. Section
28-Day Toxicity and TK	Mouse/CByB6F1/Tg rasH2 Hemizygous	Oral (gavage)	0, 30, 60, 150, 600	Yes	TT #[redacted]-9012	[4.2.3.2.1: TT[redacted]9012]
Exploratory 28-Day Toxicity and TK with 65-Day Recovery Period	Rat / SD	Oral (gavage)	0, 3, 10, 30, 100 BID (0, 6, 20, 60, 200)	No	TT #[redacted]-7823	[4.2.3.2.2: TT[redacted]7823]
1-Month Toxicity and TK	Rat / Crl:WI(Han)	Oral (gavage)	0, 100, 300	No	TT #[redacted]-1032	[4.2.3.2.3: TT[redacted]1032]
28-Day Toxicity and TK with 28-Day and 90-Day Recovery Periods, FOB, and Respiratory Function	Rat / Crl:CD(SD)IGS	Oral (gavage)	0, 3, 10, 100 BID (0, 6, 20, 200)	Yes	TT #[redacted]-7820	[4.2.3.2.4: TT[redacted]7820]
13-Week Toxicity and TK with 28-Day and 26-Week Recovery Periods	Rat / Crl:CD(SD)IGS	Oral (gavage)	1[a], 3, 10, 100 BID (2[a], 6, 20, 200)	Yes	TT #[redacted]-7809	[4.2.3.2.5: TT[redacted]7809]
13-Week Toxicity and TK	Rat / Crl:WI(Han)	Oral (gavage)	0, 30, 100, 300	Yes	TT #[redacted]-9011	[4.2.3.2.6: TT[redacted]9011]
28-Day Toxicity and TK with 28- and 90-Day Recovery Periods and ECG and BP Assessments	Dog / Beagle	Oral (gavage)	0, 1, 5, 30	Yes	TT #[redacted]-7821	[4.2.3.2.7: TT[redacted]7821]
13-Week Toxicity and TK with a 28-Day Recovery Period and ECG and BP Assessments	Dog / Beagle	Oral (gavage)	0, 1, 5, 30	Yes	TT #[redacted]-7808	[4.2.3.2.8: TT[redacted]7808]
Preliminary Embryo-Fetal Development with TK	Rat / Crl:CD(SD)	Oral (gavage)	0, 3, 30, 100 BID (0, 6, 60, 200)	No	TT #[redacted]-7004	[4.2.3.5.2.1: TT[redacted]7004]
Tolerability in Nonpregnant Rabbits with TK	Rabbit / Dutch Belted (Nonpregnant)	Oral (gavage)	3, 30, 100 and 0, 100 BID (0, 200)	No	TT #[redacted]-7003	[4.2.3.5.2.2: TT[redacted]7003]

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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）

被験物質：ベルズチファン

Type of Study	Test System	Method of Adminis-tration	Doses (mg/kg/day)	GLP Compliance	Study Number	Location Vol. Section
13-Week Impurity Qualification Study	Rat /Crl:CD(SD)	Oral (gavage)	0, 0.4, 1 BID (0, 0.8, 2)	Yes	TT #[redacted]-9010	[4.2.3.7.6.1: TT[redacted]9010]
Exploratory Single-Dose TK	Mouse / Crl:CD1(ICR) [a]	Oral (gavage)	60, 200, 600	No	TT #[redacted]-1033	[4.2.3.7.7.2: TT[redacted]1033]
Exploratory Single-Dose TK	Rat / Crl:CD(SD) and Crl:WI(Han) [a]	Oral (gavage)	100, 300	No	TT #[redacted]-1023	[4.2.3.7.7.3: TT[redacted]1023]

BID = Twice daily; BP = Blood pressure; ECG = Electrocardiography; GLP = Good Laboratory Practice; TK = Toxicokinetics

a　Males only.

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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

2.6.7.3.A　MK-6482のトキシコキネティクス試験成績の一覧

被験物質：ベルズチファン

MK-6482 Steady State AUC0-24hr (µg*hr/mL)							
	Mice		Rats		Dogs		Rabbits
Daily Dose (mg/kg/day)	Female	Male	Female	Male	Female	Male	Female
Dose (SD/GD)							
0.8 / 0.4 BID (SD91)			0.610*[a]	0.864*[a]			
1 QD (SD28)					7.84[b]	6.89[b]	
1 QD (SD91)					7.13[c]	6.75[c]	
2 / 1 BID (SD91)			1.96*[a]	2.38*[a]			
2 / 1 BID (SD91)			-[d]	1.64*[d]			
3 QD (SD1)							1.35[h]
5 QD (SD28)					18.2[b]	21.3[b]	
5 QD (SD91)					19.7[c]	16.9[c]	
6 / 3 BID (SD28)			-	1.594*[e]			
			3.20*[f]	4.42*[f]			
6 / 3 BID (SD91)			2.96*[d]	3.36*[d]			
6 / 3 BID (GD7)			2.60*[g]				
20 / 10 BID (SD28)			-	4.788*[e]			
			8.40*[f]	9.44*[f]			
20 / 10 BID (SD91)			7.76*[d]	8.40*[d]			
30 QD (SD1)							8.59[h]
30 QD (SD28)	104[i]	100[i]			37.8[b]	38.4[b]	
30 QD (SD91)			58.7[j]	73.9[j]	30.2[c]	29.0[c]	
60 QD (SD1)		96.6[k]					
60 QD (SD28)	178[i]	195[i]					

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2.6.7.3.A　MK-6482のトキシコキネティクス試験成績の一覧（続き）

被験物質：ベルズチファン

MK-6482 Steady State AUC0-24hr (µg*hr/mL)							
	Mice		Rats		Dogs		Rabbits
Daily Dose (mg/kg/day)	Female	Male	Female	Male	Female	Male	Female
Dose (SD/GD)							
60 / 30 BID (SD28)			-	9.02*[d]			
60 / 30 BID (GD7)			14.86*[g]				
100 QD (SD1)				18.1[l,m]			11.8[h]
				21.6[l,n]			
				22.3[l,o]			
				24.8[l,p]			
				123[l,q]			
				135[l,r]			
100 QD (SW2)			188[s]	265[s]			
100 QD (SW4)			208[s]	248[s]			
100 QD (SD91)			206[j]	223[j]			
150 QD (SD28)	249[i]	252[i]					
200 QD (SD1)		362[k]					
200 / 100 BID (SD1)							10.96*[h]
200 / 100 BID (SD28)			-	14.06*[e]			
			34.6*[f]	36.0*[f]			
200 / 100 BID (SD91)			19.86*[d]	15.70*[d]			
200 / 100 BID (GD7)			28.2*[g]				
200 QD (SD1)		362[k]					
300 QD (SD1)				27.2[l,m]			
				22.6[l,n]			
				18.8[l,o]			

2.6.7.3.A　MK-6482のトキシコキネティクス試験成績の一覧（続き）

被験物質：ベルズチファン

MK-6482 Steady State AUC0-24hr (µg*hr/mL)							
Daily Dose (mg/kg/day)	**Mice**		**Rats**		**Dogs**		**Rabbits**
	Female	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Dose (SD/GD)							
300 QD (SD1)				26.5[l,p]			
				429[l,q]			
				408[l,r]			
300 QD (SW2)			477[s]	502[s]			
300 QD (SW4)			439[s]	361[s]			
300 QD (SD91)			504[j]	429[j]			
600 QD (SD1)		590[k]					
600 QD (SD28)	618[i]	528[i]					

AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; BID = Twice daily; GD = Gestation day; HPMCAS=hydroxypropyl methylcellulose acetate succinate; MC=methylcellulose; QD = Once daily; SD = Study day; SW=study week; TRIS=tromethamine

*= AUC0-24hr was calculated by multiplying AUC0-12hr by 2 due to BID dosing; - = not determined/not reported

a TT #[redacted]-9010 [4.2.3.7.6.1: TT[redacted]9010] A 13-Week (Twice Daily) Oral Gavage Impurity Qualification Study in the Sprague-Dawley Rat
b TT #[redacted]-7821 [4.2.3.2.7: TT[redacted]7821] A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Beagle Dogs
c TT #[redacted]-7808 [4.2.3.2.8: TT[redacted]7808] A 13-Week Oral Gavage Toxicity Study Followed by a 28-Day Recovery Periods in Beagle Dogs
d TT #[redacted]-7809 [4.2.3.2.5: TT[redacted]7809] 13-Week Oral Gavage Toxicity Study Followed by 28-Day and 26-Week Recovery Periods in Sprague-Dawley Rats; Males only in 2 mg/kg/day dose group
e TT #[redacted]-7823 [4.2.3.2.2: TT[redacted]7823] 28-Day Oral Gavage Toxicity Study with MK-6482 in Male SD Rats with 65-Day Recovery Period
f TT #[redacted]-7820 [4.2.3.2.4: TT[redacted]7820] A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Sprague-Dawley Rats
g TT #[redacted]-7004 [4.2.3.5.2.1: TT[redacted]7004] Preliminary Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats
h TT #[redacted]-7003 [4.2.3.5.2.2: TT[redacted]7003] Exploratory Oral 9-Day Tolerability and Toxicokinetic Study in Nonpregnant Rabbits
i TT #[redacted]-9012 [4.2.3.2.1: TT[redacted]9012] A 28-Day Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice
j TT #[redacted]-9011 [4.2.3.2.6: TT[redacted]9011] A 13-Week Study by Oral Gavage in Wistar Han Rats
k TT #[redacted]-1033 [4.2.3.7.7.2: TT[redacted]1033] Exploratory Single-Dose Oral Toxicokinetic Study in Mice
l TT #[redacted]-1023 [4.2.3.7.7.3: TT[redacted]1023] Exploratory Single-Dose Oral Toxicokinetic Study in Sprague Dawley and Wistar Han Rats
m Vehicle: 0.5% Tween 80/0.5% MC; Strain: Sprague Dawley
n Vehicle: 0.5% Tween 80/0.5% MC; Strain: Wistar Han
o Vehicle: 10% Tween 80; Strain: Sprague Dawley
p Vehicle: 10% Tween 80; Strain: Wistar Han
q Vehicle: 0.5% MC/0.1% HPMCAS-HF/20 mM TRIS pH 7.2 ± 0.1; Strain: Sprague Dawley
r Vehicle: 0.5% MC/0.1% HPMCAS-HF/20 mM TRIS pH 7.2 ± 0.1; Strain: Wistar Han
s TT #[redacted]-1032 [4.2.3.2.3: TT[redacted]1032] Exploratory Four-Week Oral Toxicity and Toxicokinetic Study in Rats

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2.6.7.3.B　PT3317のトキシコキネティクス試験成績の一覧

被験物質：ベルズチファン

PT3317 Steady State AUC0-24hr (µg*hr/mL)					
	Rats		Dogs		Rabbits
Daily Dose (mg/kg/day)	Female	Male	Female	Male	Female
Dose (SD/GD)					
1 QD (SD28)			1.83[a]	1.92[a]	
1 QD (SD91)			1.71[b]	1.93[b]	
2 / 1 BID (SD91)	-	-[c]			
3 QD (SD1)					3.77[f]
5 QD (SD28)			5.95[a]	5.62[a]	
5 QD (SD91)			7.11[b]	6.31[b]	
6 / 3 BID (SD28)	-	0.0198*[d]			
	-[e]	-[e]			
6 / 3 BID (SD91)	-[c]	-[c]			
20 / 10 BID (SD28)	-	0.07506*[d]			
	-[e]	-[e]			
20 / 10 BID (SD91)	-[c]	0.0626*[c]			
30 QD (SD1)					22.6[f]
30 QD (SD28)			20.6[a]	12.9[a]	
30 QD (SD91)			15.9[b]	7.54[b]	

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2.6.7.3.B　PT3317のトキシコキネティクス試験成績の一覧（続き）

被験物質：ベルズチファン

PT3317 Steady State AUC0-24hr (µg*hr/mL)					
	Rats		Dogs		Rabbits
Daily Dose (mg/kg/day)	Female	Male	Female	Male	Female
Dose (SD/GD)					
60 / 30 BID (SD28)	-	0.19694*[d]			
100 QD (SD1)					29.4[f]
200 / 100 BID (SD1)					34.8*[f]
200 / 100 BID (SD28)	-	0.352*[d]			
	-[e]	0.1692*[e]			
200 / 100 BID (SD91)	-[c]	0.0906*[c]			

AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; BID = Twice daily; BLQ = Below the limit of quantitation; GD = Gestation day; QD = Once daily; SD = Study day; *= AUC0-24hr was calculated by multiplying AUC0-12hr by 2 due to BID dosing; - = not determined/not reported

a TT #[redacted]-7821 [4.2.3.2.7: TT[redacted]7821] A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Beagle Dogs

b TT #[redacted]-7808 [4.2.3.2.8: TT[redacted]7808] A 13-Week Oral Gavage Toxicity Study Followed by a 28-Day Recovery Periods in Beagle Dogs

c TT #[redacted]-7809 [4.2.3.2.5: TT[redacted]7809] 13-Week Oral Gavage Toxicity Study Followed by 28-Day and 26-Week Recovery Periods in Sprague-Dawley Rats; Males only in 2 mg/kg/day dose group.TK parameters were not determined for 2 mg/kg/day males on day 91, since all plasma concentrations were BLQ.　TK Parameters for 3 mg/kg/day males and females on Day 91 were determined with only one individual non-zero plasma concentration, and consequently, presented for information only.

d TT #[redacted]-7823 [4.2.3.2.2: TT[redacted]7823] 28-Day Oral Gavage Toxicity Study with MK-6482 in Male SD Rats with 65-Day Recovery Period

e TT #[redacted]-7820 [4.2.3.2.4: TT[redacted]7820] A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Sprague-Dawley Rats

f TT #[redacted]-7003 [4.2.3.5.2.2: TT[redacted]7003] Exploratory Oral 9-Day Tolerability and Toxicokinetic Study in Nonpregnant Rabbits

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2.6.7.4　毒性試験：被験物質（バッチ毎）一覧

被験物質：ベルズチファン

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, %)[3]													Study Number and Type
		A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	I[12]	J[13]	K[14]	L[15]	M[16]	
PROPOSED SPECIFICATION:[1]		≤	≤	≤	≤	≤	≤	≤	≤	≤	≤	≤	≤	≤	
															TT#-7842 : Non-GLP Microbial Mutagenesis Assay TT#-7843 : Non-GLP In Vitro Micronucleus Assay
/[17]															TT#-7820 : 28-Day Oral Toxicity and TK in Rats TT#-7821 : 28-Day Oral Toxicity in Beagle Dogs
															TT#-7823 : Exploratory 28-Day Oral Toxicity and TK in Rats
[17]															TT#-7825 : GLP Microbial Mutagenesis Assay TT#-7826 : GLP In Vitro Micronucleus Assay
/[18]															TT#-7809 : 13-Week Oral Toxicity and TK in Rats TT#-7808 : 13-Week Oral Toxicity and TK in Beagle Dogs TT#-7003 : Exploratory Oral 9-Day Tolerability and TK in Nonpregnant Rabbits TT#-7004 : Preliminary Oral EFD Toxicity and TK in Rats TT #-1023 : Exploratory Single-Dose TK in Rats

2.6.7.4　毒性試験：被験物質（バッチ毎）一覧（続き）

被験物質：ベルズチファン

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, %)[3]												Study Number and Type
		A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	I[12]	J[13]	K[14]	L[15]	M[16]	
PROPOSED SPECIFICATION:[1]		≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	≤[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT#[redacted]-9011 : Three-Day Oral Phototoxicity and TK in Pigmented Rats TT#[redacted]-9018 : Two-Day Oral In Vivo Micronucleus Test in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT#[redacted]-9010 : 13-Week Oral Impurity Qualification Study in Rats
[redacted] 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT#[redacted]-9011 : 13-Week Study in Wistar Han Rats TT#[redacted]-9012 : 28-Day Study in CByB6F1/Tg rasH2 Hemizygous Mice TT #[redacted]-1032 : Exploratory 4-week toxicity and TK in Rats TT #[redacted]-1033 : Exploratory Single-Dose TK in Mice
[redacted] 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT#[redacted]-9011 : 13-Week Study in Wistar Han Rats TT#[redacted]-9012 : 28-Day Study in CByB6F1/Tg rasH2 Hemizygous Mice TT #[redacted]-1032 : Exploratory 4-week toxicity and TK in Rats TT #[redacted]-1033 : Exploratory Single-Dose TK in Mice TT #[redacted]-1023 : Exploratory Single-Dose TK in Rats

2.6.7.4　毒性試験：被験物質（バッチ毎）一覧（続き）

被験物質：ベルズチファン

EFD: Embryo-Fetal Development; GLP = Good Laboratory Practice; HPLC = High performance liquid chromatography; ND = Not detected; NQ = Not quantifiable; NT = Not tested; TK = Toxicokinetics

1　See [Sec. 3.2.S.4.1] for complete specification.
2　Purity: HPLC weight percent.
3　Specified impurities: HPLC percent.
4　[redacted]
5　[redacted]
6　[redacted]
7　[redacted]
8　[redacted]
9　[redacted]
10　[redacted]
11　[redacted]
12　[redacted]
13　[redacted]
14　[redacted]
15　Individual, unspecified impurity. For lots with multiple unspecified impurities, this value represents the unspecified impurity present at the highest level.
16　Total impurities
17　See [Sec 3.2.S.4.4] for final batch analysis
18　Batch used for impurity qualification

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2.6.7.5　単回投与毒性試験

急性毒性を評価するための独立した毒性試験は行わなかった。しかしながら、単回投与後の毒性は、ラット（2から200 mg/kg/日）及びイヌ（1から30 mg/kg/日）の反復経口投与毒性試験で評価し、その結果を2.6.6.3項に記載した。概して、これらの動物種では急性毒性を示唆する所見はみられなかった。

2.6.7.6　反復投与毒性試験：重要な試験以外の試験

被験物質：ベルズチファン

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Sex and No. per Group	NOAEL[a] (mg/kg/day)	Noteworthy Findings	Study Number
Rat/SD	Oral (gavage) (0.5% methyl cellulose, 0.5% Tween 80 in water)	28 days	0, 3, 10, 30, 100 BID (0, 6, 20, 60, 200)	8M (Toxicity groups); 3M (TK groups)	MTD = ≥200 (≥100 BID)	No mortality or test article related clinical observations or changes in body weight or food consumption. At ≥20 mg/kg/day, effects on RBC parameters (including decreases in RBC counts, hemoglobin and hematocrit) were observed and considered treatment-related and due to the pharmacological effects of MK-6482. At 200 mg/kg/day, degeneration of spermatocytes and spermatids was observed in seminiferous tubules in the testis, and detached spermatogenic cells were observed in epididymal ducts. Following the 65-day recovery period, findings of atrophy of seminiferous tubules in the testis, and sperm reduction and detached spermatogenic cells in the epididymal ducts were seen at 200 mg/kg/day.	TT #[redacted]-7823 (Non-GLP) [4.2.3.2.2: TT[redacted]7823]

(continued)

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<table>
<tr><th>Species/
Strain</th><th>Method of
Administration</th><th>Duration
of Dosing</th><th>Doses
(mg/kg/day)</th><th>Sex and No.
per Group</th><th>Noteworthy Findings</th><th>Study
Number</th></tr>
<tr><td>Rat/Crl: WI(Han)</td><td>Oral (gavage)
(0.5% (w/v) methylcellulose 0.1% (w/v) hydroxypropyl methylcellulose acetate succinate-HF with 20mM tromethamine in deionized water, pH 7.2 ± 0.1)</td><td>28 Days</td><td>0, 100, 300</td><td>6M, 6F</td><td>No test article-related unscheduled deaths or clinical signs.
Slight decreases in mean body weight gain in Study Week 4 from pretest at both doses in males only.
Test article-related histomorphologic changes were present in testis and consisted of seminiferous tubular degeneration in all treated male rats at both 100 and 300 mg/kg/day.
Plasma concentrations for MK-6482 are presented below:
<table>
<tr><th>Dose (mg/kg/day)</th><th>Study Week 2 AUC0-24hr (µg*hr/mL)</th><th>Study Week 4 AUC0-24hr (µg*hr/mL)</th></tr>
<tr><td>100</td><td>227</td><td>228</td></tr>
<tr><td>300</td><td>489</td><td>400</td></tr>
</table></td><td>TT #[redacted]-1032
(Non-GLP)
[4.2.3.2.3:
TT[redacted]1032]</td></tr>
<tr><td colspan="7">AUC0-24hr=Area under the plasma concentration-time curve from time 0 to 24 hours; BID = Twice daily; F=female; GLP = Good Laboratory Practice; M = Male; MTD = Maximum tolerated dose; No.=Number; RBC=red blood cell;TK = Toxicokinetics; (w/v)=weight/volume
a　No Observed Adverse-Effect Level.</td></tr>
</table>

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2.6.7.7 反復投与毒性試験：重要な試験

2.6.7.7.A 反復投与毒性試験：CByB6F1/Tg rasH2ヘミ接合マウスを用いた28日間反復経口投与毒性試験

被験物質：ベルズチファン

Species/Strain: Mouse/CByB6F1/Tg rasH2 Hemizygous **Initial Age:** 9 weeks **Date of First Dose:** [redacted] **Dose Volume:** 10 mL/kg	**Duration of Dosing:** 28 days **Duration of Postdose:** N/A **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 20 mM pH 7.2 TRIS buffered 0.5% methylcellulose/0.1% HPMCAS-HF	**Study Number:** TT #[redacted]-9012 **Location in CTD:** [4.2.3.2.1: TT[redacted]9012] **GLP Compliance:** Yes
Special Features: N/A **No-Observed-Adverse-Effect Level:** 60 mg/kg/day and ≥600 mg/kg/day for males and females, respectively		

Daily Dose (mg/kg/day)	0 (Control)		30		60		150		600	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals (TK)	F:3	M:3	F:18	M:18	F:18	M:18	F:18	M:18	F:18	M:18
Toxicokinetics – Study Day 28										
AUC0-24hr (µg*hr/mL)	N/A[a]		102		186		250		573	
Cmax (µg/mL)	N/A[a]		9.65		17.4		27.3		38.2	
Tmax (hr)	N/A[a]		2.00		1.00		2.00		7.00	
Noteworthy Findings										
Mortality (No. of Animals)	0	0	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-

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2.6.7.7.A　反復投与毒性試験

試験番号: TT #[redacted]-9012（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		60		150		600	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Hematology – Study Day 29[b]										
HCT (%)	48.12	49.50	[37.36**]	[41.52]	[35.74**]	[39.24]	[34.42**]	[37.96*]	[33.42**]	[32.72**]
HGB (g/dL)	14.78	15.38	[11.60**]	[12.66]	[11.06**]	[11.88]	[10.56**]	[11.54*]	[10.02**]	[9.92**]
MCH (pg)	15.58	14.88	[14.58**]	[14.22**]	[14.40**]	[14.22**]	[14.40**]	[14.24**]	[14.40**]	[14.04**]
RBC Count (x10^6/uL)	9.49	10.33	[7.97**]	[8.90]	[7.69**]	[8.35]	[7.32**]	[8.10*]	[6.96**]	[7.04**]
Reticulocyte (x10^9/L)	-	276.94	-	267.76	-	273.34	-	243.36	-	[223.84**]
Clinical Chemistry – Study Day 29[b]										
ALP (U/L)	135.0	118.0	132.4	99.4	127.6	108.4	139.4	123.8	[169.4**]	[161.4]
Phosphorus (mg/dL)	7.24	-	7.26	-	6.38	-	7.00	-	[8.35]	-
Gross Pathology (Incidence)	-	-	-	-	-	-	-	-	-	-

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2.6.7.7.A　反復投与毒性試験

試験番号: TT #[redacted]-9012（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		60		150		600	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Organ Weights (Absolute,g) – Study Day 29[c]										
Heart	0.1251 g	0.1508 g	6.16	-1.53	7.27	4.51	9.43	7.63	[16.55][d]	[14.99][d]
Liver/Gallbladder	1.1488 g	-	-6.42	-	-0.03	-	10.02	-	[17.89][e]	-
Testis	N/A	0.2682 g	N/A	-4.88	N/A	[-8.84]	N/A	[-9.25]	N/A	[-11.63]
Organ Weights (Relative to Brain, %)[c]										
Heart	26.13083	33.27865	4.85	-2.68	5.28	1.41	8.12	6.10	[16.20][d]	[14.09][d]
Liver/Gallbladder	239.87513	-	-7.60	-	-1.84	-	8.76	-	[17.23][e]	-
Testis	N/A	59.10405	N/A	-5.91	N/A	[-11.15]	N/A	[-10.57]	N/A	[-12.37]
Histomorphology (Incidence) – Study Day 29										
Testis										
Seminiferous Tubule, Degeneration										
Minimal	N/A	0/10	N/A	NE	N/A	0/10	N/A	[5/10]	N/A	[9/10]

(footnotes presented on following page)

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2.6.7.7.A　反復投与毒性試験

試験番号: TT #[redacted]-9012（続き）

被験物質：ベルズチファン

ALP=alkaline phosphatase; AUC0-24hr=area under the plasma concentration-time curve from time 0 to 24 hours; Cmax=maximum plasma concentration; F=female; GLP=Good Laboratory Practice; HCT=hematocrit; HGB=hemoglobin; HPMCAS-HF =Hydroxypropyl methylcellulose acetate succinate-HF; M=male; MCH=mean corpuscular hemoglobin; N/A=not applicable; NE=group not examined; No.=number; RBC=red blood cell; TK=toxicokinetics; Tmax=time at maximum plasma concentration; TRIS=tromethamine; - = no noteworthy findings; #/# =number affected/number examined; [ ]=test article-related change based on incidence and/or severity.

All female HCT, HGB, male and female MCH, female RBC, male reticulocyte, and female Clinical Chemistry ALP p values for Study Day 29: ANOVA & Dunnett **=p≤0.01
Male HCT, HGB, and RBC p values for Study Day 29: Kruskal-Wallis & Dunn: *=p≤0.05; **=p≤0.01.

a. MK-6482 concentrations in plasma from all control group animals at 1 hr postdose were below the lower limit of quantitation (10.0 ng/mL) of the bioanalytical method.
b. Control and treatment group values are mean absolute values.
c. For controls, the mean organ weight (absolute or as percent of brain weight) is shown. For treatment groups, percent differences from controls are shown.
d. Increased heart weight is considered an adaptive response to reduced HGB concentration (mild to moderate dose-dependent decrease in red cell mass at ≥30 mg/kg/day) and is expected to be reversible and, therefore, of minimal toxicological significance.
e. Liver weight increase was considered to be of minimal toxicological significance because of the low magnitude and lack of any histomorphologic correlates.

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2.6.7.7.B　反復投与毒性試験：SD ラットを用いた28日間反復経口投与毒性試験（28日間及び90日間の回復期間を含む）

被験物質：ベルズチファン

Species/Strain: Rat/SD **Initial Age**: 6 weeks **Date of First Dose**: [redacted] **Dose Volume**: 5 mL/kg/dose	**Duration of Dosing:** 28 days **Duration of Postdose:** 28 days and 90 days **Method of Administration:** Oral (gavage) **Vehicle/Formulation**: 0.5% methylcellulose and 0.5% Tween 80 in reverse osmosis water	**Study Number:** TT #[redacted]-7820 **Location in CTD:** [4.2.3.2.4: TT[redacted]7820] **GLP Compliance:** Yes[a]
Special Features: Male reproductive assessment; BID dosing (dosing was administered 12 hours ± 30 minutes apart); functional observational battery; respiratory function monitoring **No-Observed-Adverse-Effect Level:** Male rats: 6 mg/kg/day (3 mg/kg BID); Female rats: ≥200 mg/kg/day (≥100 mg/kg BID)		

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals (28-Day Recovery)	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Number of Animals (90-Day Recovery)	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Number of Animals (TK)	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 1 (MK-6482) [b]								
AUC0-12hr (µg*hr/mL)	N/A	N/A	1.38	1.51	4.11	5.00	16.0	17.5
Cmax (µg/mL)	N/A	N/A	0.480	0.362	0.850	0.773	2.30	2.53
Tmax (hr)	N/A	N/A	0.50	1.00	1.00	1.00	2.00	1.00

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (TK)	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 28 (MK-6482) [b]								
AUC0-12hr (µg*hr/mL)	N/A	N/A	1.60	2.21	4.20	4.72	17.3	18.0
Cmax (µg/mL)	N/A	N/A	0.513	0.549	1.12	1.12	3.48	3.31
Tmax (hr)	N/A	N/A	1.00	1.00	1.00	1.00	1.50	1.50
Toxicokinetics – Study Day 1 (PT3317) [b]								
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	N/A	N/A	0.0703	N/A	0.183
Cmax (µg/mL)	N/A	N/A	BLQ	0.006	0.005	0.012	0.023	0.042
Tmax (hr)	N/A	N/A	NR	1.50	2.00	1.50	0.50	1.00
Toxicokinetics – Study Day 28 (PT3317) [b]								
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.0846
Cmax (µg/mL)	N/A	N/A	0.003	0.003	0.004	0.005	0.020	0.019
Tmax (hr)	N/A	N/A	1.00	1.50	1.00	1.00	2.00	2.00

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings								
Mortality (No. of Animals)	0	0	1[c]	0	0	0	1[d]	0
Body Weight – Main	-	-	-	-	-	-	-	-
Body Weight – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Food Consumption – Main	-	-	-	-	-	-	-	-
Food Consumption – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Clinical Observations – Main	-	-	-	-	-	-	-	-
Clinical Observations – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Ophthalmoscopy – Main	-	-	-	-	-	-	-	-
Ophthalmoscopy – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Functional Observational Battery (FOB) – Main[e]	NE	-	NE	-	NE	-	NE	-
Respiratory Function Monitoring – Main[f]	-	NE	-	NE	-	NE	-	NE

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Hematology – Main[g]								
Red Blood Cell Count (x10^{12}/L)	7.796	8.192	7.518	[7.314]	[7.049***]	[6.477^^^]	[6.197***]	[5.713^^^]
HGB (g/L)	152.3	155.3	143.7	[138.9***]	[134.8^^]	[119.0***]	[115.7^^^]	[105.4***]
HCT (L/L)	0.439	0.467	0.415	[0.412***]	[0.386^^^]	[0.353***]	[0.334^^^]	[0.313***]
Mean Corpuscular Volume (fL)	56.34	56.78	55.00	56.32	[54.84*]	[54.57**]	[53.79***]	[54.70*]
Mean Corpuscular Hemoglobin (pg)	19.53	-	19.12	-	19.12	-	[18.66^^]	-
Red Cell Distribution Width (%)	10.45	11.54	10.51	11.59	10.65	12.21	[10.97^]	[12.38*]
Reticulocytes (x10^{9}/L)	167.11	197.20	[149.58]	[180.22]	[139.69]	199.24	[106.07***]	[183.33]
% Reticulocytes	-	2.42	-	2.47	-	[3.09^]	-	[3.22^]
Platelets (x10^{9}/L)	1171.1	1203.2	1213.0	1211.2	[1309.8]	[1347.7*]	[1505.7^]	[1325.9]
White Blood Cells (x10^{9}/L)	8.788	-	[6.534*]	-	[5.875**]	-	[5.630**]	-
Neutrophils (x10^{9}/L)	0.554	-	[0.429]	-	[0.399*]	-	[0.304**]	-
Lymphocytes (x10^{9}/L)	7.895	-	[5.788]	-	[5.220]	-	[5.091]	-
Monocytes (x10^{9}/L)	0.164	-	0.170	-	[0.134]	-	[0.109]	-
Hematology – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Coagulation – Main and 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Urinalysis – Main and 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Bone Marrow Histopathology – Main								
Myeloid:Erythroid Ratio - Main	2.01	-	1.96	-	2.15	-	[3.08]	-
% Lymphocytes - Main	37.1	-	31.7	-	30.8	-	[25.8]	-
Bone Marrow Histopathology – 28-Day Recovery	-	-	-	-	-	-	-	-
Clinical Chemistry – Main								
Serum Bicarbonate Levels (mmol/L)	21.0	21.6	22.2	[23.9]	[23.2*]	[24.4^]	[24.8***]	[26.7^^^]
Triglycerides (mmol/L)	0.368	-	0.376	-	[0.318]	-	[0.260***]	-
Clinical Chemistry – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Organ weights (Absolute) – Main study[h] (g)								
Testes	N/A	3.65433	N/A	-1.2	N/A	[-7.1*]	N/A	[-28.7***]
Epididymis (Left)	N/A	0.46575	N/A	-5.2	N/A	[-16.9***]	N/A	[-24.6***]
Epididymis (Right)	N/A	0.47090	N/A	-2.7	N/A	[-16.5^^]	N/A	[-23.9^^^]
Organ weights (Relative to Brain) – Main study[h] (%)								
Testes	N/A	173.34653	N/A	+0.5	N/A	[-7.6*]	N/A	[-29.9***]
Epididymis (Left)	N/A	22.10253	N/A	-3.6	N/A	[-17.4***]	N/A	[-26.0***]
Epididymis (Right)	N/A	22.32818	N/A	-1.0	N/A	[-16.8^^]	N/A	[-25.2^^^]
Organ weights (Absolute) – Recovery Day 28[h] (g)								
Testes	N/A	3.81412	N/A	+2.3	N/A	[-24.3*]	N/A	[-40.3***]
Epididymis (Left)	N/A	0.64376	N/A	+4.0	N/A	[-24.9**]	N/A	[-39.0***]
Epididymis (Right)	N/A	0.64134	N/A	+5.0	N/A	[-21.2*]	N/A	[-34.3***]
Prostate Gland	N/A	1.29588	N/A	-17.9	N/A	-23.2	N/A	[-26.3]

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2.6.7.7.B 反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Organ weights (Relative to Brain) – Recovery Day 28 [h](%)								
Testes	N/A	175.29373	N/A	+2.1	N/A	[-24.2*]	N/A	[-39.5***]
Epididymis (Left)	N/A	29.60198	N/A	+3.7	N/A	[-25.0**]	N/A	[-38.8***]
Epididymis (Right)	N/A	29.49075	N/A	+4.7	N/A	[-21.3**]	N/A	[-34.1***]
Prostate Gland	N/A	59.54652	N/A	-17.6	N/A	-23.0	N/A	[-26.3*]
Organ weights (Absolute) – Recovery Day 90[h] (g)								
Testes	N/A	4.07156	N/A	-3.8	N/A	[-34.6^^]	N/A	[-21.1]
Epididymis (Left)	N/A	0.73770	N/A	-6.2	N/A	[-24.2*]	N/A	[-14.4]
Epididymis (Right)	N/A	0.73160	N/A	-5.1	N/A	[-29.0^]	N/A	[-21.3]
Organ weights (Relative to Brain) – Recovery Day 90[h] (%)								
Testes	N/A	177.22484	N/A	0	N/A	[-32.7^]	N/A	[-21.2]
Epididymis (Left)	N/A	32.09377	N/A	-1.9	N/A	[-22.0*]	N/A	[-14.6]
Epididymis (Right)	N/A	31.86878	N/A	-1.0	N/A	[-26.6^]	N/A	[-21.6]
Gross Pathology – Main (Incidence)	-	-	-	-	-	-	-	-

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Gross Pathology – Recovery Day 28 (Incidence)								
Testes								
Soft; Bilateral	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Soft; Right	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Gross Pathology – Recovery Day 90 (Incidence)								
Testes								
Small; Bilateral	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[1/5]
Soft; Bilateral	N/A	0/5	N/A	0/5	N/A	[3/5]	N/A	[1/5]
Histomorphology (Incidence) – Main								
Testes								
Hypospermatogenesis, Bilateral								
Minimal	N/A	0/10	N/A	0/10	N/A	[4/10]	N/A	0/10
Moderate	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[10/10]
Multinucleated Giant Cells, Bilateral								
Minimal	N/A	0/10	N/A	0/10	N/A	[2/10]	N/A	0/10
Mild	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[4/10]
Moderate	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[6/10]

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Degeneration, Germ cells, Bilateral								
Minimal	N/A	0/10	N/A	0/10	N/A	[4/10]	N/A	0/10
Mild	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[3/10]
Moderate	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[7/10]
Seminiferous Tubule, Vacuolation, Bilateral								
Minimal	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[10/10]
Epididymis								
Oligospermia								
Mild	N/A	0/10	N/A	0/10	N/A	[6/10]	N/A	0/10
Moderate	N/A	0/10	N/A	0/10	N/A	[4/10]	N/A	0/10
Marked	N/A	0/10	N/A	0/10	N/A	0/10	N/A	[10/10]
Cellular Debris								
Minimal	N/A	0/10	N/A	0/10	N/A	[2/10]	N/A	0/10
Mild	N/A	0/10	N/A	0/10	N/A	[7/10]	N/A	[9/10]
Moderate	N/A	0/10	N/A	0/10	N/A	[1/10]	N/A	[1/10]

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Histomorphology (Incidence) – Recovery Day 28								
Testes								
Hypospermatogenesis, Bilateral								
Minimal	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[2/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Marked	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Multinucleated Giant cells, Bilateral								
Moderate	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Degeneration, Germ cells, Bilateral								
Mild	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Seminiferous Tubule, Vacuolation, Bilateral								
Minimal	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	[3/5]	N/A	[3/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]

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2.6.7.7.B　反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Epididymis								
Oligospermia								
Minimal	N/A	0/5	N/A	0/5	N/A	[3/5]	N/A	0/5
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[4/5]
Marked	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Cellular Debris								
Minimal	N/A	0/5	N/A	0/5	N/A	[3/5]	N/A	0/5
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[4/5]
Moderate	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Histomorphology (Incidence) – Recovery Day 90								
Testes								
Atrophy, Seminiferous Epithelium, Bilateral								
Minimal	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[1/5]
Marked	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Severe	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5

2.6.7.7.B 反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Multinucleated Giant cells, Unilateral								
Minimal	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Degeneration, Germ cells, Bilateral								
Moderate	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Epididymis								
Oligospermia								
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Moderate	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Marked	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5
Cellular Debris								
Minimal	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[2/5]
Mild	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5
Moderate	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5

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2.6.7.7.B 反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Male Reproductive Assessment – Main (n=10)								
Motility								
Grade 1	N/A	-	N/A	-	N/A	[4/10$^{\#\#}$]	N/A	[10/10$^{\#\#\#}$]
Grade 2	N/A	1/10	N/A	3/10	N/A	[5/10]	N/A	0/10
Grade 3	N/A	7/10	N/A	3/10	N/A	[1/10]	N/A	0/10
Mean Sperm Count	N/A	106.75	N/A	96.35	N/A	[45.85$^{\wedge}$]	N/A	[9.20$^{\wedge\wedge\wedge}$]
Sperm Morphology (% abnormal)	N/A	7.10	N/A	7.55	N/A	[71.45$^{\wedge\wedge}$]	N/A	[92.30$^{\wedge\wedge\wedge}$]
Male Reproductive Assessment – 28-Day Recovery (n=5)								
Motility								
Grade 1	N/A	-	N/A	-	N/A	1/5	N/A	[2/5]
Grade 2	N/A	1/5	N/A	1/5	N/A	-	N/A	[3/5]
Mean Sperm Count	N/A	205.60	N/A	114.60***	N/A	[64.10***]	N/A	[33.80***]
Sperm Morphology (% abnormal)	N/A	14.50	N/A	18.30	N/A	[39.60]	N/A	[73.10$^{\wedge\wedge}$]

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2.6.7.7.B 反復投与毒性試験

試験番号: TT #[redacted]-7820（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Male Reproductive Assessment – 90-Day Recovery (n=5)								
Motility								
Grade 1	N/A	-	N/A	-	N/A	[2/5]	N/A	-
Grade 2	N/A	1/5	N/A	1/5	N/A	[1/5]	N/A	1/5
Mean Sperm Count	N/A	229.30	N/A	206.90	N/A	[100.00^^]	N/A	[143.40^]
Sperm Morphology(% abnormal)	N/A	4.60	N/A	4.20	N/A	[39.80^]	N/A	[6.80]

AUC0-12hr = Area under the plasma concentration-time curve from time 0 to 12 hours; BID = Twice daily; BLQ = Below Limit of Quantitation ; Cmax = Maximum plasma concentration; F = Female; GLP = Good Laboratory Practice; HCT = Hematocrit; HGB = Hemoglobin; M = Male; N/A = Not applicable; NE = Group not examined; NR = Not reportable; TK = Toxicokinetics; Tmax = Time at maximum plasma concentration;
[ ] = Test article-related change based on incidence and/or severity;- = No noteworthy findings; Dunnett: * p≤0.05 **p≤0.01 ***p≤0.001; Dunn:^ p≤0.05 ^^p≤0.01 ^^^p≤0.001; Fisher's Exact Test: # p≤0.05 ##p≤0.01 ###p≤0.001

a GLP compliant with the exceptions of the test item was manufactured and characterized outside the scope of GMP regulations, the initial toxicokinetic analysis was performed as non-GLP, photos of individual microscopic findings (sperm morphology) were taken for illustrative purposes only.
b No quantifiable concentrations of MK-6482 or PT3317 were detected in any of the pre-dose samples on Day 1 or in any plasma samples from the control group.
c Unrelated to test-article administration, euthanized on Day 6 due to clinical signs of gasping, decreased activity level, slow skin turgor, and skin pallor. Post mortem changes were consistent with gavage error.
d Unrelated to test-article administration, found dead on Day 25 after atropine drop administration for eye exam. Necropsy findings included heavy and mottled lungs correlated microscopically with pulmonary edema, the cause of which is unclear, but unlikely to be test article-related.
e FOB was performed on the main study male rats in each group.
f Respiratory function monitoring was performed on the main study female rats in each group.
g Control and treatment group values are mean absolute values.
h For controls, the mean organ weight (absolute or as percent of brain weight) is shown. For treatment groups, percent differences from controls are shown.

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2.6.7.7.C　反復投与毒性試験：SD ラットを用いた13週間反復経口投与毒性試験（28日間及び26週間の回復期間を含む）

被験物質：ベルズチファン

Species/Strain: Rat/SD **Initial Age**: 6 weeks **Date of First Dose**: [redacted] **Dose Volume**: 5 mL/kg/dose	**Duration of Dosing:** 13 weeks **Duration of Postdose:** 28 days and 26 weeks **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 0.5% methylcellulose and 0.5% Tween 80 in reverse osmosis water	**Study Number:** TT #[redacted]-7809 **Location in CTD:** [4.2.3.2.5: TT[redacted]7809] **GLP Compliance:** Yes[a]
Special Features: Male reproductive assessment; BID dosing(dosing was administered 12 hours ± 30 minutes apart) **No-Observed-Adverse-Effect Level:** Male rats: 2 mg/kg/day (1 mg/kg BID); Female rats: ≥200 mg/kg/day (≥100 mg/kg BID)		

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Number of Animals (28-Day Recovery)	F:5	M:5	F:0	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Number of Animals (26-Week Recovery)	F:0	M:5	F:0	M:5	F:0	M:5	F:0	M:5	F:0	M:5
Number of Animals (TK)	F:3	M:3	F:0	M:9	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 1 (MK-6482) [b]										
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	0.408	1.16	1.28	3.36	4.11	9.80	10.8
Cmax (µg/mL)	N/A	N/A	N/A	0.120	0.298	0.316	0.665	0.822	1.27	1.47
Tmax (hr)	N/A	N/A	N/A	1.00	1.00	1.50	1.00	2.00	4.00	2.00

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (TK)	F:3	M:3	F:0	M:9	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 91 (MK-6482) [b]										
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	0.822	1.48	1.68	3.88	4.20	9.93	7.85
Cmax (µg/mL)	N/A	N/A	N/A	0.211	0.511	0.397	0.893	0.917	1.54	1.20
Tmax (hr)	N/A	N/A	N/A	1.00	0.50	1.50	1.50	1.50	1.00	2.00
Toxicokinetics – Study Day 1 (PT3317) [b]										
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	N/A	N/A	0.0506	0.0431	0.0622	N/A	0.254
Cmax (µg/mL)	N/A	N/A	N/A	0.00251	0.00691	0.0183	0.0398	0.00691	0.00864	0.134
Tmax (hr)	N/A	N/A	N/A	1.00	0.50	0.50	0.50	2.00	1.00	1.00
Toxicokinetics – Study Day 91 (PT3317) [b]										
AUC0-12hr (µg*hr/mL)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.0313	N/A	0.0453
Cmax (µg/mL)	N/A	N/A	N/A	N/A	0.00257	0.00290	0.0200	0.0102	0.0115	0.00647
Tmax (hr)	N/A	N/A	N/A	N/A	0.50	0.50	1.00	1.00	1.00	1.00

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2.6.7.7.C 反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Noteworthy Findings										
Mortality – Main Study (No. of Animals)	-	-	N/A	1[e]	-	-	-	-	-	1[f]
Mortality – 26-Week Recovery (No. of Animals)	N/A	1[c]	N/A	1[d]	N/A	-	N/A	-	N/A	-
Body Weight– Main	-	-	N/A	-	-	-	-	-	-	-
Body Weight – 28-Day Recovery	-	-	N/A	-	-	-	-	-	-	-
Body Weight –26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-
Food Consumption – Main	-	-	N/A	-	-	-	-	-	-	-
Food Consumption – 28-Day Recovery	-	-	N/A	-	-	-	-	-	-	-
Food Consumption –26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-
Clinical Observations – Main	-	-	N/A	-	-	-	-	-	-	-
Clinical Observations – 28-Day Recovery	-	-	N/A	-	-	-	-	-	-	-
Clinical Observations – 26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-

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2.6.7.7.C 反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Ophthalmoscopy – Main	-	-	N/A	-	-	-	-	-	-	-
Ophthalmoscopy – Week 13 Recovery	-	-	N/A	-	-	-	-	-	-	-
Hematology – Main [g]										
Red Blood Cell Count (x10^{12}/L)	7.656	8.151	N/A	[7.555***]	[7.080***]	[7.253***]	[6.791***]	[6.920***]	[6.391***]	[6.117***]
HGB (g/L)	139.8	139.3	N/A	[127.7***]	[126.1]	[121.9***]	[118.5^^^]	[113.7***]	[111.5^^^]	[100.9***]
HCT (L/L)	0.415	0.427	N/A	[0.392***]	[0.379]	[0.375***]	[0.356^^^]	[0.352***]	[0.335^^^]	[0.311***]
Mean Corpuscular Volume (fL)	54.45	52.43	N/A	51.86	53.53	51.98	[52.42***]	[50.91*]	[52.51**]	[50.96*]
Mean Corpuscular Hemoglobin (pg)	18.26	17.08	N/A	16.91	[17.80*]	16.82	[17.45***]	[16.43**]	[17.48***]	[16.49**]
Reticulocytes (x10^{9}/L)	154.96	220.95	N/A	223.23	[145.19]	[205.75]	[123.05***]	[206.00]	[114.17***]	[169.12**]
Hematology – 28-Day Recovery [g]										
Reticulocytes (x10^{9}/L)	-	214.90	N/A	173.52	-	217.30	-	176.06	-	[148.36*]
Hematology – 26-Week Recovery [g]	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Coagulation - Main	-	-	N/A	-	-	-	-	-	-	-
Coagulation – 28-Day Recovery	-	-	N/A	-	-	-	-	-	-	-
Coagulation – 26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-
Urinalysis – Main	-	-	N/A	-	-	-	-	-	-	-
Urinalysis – 28-Day Recovery	-	-	N/A	-	-	-	-	-	-	-
Urinalysis – 26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-
Clinical Chemistry – Main										
Serum Bicarbonate Levels (mmol/L)	22.1	24.0	N/A	25.1	23.4	[26.2*]	23.3	[27.2**]	[25.1***]	[27.4***]
Triglycerides (mmol/L)	0.940	-	N/A	-	[0.715]	-	[0.836]	-	[0.585^]	-
Clinical Chemistry – 28-Day Recovery										
Triglycerides (mmol/L)	0.922	-	N/A	-	0.902	-	[0.478*]	-	[0.552]	-
Clinical Chemistry – 26-Week Recovery	N/A	-	N/A	-	N/A	-	N/A	-	N/A	-

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Organ weights (Absolute) – Main (g) [h]										
Testes	N/A	4.00890	N/A	-1.3	N/A	-1.6	N/A	[-48.1^^^]	N/A	[-47.1^^^]
Epididymis (Left)	N/A	0.72215	N/A	-3.6	N/A	[-10.1]	N/A	[-34.0^^^]	N/A	[-35.7^^^]
Epididymis (Right)	N/A	0.75107	N/A	-0.9	N/A	[-13.1**]	N/A	[-34.8***]	N/A	[-37.9***]
Heart	-	1.96712	-	+3.6	-	+7.9	-	[+10.2*]	-	[+17.4***]
Organ weights (Relative to Brain) – Main (%) [h]										
Testes	N/A	172.21079	N/A	-0.9	N/A	-1.6	N/A	[-48.2***]	N/A	[-46.3***]
Epididymis (Left)	N/A	31.00793	N/A	-2.8	N/A	[-10.1]	N/A	[-34.1^^^]	N/A	[-34.6^^^]
Epididymis (Right)	N/A	32.26799	N/A	-0.8	N/A	[-13.1**]	N/A	[-34.9***]	N/A	[-36.8***]
Heart	-	84.35944	-	+3.8	-	+8.0	-	[+9.8*]	-	[+19.6***]

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試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Organ weights (Absolute) – 28-Day Recovery (g) [h]										
Testes	N/A	4.12556	N/A	+0.2	N/A	-4.1	N/A	[-55.5***]	N/A	[-51.7***]
Epididymis (Left)	N/A	0.74932	N/A	-0.4	N/A	[-8.4]	N/A	[-37.3***]	N/A	[-38.9***]
Epididymis (Right)	N/A	0.79288	N/A	-3.3	N/A	[-11.8]	N/A	[-39.3***]	N/A	[-39.8***]
Organ weights (Relative to Brain) – 28-Day Recovery (%)[h]										
Testes	N/A	175.66609	N/A	+1.5	N/A	-3.7	N/A	[-55.9***]	N/A	[-50.7***]
Epididymis (Left)	N/A	31.89965	N/A	+0.7	N/A	[-7.9]	N/A	[-37.8***]	N/A	[-37.8***]
Epididymis (Right)	N/A	33.75874	N/A	-2.2	N/A	[-11.4]	N/A	[-39.8***]	N/A	[-38.6***]
Organ weights (Absolute) – 26-Week Recovery (g) [h]										
Testes	N/A	4.49278	N/A	-2.7	N/A	[-14.6]	N/A	[-51.9^]	N/A	[-41.2]
Epididymis (Left)	N/A	0.77345	N/A	+21.0	N/A	[-16.9]	N/A	[-34.0]	N/A	[-25.4]
Epididymis (Right)	N/A	0.84245	N/A	+5.4	N/A	[-12.5]	N/A	[-37.6*]	N/A	[-23.0]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Organ weights (Relative to Brain) – 26-Week Recovery (%)[h]										
Testes	N/A	185.56887	N/A	-4.5	N/A	[-14.8]	N/A	[-50.3^]	N/A	[-42.3]
Epididymis (Left)	N/A	31.96312	N/A	+18.9	N/A	[-16.5]	N/A	[-31.4]	N/A	[-26.9]
Epididymis (Right)	N/A	34.70827	N/A	+3.8	N/A	[-12.3]	N/A	[-35.0]	N/A	[-24.4]
Gross Pathology – Main (Incidence)										
Testes										
Small; Bilateral	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[15/15]	N/A	[14/14]
Soft; Bilateral	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[15/15]	N/A	[10/14]
Epididymis Left										
Small	N/A	0/15	N/A	1/14	N/A	0/15	N/A	[15/15]	N/A	[14/14]
Soft	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	0/14
Pale discoloration; beige; all regions	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[3/15]	N/A	[3/14]
Epididymis Right										
Small	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[15/15]	N/A	[14/14]
Soft	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	0/14
Pale discoloration; beige; all regions	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[3/15]	N/A	[3/14]

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被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Gross Pathology – 28-Day Recovery (Incidence)										
Testes										
Small; Bilateral	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[4/5]
Soft; Bilateral	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[4/5]
Epididymis Left										
Small, all regions	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[4/5]
Epididymis Right										
Small, all regions	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[4/5]
Gross Pathology – 26-Week Recovery (Incidence)										
Testes										
Small; Bilateral	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[3/5]
Soft; Bilateral	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[3/5]	N/A	[1/5]
Epididymis Left										
Small, all regions	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[2/5]
Epididymis Right										
Small, all regions	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[2/5]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Histomorphology – Main (Incidence)										
Testis										
Atrophy, tubular										
Minimal	N/A	0/15	N/A	0/14	N/A	[2/15]	N/A	[1/15]	N/A	[5/14]
Mild	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	0/15	N/A	[5/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	[2/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[7/15]	N/A	[1/14]
Severe	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[6/15]	N/A	0/14
Degeneration, tubular										
Minimal	N/A	0/15	N/A	0/14	N/A	[8/15]	N/A	[6/15]	N/A	0/14
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[4/15]	N/A	[1/14]
Moderate	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[2/15]	N/A	[10/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[3/14]
Subtypes of tubular degeneration:										
Retained spermatids, epithelial surface										
Minimal	N/A	0/15	N/A	[3/14]	N/A	[9/15]	N/A	[3/15]	N/A	[8/14]
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	0/15	N/A	[2/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	[1/14]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Retained spermatids, basement membrane										
Minimal	N/A	0/15	N/A	0/14	N/A	[11/15]	N/A	[2/15]	N/A	[3/14]
Mild	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[1/14]
Retained large residual bodies										
Minimal	N/A	0/15	N/A	0/14	N/A	[8/15]	N/A	[2/15]	N/A	[5/14]
Mild	N/A	0/15	N/A	0/14	N/A	[4/15]	N/A	[3/15]	N/A	[2/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[2/15]	N/A	[7/14]
Multinucleated giant cells										
Minimal	N/A	0/15	N/A	0/14	N/A	[3/15]	N/A	[1/15]	N/A	[6/14]
Mild	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[4/15]	N/A	[5/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[3/15]	N/A	[3/14]
Vacuolated spermatid nuclei										
Minimal	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[1/15]	N/A	[6/14]
Mild	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[2/15]	N/A	[3/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[5/15]	N/A	[1/14]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Exfoliated epithelial cells in lumen										
Minimal	N/A	0/15	N/A	0/14	N/A	[8/15]	N/A	[3/15]	N/A	[1/14]
Mild	N/A	0/15	N/A	0/14	N/A	[2/15]	N/A	[6/15]	N/A	[1/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	[11/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[1/14]
Apoptotic pachytene and meiotic germ cells										
Minimal	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[2/15]	N/A	[6/14]
Mild	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[4/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[3/14]
Apoptosis/disorganization of elongating spermatids										
Minimal	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[1/15]	N/A	[1/14]
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[2/15]	N/A	[2/14]
Moderate	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[9/15]	N/A	[8/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[3/14]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Decreased elongating spermatids										
Minimal	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[1/15]	N/A	0/14
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[2/15]	N/A	[1/14]
Moderate	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[9/15]	N/A	[9/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[4/14]
Focal germ cell dropout										
Minimal	N/A	0/15	N/A	0/14	N/A	[7/15]	N/A	[1/15]	N/A	0/14
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[2/15]	N/A	[1/14]
Moderate	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	[9/15]	N/A	[9/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[4/14]
Vacuolation of Sertoli cells										
Minimal	N/A	0/15	N/A	0/14	N/A	[9/15]	N/A	[5/15]	N/A	[8/14]
Mild	N/A	0/15	N/A	0/14	N/A	[5/15]	N/A	[4/15]	N/A	[3/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	[3/14]
Interstitial cell hyperplasia/hypertrophy										
Minimal	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[13/15]	N/A	[7/14]
Sperm Granuloma										
Minimal	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	[0/14]

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Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Epididymis - Paired										
Hypospermia										
Minimal	N/A	0/15	N/A	0/14	N/A	[1/15]	N/A	0/15	N/A	0/14
Mild	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[1/15]	N/A	0/14
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[3/15]	N/A	[10/14]
Severe	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[11/15]	N/A	[4/14]
Cellular Debris										
Minimal	N/A	0/15	N/A	0/14	N/A	[7/15]	N/A	[2/15]	N/A	0/14
Mild	N/A	0/15	N/A	0/14	N/A	[6/15]	N/A	[5/15]	N/A	[5/14]
Moderate	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[3/15]	N/A	[6/14]
Marked	N/A	0/15	N/A	0/14	N/A	0/15	N/A	0/15	N/A	[3/14]
Liver[i]										
Necrosis, Hepatocellular										
Minimal	1/15	0/15	N/A	2/15	0/15	1/15	1/15	2/15	0/15	3/15
Moderate	-	0/15	N/A	0/15	-	0/15	-	0/15	-	2/15
Kidneys[i]										
Increased hyaline droplets, Tubular epithelium										
Mild	-	2/15	N/A	1/15	-	1/15	-	1/15	-	6/15

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Histomorphology – 28-Day Recovery (Incidence)										
Testes										
Atrophy, tubular										
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Severe	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[1/5]
Degeneration, tubular										
Minimal	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[4/5]	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Subtypes of tubular degeneration:										
Retained spermatids, epithelial surface										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]
Multinucleated giant cells										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Vacuolated spermatid nuclei										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Exfoliated epithelial cells in lumen										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[2/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Apoptotic pachytene and meiotic germ cells										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Apoptosis/disorganization of elongating spermatids										
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[3/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]

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2.6.7.7.C 反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Decreased elongating spermatids										
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[3/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Focal germ cell dropout										
Minimal	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[1/5]	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	[3/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Vacuolation of Sertoli cells										
Minimal	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5	N/A	[5/5]
Mild	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5	N/A	0/5
Interstitial cell hyperplasia/hypertrophy										
Minimal	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[4/5]	N/A	[3/5]
Epididymis - Paired										
Hypospermia										
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[3/5]
Severe	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[1/5]

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Cellular Debris										
Minimal	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5	N/A	[1/5]
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[2/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	[1/5]
Marked	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[2/5]	N/A	0/5
Cribriform Change										
Mild	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[3/5]	N/A	[1/5]
Moderate	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[1/5]	N/A	0/5
Histomorphology – 26-Week Recovery (Incidence)										
Testes										
Atrophy, tubular										
Minimal	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	0/5	N/A	[1/5]
Mild	N/A	0/4	N/A	0/4	N/A	0/5	N/A	0/5	N/A	[1/5]
Moderate	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[1/5]	N/A	0/5
Severe	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[2/5]
Degeneration, tubular										
Minimal	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	0/5	N/A	[3/5]
Mild	N/A	0/4	N/A	0/4	N/A	0/5	N/A	[1/5]	N/A	0/5

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Exfoliated epithelial cells in lumen										
Mild	N/A	0/4	N/A	0/4	N/A	0/5	N/A	[1/5]	N/A	0/5
Focal germ cell dropout										
Minimal	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[1/5]	N/A	[2/5]
Sperm statis										
Minimal	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	0/5	N/A	0/5
Epididymis – Paired										
Hypospermia										
Mild	N/A	0/4	N/A	0/4	N/A	0/5	N/A	[1/5]	N/A	0/5
Severe	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[2/5]
Cellular Debris										
Minimal	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[1/5]	N/A	0/5
Mild	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[1/5]	N/A	[1/5]

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2.6.7.7.C 反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Additional Examinations										
Male Reproductive Assessment – Main										
Motility										
Grade 1	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[9/15###]	N/A	[12/14###]
Grade 2	N/A	0/15	N/A	0/14	N/A	0/15	N/A	[4/15###]	N/A	[2/14###]
Grade 3	N/A	0/15	N/A	0/14	N/A	[4/15]	N/A	[2/15###]	N/A	0/14
Mean Sperm Count (millions) [j]	N/A	194.70	N/A	196.36	N/A	[115.03]	N/A	[38.33]	N/A	[18.29]
Sperm Morphology (% abnormal)	N/A	6.433	N/A	7.964	N/A	[31.633^^]	N/A	[83.333^^^]	N/A	[90.001^^^]
Male Reproductive Assessment – 28-Day Recovery										
Motility (%)										
Grade 1	N/A	0/5	N/A	0/5	N/A	0/5	N/A	[5/5]	N/A	[5/5]
Mean Sperm Count (millions) [j]	N/A	244.20	N/A	215.80	N/A	173.10	N/A	[34.90]	N/A	[27.60]
Sperm Morphology (% abnormal)	N/A	3.100	N/A	4.000	N/A	7.000	N/A	[99.000^^]	N/A	[98.900^^]

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2.6.7.7.C　反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		2 (1 BID)		6 (3 BID)		20 (10 BID)		200 (100 BID)	
Number of Animals (Main)	F:15	M:15	F:0	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Male Reproductive Assessment – 26-Week Recovery										
Motility (Incidence)										
Grade 1	N/A	0/4	N/A	0/4	N/A	[1/5]	N/A	[4/5]	N/A	[2/5]
Grade 4	N/A	4/4	N/A	4/4	N/A	4/5	N/A	[1/5]	N/A	[3/5]
Mean Sperm Count (millions) [j]	N/A	255.25	N/A	232.63	N/A	213.30	N/A	[62.50]	N/A	[156.70]
Sperm Morphology (% abnormal)	N/A	5.000	N/A	3.750	N/A	23.600	N/A	[77.500]	N/A	[40.700]

(footnotes presented on following page)

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2.6.7.7.C 反復投与毒性試験

試験番号: TT #[redacted]-7809（続き）

被験物質：ベルズチファン

AUC0-12hr = Area under the plasma concentration-time curve from time 0 to 12 hours; BID = Twice daily; Cmax = Maximum plasma concentration; F = Female; GLP = Good Laboratory Practice; HCT = Hematocrit; HGB = Hemoglobin; M = Male; N/A = Not applicable; TK = Toxicokinetics; Tmax = Time at maximum plasma concentration; [ ] = Test article-related change based on incidence and/or severity.; - = No noteworthy findings

Dunnett: * p≤0.05 **p≤0.01 ***p≤0.001; Dunn: ^ p≤0.05 ^^p ≤0.01 ^^^p≤0.001; Fisher's Exact Test: # p≤0.05 ##p≤0.01 ###p≤0.001

a GLP compliant with the exception of the test item was manufactured and characterized outside the scope of GMP regulations, the initial toxicokinetic analysis was performed as non-GLP.

B No quantifiable concentrations of MK-6482 or PT3317 were detected in any of the pre-dose samples on Day 1 or in any plasma samples from the control group

c Found dead on Day 228. No abnormal clinical signs were noted on days preceding death. There were no significant macroscopic or microscopic findings to indicate the cause of death, and there were no test article-related gross or microscopic findings in the epididymides or testes.

D Found dead on Day 171. No abnormal clinical signs were noted on days preceding death. There were no significant macroscopic or microscopic findings to indicate the cause of death, and there were no test article-related gross or microscopic findings in the epididymides or testes.

E Found dead on Day 61, prior to PM dose administration. No abnormal clinical signs were noted on days preceding death, but animal was recorded as gasping immediately prior to death. There were no macroscopic findings to indicate the cause of death, however moderate alveolar edema was observed microscopically. This was considered unrelated to the test article.

F Euthanized on Day 18 with possible MK-6482 related mortality. At necropsy, observed to have moderate hepatocellular necrosis that was considered adverse. The brain had moderate, bilaterally symmetrical neuronal degeneration/necrosis. This animal also had microscopic findings in the testes described as seminiferous tubule degeneration and secondary findings of hypospermia and increased cellular debris in the epididymis.

G Control and treatment group values are mean absolute values.

H For controls, the mean organ weight (absolute or as percent of brain weight) is shown. For treatment groups, percent differences from controls are shown.

I Includes found dead/early sacrifice pre-terminal male animals in Groups 2 and 5.

J No statistical comparisons were performed.

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2.6.7.7.D　反復投与毒性試験：Wistar Han ラットを用いた13週間反復経口投与毒性試験

被験物質：ベルズチファン

Species/Strain: Rat/Wistar Han **Initial Age**: 8 weeks **Date of First Dose:** [redacted] **Dose Volume:** 5 mL/kg	**Duration of Dosing:** 91 days **Duration of Postdose:** N/A **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 20 mM pH 7.2 TRIS buffered 0.5% methylcellulose/0.1% HPMCAS-HF	**Study Number:** TT #[redacted]-9011 **Location in CTD:** [4.2.3.2.6: TT[redacted]9011] **GLP Compliance:** Yes
Special Features: N/A **No-Observed-Adverse-Effect Level:** <30 mg/kg/day for males, ≥300 mg/kg for females		

Daily Dose (mg/kg/day)	0 (Control)		30		100		300	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals (TK)	F:6	M:6	F:6	M:6	F:6	M:6	F:6	M:6
Toxicokinetics (MK-6482) – Study Day 91								
AUC0-24hr (µg*hr/mL)	N/A[a]		66.3		215		466	
Cmax (µg/mL)	N/A[a]		10.6		27.8		39.6	
Tmax (hr)	N/A[a]		0.500		1.00		1.00	
Toxicokinetics (PT3317) – Study Day 91								
AUC0-24hr (µg*hr/mL)	N/A[a]		0.391		3.85		22.7	
Cmax (µg/mL)	N/A[a]		0.0830		1.06		3.13	
Tmax (hr)	N/A[a]		1.00		1.00		1.00	

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2.6.7.7.D　反復投与毒性試験

試験番号: TT #[redacted]-9011（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		100		300	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings								
Mortality (No. of Animals)	0	0	0	0	0	0	2[b]	0
Body Weight	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Ophthalmic Examinations	-	-	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-	-	-
Hematology – Study Day 22[c]								
HCT (%)	42.75	46.11	[38.97**]	[40.65**]	[33.56**]	[34.89**]	[28.81**]	[31.49**]
HGB (g/dL)	14.34	15.11	[13.05**]	[13.36**]	[11.36**]	[11.54**]	[9.69**]	[10.44**]
Platelets Count($x10^3/\mu L$)	911.8	918.0	[953.2]	1003.7	[964.5]	[1058.4]	[1051.6]	[1184.0**]
RBC Count ($x10^6/\mu L$)	7.822	8.542	[7.256**]	[7.572**]	[6.423**]	[6.624**]	[5.407**]	[6.057**]
Reticulocytes ($x10^9/L$)	217.78	224.61	164.13*	[169.67**]	[126.18**]	[122.96**]	[95.69**]	[89.60**]

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2.6.7.7.D　反復投与毒性試験

試験番号: TT #[redacted]-9011（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		100		300	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Hematology – Study Day 92[c]								
HCT (%)	41.20	42.76	[37.14**]	[34.48**]	[30.03**]	[30.04**]	[25.80**]	[26.45**]
HGB (g/dL)	14.14	14.18	[12.49**]	[11.46**]	[10.03**]	[9.82**]	[8.51**]	[8.65**]
Platelets ($x10^3/\mu L$)	763.9	807.3	[907.8]	883.6	[905.6]	[927.1*]	[1078.8**]	[1074.8**]
Red Blood Cell Count ($x10^6/uL$)	7.569	8.449	7.000	[6.955**]	[5.873**]	[6.256**]	[5.095**]	[5.579**]
Reticulocytes ($x10^9/L$)	196.03	180.60	186.62	[144.72**]	[170.70]	[118.36**]	[132.99]	[96.79**]
Clinical Chemistry – Study Day 22[c]								
Chloride (mEq/L)	102.6	101.3	102.7	99.7	[99.7**]	[97.5**]	[98.5**]	[97.3**]
Clinical Chemistry – Study Day 92[c]								
Chloride (mEq/L)	103.3	105.2	103.8	103.1**	[101.5**]	[101.7**]	[100.9**]	[101.9**]
Urinalysis	-	-	-	-	-	-	-	-
Gross Pathology (Incidence) – Study Day 92								
Epididymis – Small	N/A	0/10	N/A	[1/10]	N/A	0/10	N/A	0/10
Testis – Small	N/A	0/10	N/A	[1/10]	N/A	0/10	N/A	[1/10]

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2.6.7.7.D　反復投与毒性試験

試験番号: TT #[redacted]-9011（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		100		300	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Organ Weights (Absolute, g) – Study Day 92[d]								
Epididymis	N/A	1.2196	N/A	[-34.85**]	N/A	[-32.64**]	N/A	[-28.30**]
Heart[e]	0.7581	1.1738	0.21	-0.83	[26.17**]	[12.73*]	[46.34**]	[29.06**]
Liver[f]	5.7816	10.7683	-0.32	0.17	15.25*	11.45	[30.41**]	[18.80^^]
Testis	N/A	3.6593	N/A	[-34.75^]	N/A	[-52.42^^]	N/A	[-49.33^^]
Organ Weights (Relative to Body Weight, %) – Study Day 92[d]								
Epididymis	N/A	0.27349	N/A	[-31.72**]	N/A	[-31.86**]	N/A	[-23.74*]
Heart[e]	0.30842	0.26235	0.06	4.56	[23.07**]	[14.13**]	[49.37**]	[37.27**]
Liver[f]	2.34838	2.40542	-0.80	5.35	12.62**	11.77^	[32.41**]	[26.22^^]
Testis	N/A	0.82147	N/A	[-30.99]	N/A	[-50.90^^]	N/A	[-46.05^^]
Organ Weights (Relative to Brain Weight, %) – Study Day 92[d]								
Epididymis	N/A	58.64113	N/A	[-33.19**]	N/A	[-30.55**]	N/A	[-26.18**]
Heart[e]	40.05575	56.32082	1.11	1.92	[25.67**]	[16.15*]	[50.85**]	[32.93**]
Liver[f]	306.20629	517.12323	0.28	2.96	14.51*	14.54	[33.64**]	[22.68**]
Testis	N/A	175.86262	N/A	[-33.29]	N/A	[-51.08^^]	N/A	[-47.74^^]

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2.6.7.7.D　反復投与毒性試験

試験番号: TT #[redacted]-9011（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		30		100		300	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Histomorphology (Incidence) – Study Day 92								
Epididymis								
Reduced sperm, lumen								
Minimal	N/A	0/10	N/A	[3/10]	N/A	0/10	N/A	[1/10]
Mild	N/A	0/10	N/A	[2/10]	N/A	[3/10]	N/A	[1/10]
Moderate	N/A	0/10	N/A	[3/10]	N/A	[3/10]	N/A	[7/10]
Marked	N/A	0/10	N/A	0/10	N/A	[4/10]	N/A	[1/10]
Harderian Gland[g]								
Single cell necrosis, acinar								
Minimal	0/10	1/10	NE	[1/10]	NE	[4/10]	0/10	[7/10]
Mild	0/10	0/10	NE	[1/10]	NE	0/10	0/10	0/10
Testis								
Degeneration, Seminiferous Tubule								
Minimal	N/A	0/10	N/A	[3/10]	N/A	[1/10]	N/A	0/10
Mild	N/A	0/10	N/A	[1/10]	N/A	[2/10]	N/A	[2/10]
Moderate	N/A	0/10	N/A	[1/10]	N/A	[2/10]	N/A	[7/10]
Marked	N/A	0/10	N/A	[4/10]	N/A	[5/10]	N/A	[1/10]

(footnotes presented on following page)

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2.6.7.7.D　反復投与毒性試験

試験番号: TT #[redacted]-9011（続き）

被験物質：ベルズチファン

AUC0-24hr=area under the plasma concentration-time curve from time 0 to 24 hours; Cmax=maximum plasma concentration; F=female; GLP=Good Laboratory Practice; hr=hour(s); HCT=hematocrit; HGB=hemoglobin; HPMCAS-HF =Hydroxypropyl methylcellulose acetate succinate-HF; M=male; N/A=Not applicable; NE=Group not examined; No.=number; RBC=red blood cell; TK=toxicokinetics; Tmax=time at maximum plasma concentration; TRIS=tromethamine; - =no noteworthy findings; #/# =number affected/number examined; [ ]=test article-related change based on incidence and/or severity.

All Hematology p values for Study Day 22, the male Hematology p values for Study Day 92, the female Hematology HGB, HCT, and Platelet p values for Study Day 92, all Clinical Chemistry p values for Study Days 22 and 92, and Organ Weights p values : ANOVA & Dunnett: *=p≤0.05; **=p≤0.01.

Female Hematology Red Blood Cell Count and Organ Weights (Male liver of absolute and relative to body weight and testis only) p values for Study Day 92: Kruskal-Wallis & Dunn: ^=p≤0.05, ^^=p≤0.01.

a. Plasma MK-6482 and PT3317 concentrations in all control group animals were below the lower limit of quantitation (<12.5 ng/mL) of the bioanalytical method.
b. Two females at 300 mg/kg/day were found dead on Study Day 22 following the week 4 blood collection procedure. At necropsy, these animals had a large amount of red gelatinous material (blood) accumulation in the subcutis extending from the ventral cervical area to the axillary area, consistent with bleeding that resulted from the blood collection procedure. Cause of death was attributed to the blood collection procedure.
c. Control and treatment group values are mean absolute values.
d. For controls, the mean organ weight (absolute or as percent of body or brain weight) is shown. For treatment groups, percent differences from controls are shown.
e. Increased heart weight is an adaptive response secondary to the reduction of HGB concentration and is expected to be reversible and, therefore, of minimal toxicological significance.
f. The liver weight increase lacked microscopic correlates and was considered to be of minimal toxicological significance.
g. Harderian gland change was not associated with any histomorphologic changes in the eyes. Given the low severity, lack of any finding in the eyes, and since the Harderian gland is not present in humans, this finding is of no toxicological relevance to humans.

2.6.7.7.E　反復投与毒性試験：ビーグル犬を用いた28日間反復経口投与毒性試験（28日間及び90日間の回復期間を含む）

被験物質：ベルズチファン

Species/Strain: Dog / Beagle **Initial Age:** ~ 13 to 15 months **Date of First Dose:** [redacted] **Dose Volume:** 5 mL/kg	**Duration of Dosing:** 28 days **Duration of Postdose:** 28 days and 90 days **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 0.5% methylcellulose and 0.5% Tween 80 in reverse osmosis water	**Study Number:** TT #[redacted]-7821 **Location in CTD:** [4.2.3.2.7: TT[redacted]7821] **GLP Compliance:** Yes[a]
Special Features: ECG and BP evaluations, Male reproductive assessment, EPO analysis **No-Observed-Adverse-Effect Level:** ≥30 mg/kg/day		

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Toxicokinetics – Study Day 1 (MK-6482) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	5.81	5.30	17.3	14.8	41.3	32.0
Cmax (µg/mL)	N/A	N/A	0.525	0.501	1.18	1.03	2.70	2.27
Tmax (hr)	N/A	N/A	1.00	1.00	2.00	1.00	2.00	1.00

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2.6.7.7.E　反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Toxicokinetics – Study Day 28 (MK-6482) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	7.84	6.89	18.2	21.3	37.8	38.4
Cmax (µg/mL)	N/A	N/A	0.651	0.574	1.34	1.53	2.94	2.86
Tmax (hr)	N/A	N/A	2.00	1.00	1.00	1.00	1.00	2.00
Toxicokinetics – Study Day 1 (PT3317 Metabolite) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	1.16	1.06	3.22	2.95	6.71	5.80
Cmax (µg/mL)	N/A	N/A	0.170	0.143	0.285	0.263	0.665	0.538
Tmax (hr)	N/A	N/A	1.00	1.00	2.00	2.00	2.00	1.00
Toxicokinetics – Study Day 28 (PT3317 Metabolite) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	1.83	1.92	5.95	5.62	20.6	12.9
Cmax (µg/mL)	N/A	N/A	0.240	0.236	0.572	0.588	1.96	1.13
Tmax (hr)	N/A	N/A	2.00	2.00	2.00	1.00	1.00	2.00

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2.6.7.7.E　反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings								
Mortality (No. of Animals) – Main and Recovery	0	0	0	0	0	0	0	0
Body Weight – Main	-	-	-	-	-	-	-	-
Body Weight – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Food Consumption – Main	-	-	-	-	-	-	-	-
Food Consumption – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Clinical Observations – Main	-	-	-	-	-	-	-	-
Clinical Observations – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Ophthalmoscopy – Main	-	-	-	-	-	-	-	-
ECG – Main	-	-	-	-	-	-	-	-
BP Evaluation – Main	-	-	-	-	-	-	-	-

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2.6.7.7.E 反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Hematology – Main (Day 29, End of Dosing) [c]								
Red Blood Cell Count ($x10^{12}$/L)	6.147	6.253	[4.470^]	[5.044***]	[4.140^^]	[4.756***]	[4.069^^^]	[4.689***]
HGB (g/L)	142.3	146.4	[102.7***]	[116.0***]	[94.3***]	[109.1***]	[93.3***]	[108.7***]
HCT (L/L)	0.420	0.434	[0.303***]	[0.341***]	[0.276***]	[0.319***]	[0.270***]	[0.317***]
Reticulocyte ($x10^9$/L) [d]	27.53	29.76	[19.61]	[17.17*]	[7.50]	[10.10***]	[15.10]	[16.80]
Hematology – 28-Day Recovery (Day 57) [c]								
Red Blood Cell Count ($x10^{12}$/L)	6.240	6.213	6.265	6.683	[5.523]	6.575	[5.340*]	6.325
Reticulocyte ($x10^9$/L)	16.48	38.38	[50.45*]	43.10	29.85	54.13	44.25	52.53
RDW (%)	11.60	11.40	[12.40*]	[12.33**]	[12.88***]	[13.08***]	[13.10***]	[12.50***]
Clinical Chemistry – Main	-	-	-	-	-	-	-	-
Clinical Chemistry – 28-Day Recovery	-	-	-	-	-	-	-	-
Coagulation – Main	-	-	-	-	-	-	-	-
Coagulation – 28-Day Recovery	-	-	-	-	-	-	-	-
Urinalysis – Main	-	-	-	-	-	-	-	-
Urinalysis – 28-Day Recovery	-	-	-	-	-	-	-	-

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2.6.7.7.E　反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Organ weights – Main	-	-	-	-	-	-	-	-
Organ weights – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Gross Pathology (Incidence) – Main	-	-	-	-	-	-	-	-
Gross Pathology (Incidence) – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-
Histomorphology (Incidence) – Main								
Femur and Bone Marrow								
Hypocellularity; Hematopoietic [e]								
Minimal	0/3	0/3	0/3	[1/3]	[1/3]	[1/3]	0/3	[1/3]
Mild	0/3	0/3	0/3	0/3	[1/3]	[2/3]	0/3	[1/3]
Moderate	0/3	0/3	0/3	0/3	0/3	0/3	[3/3]	[1/3]
Sternum and Bone Marrow								
Hypocellularity; Hematopoietic [e]								
Minimal	0/3	0/3	0/3	[1/3]	0/3	0/3	0/3	0/3
Mild	0/3	0/3	0/3	0/3	[1/3]	[1/3]	[2/3]	[2/3]
Histomorphology (Incidence) – 28-Day and 90-Day Recovery	-	-	-	-	-	-	-	-

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2.6.7.7.E　反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Additional Examinations								
Male Reproductive Assessment – Main								
Sperm Motility	N/A	-	N/A	-	N/A	-	N/A	-
Spermatozoa Count	N/A	-	N/A	-	N/A	-	N/A	-
Sperm Morphology	N/A	-	N/A	-	N/A	-	N/A	-
Male Reproductive Assessment – 28-Day and 90-Day Recovery								
Sperm Motility	N/A	-	N/A	-	N/A	-	N/A	-
Spermatozoa Count	N/A	-	N/A	-	N/A	-	N/A	-
Sperm Morphology	N/A	-	N/A	-	N/A	-	N/A	-

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2.6.7.7.E 反復投与毒性試験

試験番号: TT #[redacted]-7821（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals (28-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Number of Animals (90-Day Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Bone Marrow Smear Evaluation – Main								
M:E Ratio [f]	1.52	0.89	1.43	[2.11]	[2.78]	[4.60]	[9.31]	[11.12]
Bone Marrow Smear Evaluation – 28-Day Recovery								
M:E Ratio [f]	-	-	-	-	-	-	-	-
EPO Analysis – Main	-	-	-	-	-	-	-	-
EPO Analysis – 28-Day Recovery	-	-	-	-	-	-	-	-

AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; BP = Blood pressure; Cmax = Maximum plasma concentration; ECG = Electrocardiography; EPO = Erythropoietin; F = Female; GLP = Good Laboratory Practice; GMP = Good Manufacturing Practice; HCT = Hematocrit; HGB = Hemoglobin; M = Male; M:E = Myeloid:Erythroid; N/A = Not applicable; RDW = Red blood cell distribution width; TK = Toxicokinetics; Tmax = Time at maximum plasma concentration; [ ] = Test article-related change based on incidence and/or severity; - = No noteworthy findings.

Dunnett: *p≤0.05 **p≤0.01 ***p≤0.001; Dunn: ^p≤0.05 ^^p≤0.01 ^^^p≤0.001

a GLP compliant with the exception that the test item was manufactured and characterized outside the scope of GMP regulations, the initial TK analysis was performed as non-GLP, and photographs of individual microscopic findings (sperm morphology) were taken for illustrative purposes only.

b No quantifiable concentrations of MK-6482 or PT3317 were detected in any of the pre-dose samples on Day 1 or in any plasma samples from the control group.

c Control and treatment group values are mean absolute values.

d Values from 1 animal in 5 mg/kg/day group (female) and 30 mg/kg/day group (male and female), and 6 animals in 5 mg/kg/day group (male) due to the detection limit.

e Considered to be related to pharmacological effect of MK-6482 and not adverse.

f 37% of the bone marrow smears were “unable to evaluate,” spread across all groups, for both terminal and recovery animals. The higher M:E ratios for main study animals dosed at ≥5 mg/kg/day were a result of a decrease in erythroid precursors. This was supported by decrease in peripheral red cell mass (red blood cell count, HGB concentrations, and HCT) and reticulocyte counts in the peripheral blood.

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2.6.7.7.F　反復投与毒性試験：ビーグル犬を用いた13週間反復経口投与毒性試験（28日間の回復期間を含む）

被験物質：ベルズチファン

Species/Strain: Dog / Beagle **Initial Age:** ~ 13 to 14 months **Date of First Dose:** [redacted] **Dose Volume:** 5 mL/kg	**Duration of Dosing:** 13 weeks **Duration of Postdose:** 28 days **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 0.5% methylcellulose and 0.5% Tween 80 in reverse osmosis water	**Study Number:** TT #[redacted]-7808 **Location in CTD:** [4.2.3.2.8: TT[redacted]7808] **GLP Compliance:** Yes[a]
Special Features: ECG and BP evaluations, LDH and haptoglobin assessment, Male reproductive assessment **No-Observed-Adverse-Effect Level:** ≥30 mg/kg/day		

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Number of Animals (Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Toxicokinetics – Study Day 1 (MK-6482) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	4.87	4.46	12.4	9.87	31.8	14.5
Cmax (µg/mL)	N/A	N/A	0.374	0.375	1.01	0.783	3.24	1.22
Tmax (hr)	N/A	N/A	2.00	1.00	24.00	2.00	24.00	1.00
Toxicokinetics – Study Day 91 (MK-6482) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	7.13	6.75	19.7	16.9	30.2	29.0
Cmax (µg/mL)	N/A	N/A	0.556	0.572	1.40	1.34	2.12	1.94
Tmax (hr)	N/A	N/A	2.00	1.00	1.00	0.50	0.25	7.00

2.6.7.7.F　反復投与毒性試験

試験番号: TT #[redacted]-7808（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Number of Animals (Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Toxicokinetics – Study Day 1 (PT3317 Metabolite) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	1.06	0.885	3.70	2.38	7.85	2.73
Cmax (µg/mL)	N/A	N/A	0.125	0.103	0.367	0.262	0.979	0.307
Tmax (hr)	N/A	N/A	3.00	2.00	24.00	2.00	24.00	2.00
Toxicokinetics – Study Day 91 (PT3317 Metabolite) [b]								
AUC0-24hr (µg*hr/mL)	N/A	N/A	1.71	1.93	7.11	6.31	15.9	7.54
Cmax (µg/mL)	N/A	N/A	0.206	0.182	0.696	0.625	1.50	0.627
Tmax (hr)	N/A	N/A	2.00	2.00	1.50	2.00	1.00	3.00

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2.6.7.7.F　反復投与毒性試験

試験番号: TT #[redacted]-7808（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Number of Animals (Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings								
Mortality (No. of Animals) – Main and Recovery	0	0	0	0	0	0	0	0
Body Weight – Main and Recovery	-	-	-	-	-	-	-	-
Food Consumption – Main and Recovery	-	-	-	-	-	-	-	-
Clinical Observations – Main and Recovery	-	-	-	-	-	-	-	-
Ophthalmoscopy – Main	-	-	-	-	-	-	-	-
ECG – Main	-	-	-	-	-	-	-	-
BP Evaluations – Main	-	-	-	-	-	-	-	-

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2.6.7.7.F　反復投与毒性試験

試験番号: TT #[redacted]-7808（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Number of Animals (Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Hematology – Main (Week 13, End of Dosing)[c]								
Red Blood Cell Count (x10^{12}/L)	7.198	7.252	[4.413]	[4.412***]	[3.888^]	[4.165***]	[3.260^^^]	[4.125***]
HGB (g/L)	163.8	164.3	[102.0]	[103.8***]	[90.5^]	[97.5***]	[76.5^^^]	[97.3***]
HCT (L/L)	0.497	0.495	[0.308]	[0.317***]	[0.278^]	[0.300***]	[0.237^^^]	[0.293***]
Reticulocytes (x10^{9}/L)	45.57	45.90	[25.40]	[21.48]	[35.00]	[49.92]	[35.48]	[59.92]
Hematology – Recovery	-	-	-	-	-	-	-	-
Haptoglobin Assessment – Main	-	-	-	-	-	-	-	-
Clinical Chemistry and LDH – Main and Recovery	-	-	-	-	-	-	-	-
Coagulation – Main and Recovery	-	-	-	-	-	-	-	-
Urinalysis – Main and Recovery	-	-	-	-	-	-	-	-

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2.6.7.7.F　反復投与毒性試験

試験番号: TT #[redacted]-7808（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		1		5		30	
Number of Animals (Main)	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Number of Animals (Recovery)	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Organ weights – Main and Recovery	-	-	-	-	-	-	-	-
Gross Pathology (Incidence) – Main and Recovery	-	-	-	-	-	-	-	-
Histomorphology (Incidence) – Main and Recovery	-	-	-	-	-	-	-	-
Additional Examinations								
Male Reproductive Assessment – Main and Recovery								
Sperm Motility	N/A	-	N/A	-	N/A	-	N/A	-
Spermatozoa Count	N/A	-	N/A	-	N/A	-	N/A	-
Sperm Morphology	N/A	-	N/A	-	N/A	-	N/A	-

AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; BP = Blood pressure; Cmax = Maximum plasma concentration; ECG = Electrocardiography; F = Female; GLP = Good Laboratory Practice; GMP = Good Manufacturing Practice; HCT = Hematocrit; HGB = Hemoglobin; LDH = Lactate dehydrogenase; M = Male; N/A = Not applicable; Tmax = Time at maximum plasma concentration; [ ] = Test article-related change based on incidence and/or severity; - = No noteworthy findings.
Dunnett: *p≤0.05　**p≤0.01　***p≤0.001; Dunn: ^p≤0.05　^^p≤0.01　^^^p≤0.001

a　GLP compliant with the exception that the test item was manufactured and characterized outside the scope of GMP regulations, the initial toxicokinetic analysis and haptoglobin analysis were performed as non-GLP.

b　No quantifiable concentrations of MK-6482 or PT3317 were detected in any of the pre-dose samples on Day 1 or in any plasma samples from the control group.

c　Control and treatment group values are mean absolute values.

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2.6.7.8　In vitro 遺伝毒性試験

2.6.7.8.A　In vitro 探索的遺伝毒性試験

被験物質：ベルズチファン

Study Type	Test System	Duration / Route	Dose Levels	Results	Study Number
In Vitro Mammalian Cell Micronucleus Screening Assay in TK6 Cells	TK6 human lymphoblastoid cells	27 hr (-S9); 4 hr (+S9)	92 to 383 µg/mL (4 hr +S9); 31.5 to 383 µg/mL (27 hr -S9)	Negative. MK-6482 was evaluated up to the maximum recommended concentration (1 mM). No significant increases were observed for the induction of micronuclei at any concentration scored in the presence or absence of S9 ($p>0.05$).	TT #[redacted]-7843 [4.2.3.3.1.3: TT[redacted]7843]

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2.6.7.8.B In vitro 遺伝毒性試験：細菌を用いた復帰突然変異試験

被験物質：ベルズチファン

Test for Induction of: Reverse mutation in bacterial cells **Strains:** *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537), *Escherichia coli* (WP2 *uvrA*) **Metabolizing System:** Aroclor-induced rat liver S9; 50 µL/plate **Treatment:** Plate incorporation, 48 to 72 hours	**No. of Independent Assays:** 2 **No. of Replicate Cultures:** 2 per dose point (TT #[redacted]-7842); 3 per dose point (TT #[redacted]-7825) **No. of Cells Analyzed/Culture:** 0.6 to 2.5 x 10^8 cells/plate (TT #[redacted]-7842); 3 to 13.3 x 10^8 cells/plate (TT #[redacted]-7825) **Vehicle for Positive Controls:** DMSO, except sterile water for sodium azide **Vehicle for Test Article**: Dimethyl sulfoxide (DMSO)	**Study No.**: TT #[redacted]-7842 and TT #[redacted]-7825 **Location in CTD:** [4.2.3.3.1.1: TT[redacted]7842] [4.2.3.3.1.2: TT[redacted]7825] **GLP Compliance**: Yes, except for test article analysis and TT #[redacted]-7842 (Dose range finding study) **Date of Treatment:** [redacted] in TT #[redacted]-7842 [redacted] in TT #[redacted]-7825
Cytotoxic Effects: In TT #[redacted]-7842, inhibition of revertant growth was noted in TA98 at 5000 µg/plate and in TA1535 at ≥1500 µg/plate without metabolic activation. No toxicity was noted in TT #[redacted]-7825. **Genotoxic Effects†:** None		
GLP = Good Laboratory Practice † Criteria for a positive result are (1) a 2-fold or greater increase in number of revertant colonies for strains TA98, TA100 and WP2 *uvrA*; a 3-fold or greater increase in number of revertant colonies for strains TA1535 and TA1537, and (2) a dose-related increase in number of revertant colonies.		

2.6.7.8.B　In vitro 遺伝毒性試験

試験番号: TT #[redacted]-7842（続き）

被験物質：ベルズチファン

Concentration (µg/plate)	TA98　Plated: [redacted]				TA100　Plated: [redacted]				TA1535　Plated: [redacted]			
	Without S9		With S9		Without S9		With S9		Without S9		With S9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO 100 µL/plate	16	1	20	8	117	4	95	18	14	4	12	4
1.5 µg	10	1	19	2	80	11	112	3	8	3	9	0
5.0 µg	12	0	11	1	89	6	114	6	12	0	10	1
15 µg	16	6	20	1	95	15	111	4	11	2	13	2
50 µg	12	10	21	7	101	10	126	12	10	6	15	1
150 µg	9	0	13	1	84	8	120	6	7	3	8	3
500 µg	11	1	21	7	88	8	111	11	8	2	9	4
1500 µg[p]	15	1	13	4	84	21	90	11	6	1	12	1
5000 µg[p]	3	2	15	1	89	8	127	33	3	1	8	2
2-Nitrofluorene, 1.0 µg	125	1	-	-	-	-	-	-	-	-	-	-
Sodium azide, 1.0 µg	-	-	-	-	369	14	-	-	470	15	-	-
2-Aminoanthracene, 2.0 µg	-	-	529	146	-	-	695	142	-	-	140	37

DMSO = dimethyl sulfoxide; p = precipitate; SD = standard deviation; - = no plate count data collected

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2.6.7.8.B　In vitro 遺伝毒性試験

試験番号: TT #[redacted]-7842（続き）

被験物質：ベルズチファン

	TA1537　Plated: [redacted]				WP2 *uvrA*　Plated: [redacted]			
	Without S9		With S9		Without S9		With S9	
Concentration (µg/plate)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO 100 µL/plate	4	0	3	4	46	1	30	5
1.5 µg	5	0	9	4	44	12	28	11
5.0 µg	6	1	8	2	34	9	35	8
15 µg	7	4	8	4	33	1	41	0
50 µg	6	1	7	4	26	2	39	4
150 µg	6	0	5	1	34	3	44	3
500 µg	4	3	5	1	29	4	37	13
1500 µg[p]	6	1	6	0	31	3	38	3
5000 µg[p]	5	0	4	0	34	2	39	2
9-Aminoacridine, 75 µg	559	14	-	-	-	-	-	-
Methyl methanesulfonate, 1000 µg	-	-	-	-	251	35	-	-
2-Aminoanthracene, 2 µg	-	-	82	28	-	-	-	-
2-Aminoanthracene, 15 µg	-	-	-	-	-	-	365	2

DMSO = dimethyl sulfoxide; p = precipitate; SD = standard deviation; - = no plate count data collected

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2.6.7.8.B　In vitro 遺伝毒性試験

試験番号: TT #[redacted]-7825（続き）

被験物質：ベルズチファン

Concentration (µg/plate)	TA98　Plated: [redacted]				TA100　Plated: [redacted]				TA1535　Plated: [redacted]			
	Without S9		With S9		Without S9		With S9		Without S9		With S9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO 100 µL/plate	15	3	13	5	89	1	82	2	11	3	10	1
50 µg	13	4	14	2	65	12	83	11	15	2	9	5
150 µg	17	4	17	6	78	6	93	11	11	2	11	3
500 µg	18	4	15	6	81	6	91	5	10	1	13	6
1500 µg[p]	16	2	13	2	73	2	78	3	12	4	7	3
5000 µg[p]	19	5	14	4	89	6	81	2	12	3	10	6
2-Nitrofluorene, 1.0 µg	105	33	-	-	-	-	-	-	-	-	-	-
Sodium azide, 1.0 µg	-	-	-	-	631	46	-	-	568	46	-	-
2-Aminoanthracene, 1.0 µg	-	-	265	164	-	-	-	-	-	-	106	21
2-Aminoanthracene, 2.0 µg	-	-	-	-	-	-	439	29	-	-	-	-

DMSO = dimethyl sulfoxide; p = precipitate; SD = standard deviation; - = no plate count data collected

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2.6.7.8.B　In vitro 遺伝毒性試験

試験番号: TT #[redacted]-7825（続き）

被験物質：ベルズチファン

	TA1537　Plated: [redacted]				WP2 *uvrA*　Plated: [redacted]			
	Without S9		With S9		Without S9		With S9	
Concentration (µg/plate)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO 100 µL/plate	5	2	7	1	17	1	25	7
50 µg	4	2	4	1	25	6	25	1
150 µg	5	2	6	1	22	5	27	2
500 µg	4	2	10	5	19	3	27	5
1500 µg[p]	4	3	4	2	22	5	22	6
5000 µg[p]	5	2	8	1	19	7	30	2
9-Aminoacridine, 75 µg	140	32	-	-	-	-	-	-
Methyl methanesulfonate, 1000 µg	-	-	-	-	293	43	-	-
2-Aminoanthracene, 2 µg	-	-	57	14	-	-	-	-
2-Aminoanthracene, 15 µg	-	-	-	-	-	-	190	57

DMSO = dimethyl sulfoxide; p = precipitate; SD = standard deviation; - = no plate count data collected

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2.6.7.8.C　In vitro 遺伝毒性試験：ヒト末梢血リンパ球（HPBL）を用いた哺乳類細胞 in vitro 小核試験

被験物質：ベルズチファン

Test for Induction of: Micronuclei **Strains**: Human Peripheral Blood Lymphocytes (HPBL) **Metabolizing System:** Aroclor-induced rat liver S9 **Vehicle for Test Article:** DMSO **Treatment:** 24 hr without S9; 4 hr with 20 hr recovery period with and without S9	**No. of Independent Assays**: 1 **No. of Replicate Cultures**: 2 **No. of Cells Analyzed/Culture**: 1000 **Vehicle for Positive Controls**: Water (CP, VB)	**Study No.:** TT #[redacted]-7826 **Location in CTD:** [4.2.3.3.1.4: TT[redacted]7826] **GLP Compliance:** Yes, except for test article analysis **Date of Treatment**: [redacted]
Cytotoxic Effects: In the micronucleus assay, cytotoxicity (50 ± 5% CBPI relative to the vehicle control) was not observed at any dose in the non-activated and S9-activated 4-hour exposure groups. Cytotoxicity was observed at doses ≥80 µg/mL in the non-activated 24-hour exposure group.		
Genotoxic Effects: None.		
Additional Comments Regarding Test: None.		
DMSO: Dimethyl sulfoxide; CBPI = cytokinesis-blocked proliferation index; CP: Cyclophosphamide; GLP = Good Laboratory Practice; hr: Hour ; VB: Vinblastine		

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2.6.7.8.C　In vitro 遺伝毒性試験

試験番号: TT #[redacted]-7826（続き）

被験物質：ベルズチファン

Metabolic Activation	Test Article	Dose (µg/mL)	CBPI[a]	Cytotoxicity[b] (% of Control)	Percentage of MNBN[c] Cells Per Total BN[d] Cells Counted
24 hr Continuous	DMSO	N/A	1.576	N/A	0.4
Treatment Without	MK-6482	10	1.518	10	0.5
Activation	MK-6482	50	1.400	31	0.5
	MK-6482	80	1.290	50	0.3
	VB	10 ng/mL	1.308	47	4.9**
4 hr Treatment	DMSO	N/A	1.738	N/A	0.4
With 20 hr Recovery	MK-6482	100	1.692	6	0.4
Without Activation	MK-6482	150	1.725	2	0.4
	MK-6482	383	1.588	20	0.3
4 hr Treatment	DMSO	N/A	1.583	N/A	0.5
With 20 hr Recovery	MK-6482	100	1.563	3	0.4
With Activation	MK-6482	150	1.570	2	0.5
	MK-6482	383	1.466	20	0.3
	CP	5	1.391	33	1.8**

CP: Cyclophosphamide; DMSO: Dimethyl sulfoxide; Fisher's Exact Test: ** p≤0.01; hr: Hour ; N/A: Not Applicable; VB: Vinblastine
a. CBPI = cytokinesis-blocked proliferation index
b. Relative to vehicle control
c. MNBN = micronucleated binucleated cells
d. BN = binucleated cells

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2.6.7.9　In vivo 遺伝毒性試験

2.6.7.9.A　In vivo 遺伝毒性試験：ラットを用いた2日間経口投与による in vivo 哺乳類骨髄赤血球小核試験

被験物質：ベルズチファン

Test for Induction of: Micronuclei in rat bone marrow polychromatic erythrocytes (PCE) **Species/Strain:** Rat, Sprague Dawley Crl:CD(SD) **Initial Age:** 49 days **Cells Evaluated:** PCE **No. of Cells Analyzed/Animal:** 4000 PCE	**Treatment Schedule:** Twice daily for 2 days with an interval of 12 hours (± 15 minutes) **Sampling Time:** 48 hours (± 30 minutes) after the first dose **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 0.5% (w/v) methylcellulose/ 0.5% (w/v) Tween 80 in ultra pure water	**Study No.:** TT #[redacted]-9018 **Location in CTD:** [4.2.3.3.2.1: TT[redacted]9018] **GLP Compliance:** Yes, except for test article analysis **Date of First Dose**: [redacted]
Dose Selection: Doses of 10, 30, and 100 mg/kg/BID (20, 60, and 200 mg/kg/day) were chosen based on the results of the dose-range finding phase of the study. Both males and females were used for the micronucleus test. The top dose of 200 mg/kg/day was based on the maximum feasible concentration of 20 mg/mL in the MK-6482 formulation.		
Additional Comments Regarding Test: None		
Toxic/Cytotoxic Effects: None **Genotoxic Effects:** Negative in both males and females. No dose group had a statistically significant increase in micronucleus frequency over concurrent control and there was no evidence of a dose response relationship. There were statistically significant increases in micronucleated PCE in positive control animals treated with cyclophosphamide. **Evidence of Exposure:** Previously obtained toxicokinetics data from a 28-day GLP study with rats indicate that the target cells were exposed to appreciable levels of the test item (Cmax and AUC0-24hr values in plasma after administration of 100 mg/kg/BID to rats were 3.4 µg/mL and 35.3 µg*hr/mL, respectively on Day 28).		

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2.6.7.9.A　In vivo 遺伝毒性試験

試験番号: TT #[redacted]-9018（続き）

被験物質：ベルズチファン

Test Material	Dose (mg/kg/day)	No. of animals/Sex	Males			Females		
			Mean % PCE/TE	Mean % MN-PCE	MN-PCE Frequency (mean ± SD)	Mean % PCE/TE	Mean % MN-PCE	MN-PCE Frequency (mean ± SD)
Negative control	0	5	51.5	0.10	3.8 ± 1.3	52.3	0.09	3.6 ± 0.9
MK-6482	20	5	64.1	0.09	3.6 ± 1.3	47.6	0.09	3.6 ± 1.8
MK-6482	60	5	56.2	0.10	4.0 ± 2.5	44.8	0.13	5.2 ± 3.7
MK-6482	200	5	56.3	0.09	3.6 ± 2.2	46.9	0.10	3.8 ± 0.8
Cyclophosphamide[a]	20	3	33.1	1.75	70.0[b] ± 23.1	N/A	N/A	N/A

BID = Twice daily; GLP = Good Laboratory Practice; N/A = Not applicable; Negative Control = 0.5% (w/v) methylcellulose/ 0.5% (w/v) Tween 80 in ultra pure water; % PCE/TE = Percentage of proportion of polychromatic erythrocytes among total erythrocytes; % MN-PCE = Percentage of micronucleated polychromatic erythrocytes; MN-PCE = Number of micronucleated cells observed per 4000 polychromatic erythrocytes examined; SD = Standard deviation
a = Positive control slides taken from male rats previously dosed with cyclophosphamide at 20 mg/kg (10 mL/kg) given 24 hours prior to sampling
b = Significantly different from negative control value: $p \leq 0.05$ (Wilcoxon)

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2.6.7.10　がん原性試験

MK-6482が長期投与された場合に発がんリスクと関連する可能性を完全には否定できないため、rasH2 Tg マウスを用いた6ヵ月間がん原性試験及びラットを用いた2年間がん原性試験をそれぞれ実施中である。

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2.6.7.11　生殖発生毒性試験：重要な試験以外の試験

被験物質：ベルズチファン

Species/ Breed	Method of Administration (Vehicle/ Formulation)	Dosing Period	Doses (mg/kg/day)	No. per Group	Noteworthy Findings	Study Number
Rabbit (Nonpregnant) / Dutch Belted	Oral (gavage)	8 days	3, 30, 100 and 0, 200 (0, 100 BID)	3F	No mortality, test article related clinical observations or changes in body weight or food consumption. Very slight to marked decreases in reticulocyte counts at ≥3 mg/kg/day resulted in very slight decreases in red cell mass parameters at ≥30 mg/kg/day. Compared to control mean values, mean red blood cell count, hemoglobin concentration and hematocrit values were decreased -7% to -16% at ≥30 mg/kg/day and mean reticulocyte counts were decreased -34% to -82% at ≥3 mg/kg/day.	TT #[redacted]-7003 [4.2.3.5.2.2: TT[redacted]7003]
BID = Twice daily; F = Female						

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2.6.7.11 生殖発生毒性試験：重要な試験以外の試験

試験番号: TT #[redacted]-7003（続き）

被験物質：ベルズチファン

Mean (± SE) Plasma MK-6482 Toxicokinetic Parameters in Rabbits Following Dosing of MK-6482: Study Day 1

Matrix	Dose	Sex	AUC0-12hr (µg*hr/mL)	AUC0-24hr (µg*hr/mL)	AUC0-∞ (µg*hr/mL)	Cmax (µg/mL)	Tmax (hr)
Plasma	3 mg/kg/day	Female	NC	1.35 ± 0.173	NC[a]	0.156 ± 0.0209	1.7 ± 0.33
	30 mg/kg/day		NC	8.59 ± 1.79	9.67 ± 1.78	0.657 ± 0.0995	2.3 ± 0.88
	100 mg/kg/day		NC	11.8 ± 2.25	NC[a]	0.703 ± 0.116	3.3 ± 0.67
	200 mg/kg/day (100 mg/kg/BID)[b]		5.48 ± 0.777	NC	NC[a]	0.592 ± 0.137	4.7 ± 0.67

AUC0-12hr = Area under the plasma concentration-time curve from time 0 to 12 hours; AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-∞ = Area under the curve from time 0 to infinity; BID = Twice daily; Cmax = Maximum plasma concentration; NC = Not Calculated; SE = Standard error; Tmax = Time at maximum plasma concentration

a Insufficient data available for the calculation

b BID = 2nd dose delivered 12 hours after the first dose for a total daily dose of 200 mg/kg

Mean (± SE) Plasma PT3317 Toxicokinetic Parameters in Rabbits Following Dosing of MK-6482: Study Day 1

Matrix	Dose	Sex	AUC0-12hr (µg*hr/mL)	AUC0-24hr (µg*hr/mL)	AUC0-∞ (µg*hr/mL)	Cmax (µg/mL)	Tmax (hr)
Plasma	3 mg/kg/day	Female	NC	3.77 ± 0.277	3.84 ± 0.313	0.465 ± 0.0777	1.7 ± 0.33
	30 mg/kg/day		NC	22.6 ± 2.24	25.9 ± 2.70	1.70 ± 0.0473	3.7 ± 1.5
	100 mg/kg/day		NC	29.4 ± 5.17	NC[a]	1.81 ± 0.395	4.0 ± 0.0
	200 mg/kg/day (100 mg/kg/BID)[b]		17.4 ± 2.89	NC	NC[a]	1.85 ± 0.265	4.7 ± 0.67

AUC0-12hr = Area under the plasma concentration-time curve from time 0 to 12 hours; AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-∞ = Area under the plasma concentration-time curve from time 0 to infinity; BID = Twice daily; Cmax = Maximum plasma concentration; NC = Not Calculated; SE = Standard error; Tmax = Time at maximum plasma concentration

a Insufficient data available for the calculation

b BID = 2nd dose delivered 12 hours after the first dose for a total daily dose of 200 mg/kg

2.6.7.12　生殖発生毒性試験：受胎能及び着床までの初期胚発生に関する試験

受胎能及び初期胚発生に関する試験は実施しなかった。しかしながら、ラットを用いた反復投与毒性試験で認められた明らかな精巣毒性及びそれに伴う精子検査所見から、MK-6482で当該試験を実施した場合、雄ラットの受胎能に影響を及ぼすと考えられる。

2.6.7.13　生殖発生毒性試験：胚・胎児発生に関する試験

2.6.7.13.A　ラットを用いた経口投与胚・胎児発生毒性及びトキシコキネティクス予備試験

被験物質：ベルズチファン

Design similar to ICH 4.1.1? Yes **Species/Strain:** Rat / Crl:CD(SD) **Initial Age:** ~ 10 weeks **Study Start Date:** [redacted] **Day of Confirmed Mating:** GD 0 **Day of Cesarean Section:** GD 21	**Duration of Dosing:** GD 6 through 17 (BID) **Duration of Postdose:** N/A **Method of Administration:** Oral (gavage) **Dose Volume:** 5 mL/kg/dose **Vehicle/Formulation:** 0.5% methylcellulose and 0.5% Tween 80 in deionized water	**Study Number:** TT #[redacted]-7004 **Location in CTD:** [4.2.3.5.2.1: TT[redacted]7004] **GLP Compliance:** No
Special Features: Hematology (GD18), BID dosing (dosing was administered approximately 12 hours ± 15 minutes apart) **No-Observed-Adverse-Effect Level:** N/A		

Daily Dose (mg/kg/day)	0 (Control)	6 (3 BID)	60 (30 BID)	200 (100 BID)
Number of Females Designated for Cesarean Section	8	8	8	8
Number of Females Designated for Toxicokinetic and Hematology Blood Collections	6	6	6	6
Toxicokinetics – GD 7				
AUC0-12hr (µg*hr/mL)	N/A	1.30	7.43	14.1
Cmax (µg/mL)	N/A	0.534	1.30	1.69
Tmax (hr)	N/A	1.00	2.00	2.00

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2.6.7.13.A　胚・胎児発生に関する試験

試験番号: TT #[redacted]-7004（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)	6 (3 BID)	60 (30 BID)	200 (100 BID)
Number of Females Designated for Cesarean Section	8	8	8	8
Noteworthy Findings				
Mortality (No. of Animals)	0	0	0	0
Clinical Signs	-	-	-	-
Maternal Body Weight Gain (%) [a]				
GD 6 to 12	33.4 g	+5.1	[-2.7] [b]	[-10.5] [b]
GD 12 to 18	58.8 g	-3.9	[-47] [b]	[-68] [b]
GD 18 to 21	44.8 g	+17	[-79] [b]	[-96] [b]
GD 6 to 21	138.1	+5.2	[-46] [b]	[-66] [b]
Food Consumption (%) [a]				
GD 14	25.6 g/day	+2.7	-3.1	[-9.4] [c]
GD 20	28.1 g/day	+1.8	-8.2	[-20] [c]
Hematology [d]				
Red Blood Cell Count ($x10^6/\mu L$)	5.99	5.71	[4.75]	[4.88]
Hemoglobin (g/dL)	11.9	11.2	[9.2]	[9.4]
Hematocrit (%)	34.1	31.9	[26.2]	[26.7]
Reticulocytes ($x10^9/L$)	226.6	215.0	185.0	[148.1]

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2.6.7.13.A　胚・胎児発生に関する試験

試験番号: TT #[redacted]-7004（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)	6 (3 BID)	60 (30 BID)	200 (100 BID)
Number of Females Designated for Cesarean Section	8	8	8	8
Caesarean Section and Litter Observations				
Females / Litters				
Mated Females	8	8	8	8
Pregnant Females	7	8	8	8
Not Pregnant Females	1	0	0	0
Whole Litter Resorptions	0	0	[3]	[8]
Live Litters Examined	7	8	5	0
Litter Parameters				
Corpora Lutea/Pregnant Female (mean)	14.6	14.6	14.4	14.5
Implantations/Pregnant Female (mean)	10.7	13.9	12.5	12.5
% Resorptions/Implant (L.M.)	10.2	5.9	[82.7]	[100]
% Dead Fetuses/Implant (L.M.)	0	0	0	0
Live Fetuses/Pregnant Female (mean)	9.9	13.0	[2.3]	[0]
% Peri-implantation Loss (L.M.)[e]	23.6	5.2	12.3	14.6
% Postimplantation Loss (L.M.) [e]	10.2	5.9	[82.7]	[100]
Live Fetal Weight – Female (L.M.) [f]	5.78 g	[-12]	[-46]	N/A
Live Fetal Weight - Male (L.M.) [f]	6.06 g	[-11]	[-42]	N/A
Fetal Sex Ratios (L.M.)	0.50	0.49	0.35	N/A
Placental Morphology	-	-	-	-

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2.6.7.13.A 胚・胎児発生に関する試験

試験番号: TT #[redacted]-7004（続き）

被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)	6 (3 BID)	60 (30 BID)	200 (100 BID)
Number of Females Designated for Cesarean Section	8	8	8	8
Live Fetuses/ Live Litters Examined	69/7	104/8	18/5	N/A
External Fetal Morphology				
Domed Head (Incidence)	0/69	0/104	[4/18] [g]	N/A
Domed Head (% L.M)	0	0	[35] [g]	N/A
Visceral Fetal Morphology	-	-	-	N/A
Skeletal Fetal Morphology				
Rib Malformations - Hypoplastic and/or Absent 13th ribs (% L.M.)	0	[1.0]	[8.3]	N/A
Ossified Sacrocaudal Vertebrae (mean)	10.4	[9.4]	[7.2]	N/A
Sternebrae Incomplete Ossification (% L.M.)	0	0	[35]	N/A

AUC0-24hr = Area under the plasma concentration-time curve from time 0 to 24 hours; BID = Twice daily; Cmax = Maximum plasma concentration; GD = Gestation Day; GLP = Good Laboratory Practice; L.M. = Litter mean; N/A = Not applicable; Tmax = Time at maximum plasma concentration; - = No noteworthy findings; [ ] = Test article-related change based on incidence and/or severity

a Control values are the mean absolute gains. Dose group values are the percent change from concurrent controls.
b Considered secondary to postimplantation loss and/or reduced fetal body weights.
c Considered secondary to postimplantation loss.
d Control and dose group values are mean absolute values.
e % Peri-implantation Loss = [(No. of corpora lutea – no. of implants)/(no. of corpora lutea)] X 100; % Postimplantation Loss = [(No. of Resorptions + no. of dead fetuses)/(no. of implants)] X 100
f Control group values are mean values. Dose group values are the percent change from concurrent controls.
g Considered secondary to developmental delays in the affected fetuses, which were among the smallest fetuses in the dose group.

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2.6.7.14　生殖発生毒性試験：出生前及び出生後の発生並びに母体の機能に関する試験

MK-6482を投与したラットにおいて胚・胎児致死がみられたことから、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は実施しなかった。

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2.6.7.15　生殖発生毒性試験：新生児を用いた試験

MK-6482の小児への投与は予定されていないため、新生児（幼若動物）へ直接投与する非臨床試験は実施しなかった。

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2.6.7.16　局所刺激性試験

被験物質：ベルズチファン

Species/ Strain	**Method of Administration**	**Doses**	**Sex and No. per Group**	**Noteworthy Findings**	**Study Number**
Isolated Bovine Corneas	In vitro	0.75 mL of a 20% MK-6482 Formulation	5 corneas	MK-6482 was classified as a non-irritant.	TT #[redacted]-7811 [4.2.3.6.1: TT[redacted]7811]
MatTek EpiDerm™ tissue samples	In vitro	100 mg	Each treatment (MK-6482: 1, 4, 24 hr, Positive control: 4 , 9 hr) was conducted in duplicate.	MK-6482 was classified as a non-irritant.	TT #[redacted]-7812 [4.2.3.6.2: TT[redacted]7812]

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2.6.7.17　その他の毒性試験

2.6.7.17.A　重要な試験以外の試験

被験物質：ベルズチファン

<table>
<tr><th>Species/
Strain</th><th>Method of
Administration</th><th>Duration
of Dosing</th><th>Doses
(mg/kg)</th><th>Sex and No.
per Group</th><th>Noteworthy Findings</th><th>Study
Number</th></tr>
<tr><td>Mouse/
Crl:CD1(ICR)
(males only)</td><td>Oral (gavage)</td><td>1 day</td><td>60, 200, 600 [a]</td><td>10M</td><td>All animals survived to scheduled study termination and were sacrificed and discarded without necropsy following the last blood sample collection.
Plasma concentrations for MK-6482 are presented below:
<table>
<tr><th>Dose (mg/kg)</th><th>Study Day 1 AUC0-24hr
(µg*hr/mL)</th></tr>
<tr><td>60</td><td>96.6</td></tr>
<tr><td>200</td><td>362</td></tr>
<tr><td>600</td><td>590</td></tr>
</table></td><td>TT #[redacted]-1033
(Non-GLP)
[4.2.3.7.7.2:
TT[redacted]1033]</td></tr>
</table>

(footnotes presented on following page)

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<table>
<tr><th>Species/
Strain</th><th>Method of
Administration</th><th>Duration
of
Dosing</th><th>Doses
(mg/kg)</th><th>Gender and
No. per Group</th><th>Noteworthy Findings</th><th>Study
Number</th></tr>
<tr><td>Rat/Crl:CD(SD) and Crl:WI(Han) (males only)</td><td>Oral (gavage)</td><td>1 day</td><td>100, 300 [b]</td><td>8M Wistar Han, 8M Sprague Dawley</td><td>All animals survived to scheduled termination.
Plasma concentrations for MK-6482 are presented below:
<table>
<tr><th>Vehicle (Strain)</th><th>Dose (mg/kg)</th><th>Study Day 1 AUC0-24hr (µg*hr/mL)</th></tr>
<tr><td>0.5% Tween 80 / 0.5% MC (SD)</td><td rowspan="6">100</td><td>18.1</td></tr>
<tr><td>0.5% Tween 80 / 0.5% MC (WH)</td><td>21.6</td></tr>
<tr><td>10% Tween 80 (SD)</td><td>22.3</td></tr>
<tr><td>10% Tween 80 (WH)</td><td>24.8</td></tr>
<tr><td>0.5% MC / 0.1% HPMCAS-HF / 20 mM TRIS pH 7.2 (SD)</td><td>123</td></tr>
<tr><td>0.5% MC / 0.1% HPMCAS-HF / 20 mM TRIS pH 7.2 (WH)</td><td>135</td></tr>
<tr><td>0.5% Tween 80 / 0.5% MC (SD)</td><td rowspan="6">300</td><td>27.2</td></tr>
<tr><td>0.5% Tween 80 / 0.5% MC (WH)</td><td>22.6</td></tr>
<tr><td>10% Tween 80 (SD)</td><td>18.8</td></tr>
<tr><td>10% Tween 80 (WH)</td><td>26.5</td></tr>
<tr><td>0.5% MC / 0.1% HPMCAS-HF / 20 mM TRIS pH 7.2 (SD)</td><td>429</td></tr>
<tr><td>0.5% MC / 0.1% HPMCAS-HF / 20 mM TRIS pH 7.2 (WH)</td><td>408</td></tr>
</table></td><td>TT #[redacted]-1023
(Non-GLP)
[4.2.3.7.7.3: TT[redacted]1023]</td></tr>
<tr><td colspan="7">AUC0-24hr=Area under the plasma concentration-time curve from time 0 to 24 hours; BID=twice daily; F=female; GLP=Good Laboratory Practice; HPMCAS-HF=Hydroxypropyl methylcellulose acetate succinate-HF; M=male; MC=methylcellulose ; SD=Sprague-Dawley; TK=toxicokinetic; TRIS=tromethamine; WH=Wistar Han
a. [redacted] form was used for each dose level in 0.5% (w/v) methylcellulose/0.1% HPMCAS-HF with 20 mM tromethamine in deionized water, pH 7.2 ± 0.1.
b. [redacted] and [redacted] forms were used for each dose level in 3 different vehicles: 0.5% (w/v) Tween 80/0.5% (w/v) methylcellulose in deionized water, 10% (w/w) Tween 80 in deionized water, and 0.5% (w/v) methylcellulose/0.1% (w/v) HPMCAS-HF with 20 mM tromethamine in deionized water, pH 7.2 ± 0.1.</td></tr>
</table>

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2.6.7.17.B　免疫毒性及び光毒性試験

被験物質：ベルズチファン

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	Sex and No. per Group	Noteworthy Findings	Study Number
Immunotoxicity						
Mouse / CBA/J	Topical, ear	3 days	25% (w/v) MK-6482 in DMF	5F	MK-6482 was not considered a dermal sensitizer.	TT #[redacted]-7813 [4.2.3.7.2.1: TT[redacted]7813]
Phototoxicity						
Rat / Crl:LE (Long-Evans)	Oral (gavage)	3 days	0, 100 BID (0, 200)	5F (Phototoxicity); 3F (Bioanalysis)[a]	There were no cutaneous reactions indicative of phototoxicity.	TT #[redacted]-9011 [4.2.3.7.7.1: TT[redacted]9011]

BID = Twice daily; DMF＝N,N-Dimethylformamide; F = Female; UVR = Ultraviolet radiation
a　Rats assigned to the bioanalysis phase were not anesthetized or exposed to UVR.

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2.6.7.17.C　その他の試験：SD ラットを用いた13週間（1日2回投与）反復経口投与不純物評価試験

被験物質：ベルズチファン

Species/Strain: Rat/Sprague-Dawley **Initial Age:** 8 weeks **Date of First Dose:** [redacted] **Dose Volume:** 5 mL/kg/dose and 2 mL/kg/dose[a]	**Duration of Dosing:** 91 days **Duration of Postdose:** N/A **Method of Administration:** Oral (gavage) **Vehicle/Formulation:** 0.5% (w/v) methylcellulose and 0.5% (w/v) Tween 80 in resverse osmosis water	**Study Number:** TT #[redacted]-9010 **Location in CTD:** [4.2.3.7.6.1: TT[redacted]9010] **GLP Compliance:** Yes [b]
Special Features: BID Dosing **No-Observed-Adverse-Effect Level:** 2 mg/kg/day		

Daily Dose (mg/kgday)	0 (Control)		0.8 (0.4 BID)		2 (1 BID)	
Number of Animals (Main)	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals (TK)	F:3	M:3	F:3	M:3	F:3	M:3
TK – Study Week 13						
AUC0-12hr (µg*hr/mL)	N/A[c]		0.381		1.08	
Cmax (µg/mL)	N/A[c]		0.176		0.385	
Tmax (hr)	N/A[c]		0.500		0.583	
Noteworthy Findings						
Mortality (No. of Animals)	0	0	1[d]	0	0	0
Body Weight	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-

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2.6.7.17.C　その他の試験

試験番号: TT #[redacted]-9010（続き）
被験物質：ベルズチファン

Daily Dose (mg/kg/day)	0 (Control)		0.8 (0.4 BID)		2 (1 BID)	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10
Hematology – Study Week 13						
HCT (L/L)	-	0.4078	-	0.3992	-	[0.3857*][e]
HGB (g/L)	-	140.9	-	136.7	-	[132.5**][e]
RBC Count (x10^{12}/L)	-	8.145	-	8.127	-	[7.614**][e]
Clinical Chemistry	-	-	-	-	-	-
Ophthalmic Examinations	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-
Histopathology	-	-	-	-	-	-

AUC0-12hr=area under the plasma concentration-time curve from time 0 to 12 hours; BID=twice daily; Cmax=maximum plasma concentration; F=female; GLP=Good Laboratory Practice; hr=hour(s); HCT=hematocrit; HGB=hemoglobin; M=male; N/A=not applicable; No.=number; RBC=Red Blood Cell; TK=toxicokinetics; Tmax=time at maximum plasma concentration; (w/v)=weight/volume; [ ]=test article-related change based on incidence and/or severity; - =no noteworthy findings; ANOVA & Dunnett: *=p≤0.05; **=p≤0.01

a. Animals assigned to control and 2 mg/kg/day dose groups were administered doses at a dose volume of 5 mL/kg/dose (10 mL/kg/day), while animals assigned to the 0.8 mg/kg/day dose group were administered MK-6482 at a dose volume of 2 mL/kg/dose (4 mL/kg/day).
b. GLP compliant with the exception of the pathology peer review was conducted on digitized tissue images using commercially available and non-validated equipment and software systems.
c. MK-6482 concentrations in plasma from all control group animals at 1 hr were below the lower limit of quantitation (12.5 ng/mL) of the bioanalystical method.
d. One TK female (0.8 mg/kg/day) was found dead on Study Day 91 approximately 15 minutes following the 2 hr postdose blood collection. This mortality was considered unrelated to MK-6482 and likely the result of blood collection.
e. Clinical pathology changes in hematology parameters were limited to very slight decreases in red cell mass parameters in males at 2 mg/kg/day, which was considered not toxicologically meaningful due to the small magnitude of change.

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