目次

2.6.3　薬理試験概要表
2.6.3.1　薬理試験：一覧表
2.6.3.2　効力を裏付ける試験
2.6.3.3　副次的薬理試験
2.6.3.4　安全性薬理試験
2.6.3.5　薬力学的薬物相互作用試験

2.6.3 薬理試験概要表

2.6.3.1 薬理試験：一覧表

被験物質：ベルズチファン

試験の種類	試験系	投与方法	試験実施施設	試験番号	記載箇所
効力を裏付ける試験（in vitro）					
SPA Displacement Assay: Binding of PT2977 and PT3317 to the Pas-B Domain of Hif-2α	In vitro: Scintillation proximity assay	NA	Peloton Therapeutics, Inc. Dallas, Texas, USA	PD005 (DEV-180)	[4.2.1.1.1: PD005]
PT2977 Inhibition of Hypoxia-Responsive Element (HRE) Dependent Luciferase Activity	In vitro: HRE-dependent luciferase-engineered 786-O ccRCC cells	NA	Peloton Therapeutics, Inc. Dallas, Texas, USA	PD001 (DEV-176)	[4.2.1.1.2: PD001]
PT2977 Inhibition of VEGFa Secretion	In vitro: 786-O ccRCC cells	NA	Peloton Therapeutics, Inc. Dallas, Texas, USA	PD002 (DEV-177)	[4.2.1.1.3: PD002]
PT2977 Inhibition of HIF-2α-dependent Gene Expression and HIF-2α-ARNT Dimerization in 786-O Cells	In vitro: 786-O ccRCC cells	NA	Peloton Therapeutics, Inc. Dallas, Texas, USA	PD003 (DEV-178)	[4.2.1.1.4: PD003]
PT2977 Selective Inhibition of HIF-2α in Hep3B Tumor Cells	In vitro: Hep3B cells	NA	Peloton Therapeutics, Inc. Dallas, Texas, USA	PD004 (DEV-179)	[4.2.1.1.5: PD004]
効力を裏付ける試験（in vivo）					
Evaluation of PT2977 Anti-Tumor Activity in the Renal Cancer 786-O Cell-Line-Derived Xenograft Model	Mouse: renal cancer 786-O-line-derived xenograft tumor model (SCID/Beige mouse)	Oral: 0, 0.3, 1, and 3 mg/kg per dose; BID at 12 hour intervals for 28 days	Peloton Therapeutics, Inc. Dallas, Texas, USA [redacted] USA	PD006 (DEV-181)	[4.2.1.1.6: PD006]
In Vivo Evaluation of Peloton Therapeutics PT2385 and PT2977 in Low Passage [redacted] Models of Human Clear Cell Renal Carcinoma in Immunocompromised Mice	Mouse: [redacted] model CTG-0824 passage 9 (ccRCC xenograft tumor model)	Oral: 0 and 3 mg/kg per dose; BID at 10 to 12 hour intervals for 28 days	[redacted], USA	PD007 (DEV-185)	[4.2.1.1.7: PD007]
Pharmacokinetic and Pharmacodynamic Evaluation of PT2977 Treatment in the Renal Cancer 786-O Xenograft Model	Mouse: renal cancer 786-O-line-derived xenograft tumor model (SCID/Beige mouse)	Oral: 0, 0.3, 1, and 3 mg/kg per dose; BID at 12 hour intervals for 3 days	Peloton Therapeutics, Inc. Dallas, Texas, USA [redacted] USA	PD008 (DEV-182)	[4.2.1.1.8: PD008]

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被験物質：ベルズチファン

試験の種類	試験系	投与方法	試験実施施設	試験番号	記載箇所
Pharmacokinetic and Pharmacodynamic Evaluation of PT2977 Treatment in the Renal Cancer A498 Xenograft Model	Mouse: renal cancer A498 cell line xenograft tumor model (SCID/Beige mouse)	Oral: 0, 0.3, and 1 mg/kg per dose; BID at 12 hour intervals for 3 days	Peloton Therapeutics, Inc. Dallas, Texas, USA [redacted] USA	PD009 (DEV-183)	[4.2.1.1.9: PD009]
Assessment of Antitumor Activity of Treatment with MK-6482 and Lenvatinib in the UMRC2 Tumor Model	Mouse: renal cancer UMRC2 cell line xenograft tumor model (SCID/Beige mouse)	Oral: MK-6482 0, 3 mg/kg per dose; BID at 12 hour intervals for 35 days Lenvatinib 10 mg/kg per dose; QD for 35 days	Merck Research Laboratories, Boston, Massachusetts, USA Merck Research Laboratories, South San Francisco, California, USA	PD011 (BOS-0062)	[4.2.1.1.10: PD011]
Assessment of Antitumor Activity of Treatment with MK-6482 and Cabozantinib in the UMRC2 Tumor Model	Mouse: renal cancer UMRC2 cell line xenograft tumor model (SCID/Beige mouse)	Oral: MK-6482 0, 3 mg/kg per dose; BID at 12 hour intervals for 35 days Cabozantinib 30 mg/kg per dose; QD for 35 days	Merck Research Laboratories, Boston, Massachusetts, USA Merck Research Laboratories, South San Francisco, California, USA	PD012 (BOS-0063)	[4.2.1.1.11: PD012]
In Vivo Evaluation of Peloton Therapeutics Agent, PT2977, in 20 Low Passage [redacted] Models of Human Non-Small Cell Lung Cancer in Immunocompromised Mice	Mouse: 20 [redacted] models (NSCLC xenograft tumor model)	Oral: 0, 10 mg/kg per dose; BID at 12 hour intervals for 60 days	[redacted], USA	PD013 (DEV-195)	[4.2.1.1.12: PD013]
In vivo Efficacy Study of Peloton's Test Article PT2977 in Subcutaneous PDX Model ([redacted]) in Female BALB/c nude mice	Mouse: [redacted] model [redacted] (bladder cancer xenograft tumor model)	Oral: 0, 3, 30 mg/kg per dose; BID at 12 hour intervals for 28 days	[redacted] China	PD016 (DEV-201)	[4.2.1.1.13: PD016]
In vivo Efficacy Study of Peloton's Test Article PT2977 in Subcutaneous PDX Model ([redacted]) in Female BALB/c nude mice	Mouse: [redacted] model [redacted] (bladder cancer xenograft tumor model)	Oral: 0, 3, 30 mg/kg per dose; BID at 12 hour intervals for 28 days	[redacted] China	PD017 (DEV-202)	[4.2.1.1.14: PD017]
In vivo Efficacy Study of Peloton's Test Article PT2977 in Subcutaneous PDX Model ([redacted]) in Female BALB/c nude mice	Mouse: [redacted] model [redacted] (cholangiocarcinoma xenograft tumor model)	Oral: 0, 3, 30 mg/kg per dose; BID at 12 hour intervals for 28 days	[redacted] China	PD014 (DEV-199)	[4.2.1.1.15: PD014]

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被験物質：ベルズチファン

試験の種類	試験系	投与方法	試験実施施設	試験番号	記載箇所
In vivo Efficacy Study of Peloton's Test Article PT2977 in Subcutaneous PDX Model ([redacted]) in Female BALB/c nude mice	Mouse: [redacted] model (cholangiocarcinoma xenograft tumor model)	Oral: 0, 3, 30 mg/kg per dose; BID at 12 hour intervals for 28 days	[redacted] China	PD015 (DEV-200)	[4.2.1.1.16: PD015]
副次的薬理試験					
Off-target Screening: PT2977 Safety Panel Screen	In vitro: FLIPR assays against a panel of 76 receptors, 8 ion channels, 40 kinases, and 2 phosphatases	NA	[redacted], USA	PD010 (DEV-189)	[4.2.1.2.1: PD010]
安全性薬理試験					
hERG Assay: FASTPatch® hERG Assay: Effects of Two Test Articles on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (HEK293)	In vitro: Stably transfected HEK293 cell line	NA	[redacted], USA	TT#[redacted]-7857	[4.2.1.3.1: TT[redacted]7857]
hERG Assay[a]: PT2977: Effect of PT2977 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (DEV-137)	In vitro: Stably transfected HEK293 cell line	NA	[redacted], USA	TT#[redacted]-7824 (DEV-137)	[4.2.1.3.2: TT[redacted]7824]
Cardiovascular function as a component of the 28-day study[a]: Revised Final Report, PT2977: A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Beagle Dogs (DEV-136)	Dog/Beagle	Oral	[redacted], Canada	TT#[redacted]-7821 (DEV-136)	[4.2.3.2.7: TT[redacted]7821]
Cardiovascular function as a component of the 13-week study[a]: Revised Final Report, PT2977: A 13-Week Oral Gavage Toxicity Study Followed by a 28-Day Recovery Periods in Beagle Dogs (DEV-206)	Dog/Beagle	Oral	[redacted] Canada	TT#[redacted]-7808 (DEV-206)	[4.2.3.2.8: TT[redacted]7808]
CNS/Respiratory function as a component of the 28-day study[a]: Revised Final Report, PT2977: A 28-Day Oral Gavage Toxicity Study Followed by a 28-Day and a 90-Day Recovery Periods in Sprague-Dawley Rats (DEV-135)	Rat	Oral: BID for 28 days	[redacted], Canada	TT#[redacted]-7820 (DEV-135)	[4.2.3.2.4: TT[redacted]7820]

ARNT=aryl hydrocarbon receptor nuclear translocator; BID=twice daily; ccRCC=clear cell renal cell carcinoma; FLIPR=fluorescence imaging plate reader; GLP=Good Laboratory Practice; HEK=human embryonic kidney cells; hERG=human ether-á-go-go related gene; HIF-2α=hypoxia-inducible factor-2 alpha; HRE=hypoxia-responsive element; mg/kg=milligram per kilogram; NA=not applicable; NSCLC=non-small cell lung cancer; PAS=Per-ARNT-Sim; PDX=patient-derived xenograft; QD=once daily; SCID=severe combined immunodeficiency; SPA=scintillation proximity assay; VEGFa=vascular endothelial growth factor A protein; USA=United States of America.
Note: MK-6482 is also known as PT2977.
[a] Report contains a GLP compliance statement.

2.6.3.2 効力を裏付ける試験

MK-6482の効力を裏付ける試験の詳細を[2.6.2.2 項]に、その概要を[2.6.3.1 項]に記載した。

2.6.3.3　副次的薬理試験

MK-6482の副次的薬理試験の詳細を[2.6.2.3 項]に、その概要を[2.6.3.1 項]に記載した。

2.6.3.4　安全性薬理試験

被験物質：ベルズチファン

試験系／評価項目	動物種／系統	投与方法	用量／測定濃度	性及び動物数	結果の概要	GLP適用	試験番号
hERG Assay	HEK293	In vitro	1, 10 µM	NA	Mean % hERG inhibition at 1 µM was 3.0% and at 10 µM was 7.6%	No	TT#[redacted]-7857 [4.2.1.3.1: TT[redacted]7857]
hERG Assay	HEK293	In vitro	0, 10, 50 µM	NA	At near-physiological temperature (33°C to 35°C), MK-6482 inhibited hERG current by (Mean ± SEM) 6.7 ± 2.0% at 10 µM and 16.3 ± 0.4% at 50 µM. The IC_{50} for the inhibitory effect was not calculated but was estimated to be greater than 50 µM.	Yes	TT#[redacted]7824 (DEV-137) [4.2.1.3.2: TT[redacted]7824]
Cardiovascular Function	Dog/ Beagle	Oral (gavage)	0, 1, 5, 30 mg/kg/day	7F, 7M	No test article-related effects on the electrocardiography and blood pressure measurements	Yes	TT#[redacted]-7821 (DEV-136) [4.2.3.2.7: TT[redacted]7821]
Cardiovascular Function	Dog/ Beagle	Oral (gavage)	0, 1, 5, 30 mg/kg/day	6F, 6M	No test article-related effects on the electrocardiography and blood pressure measurements	Yes	TT#[redacted]-7808 (DEV-206) [4.2.3.2.8: TT[redacted]7808]
Respiratory Function	Rat / Crl:CD(SD) IGS	Oral (gavage)	0, 6, 20, 200 mg/kg/day	8F	No test article-related effects on respiratory function.	Yes	TT#[redacted]-7820 (DEV-135) [4.2.3.2.4: TT[redacted]7820]
Neurobehavioral Function				10M	No test article-related quantitative or qualitative FOB changes.		
F=female; FOB = Functional Observational Battery; GLP=Good Laboratory Practice; HEK293=human embryonic kidney cells; hERG=human ether-à-go-go related gene; IC_{50}= half-maximal inhibitory concentration; M=male; mg/kg/day=milligram/kilogram/day; µM=micromolar; NA=not applicable							

2.6.3.5　薬力学的薬物相互作用試験

MK-6482はラット及びイヌの心血管系及び呼吸系、並びにラットでの一般症状及び行動に影響を及ぼさなかったため、薬力学的薬物相互作用試験を実施しなかった。