アキャルックス点滴静注 250 mg

第 2 部（モジュール 2）CTD の概要（サマリー）

2.6 非臨床試験の概要文及び概要表

2.6.3 薬理試験概要表

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2.6.3 薬理試験の概要表

1. 薬理試験：一覧表

2.6.3 薬理試験の概要表

Overview			Test Article: RM-1929		
Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location
効力を裏付ける試験					
ELISA binding assay human EGFR	Recombinant human EGFR (extracellular domain)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P001	4.2.1.1-1
Microscopic observation of PIT killing with RM-1929	A431 cells (human epidermoid carcinoma) NIH/3T3 mouse embryo fibroblast cell line	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P002	4.2.1.1-2
RM-1929 interaction with EGFR in cells	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P003	4.2.1.1-3
PIT therapeutic window: RM-1929 bound and unbound to cellular EGFR	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P004	4.2.1.1-4
RM-1929 mediated PIT: dose dependence on light fluence and power	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P005	4.2.1.1-5
RM-1929 mediated PIT: dose dependence on light energy and drug concentration	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P006	4.2.1.1-6
RM-1929 mediated PIT: dependence on antigen levels and cell killing of Head and Neck cancer cells	A431 cells (human epidermoid carcinoma), BxPC3 (human pancreas adenocarcinoma) FaDu (human hypopharyngeal tumor cells), SCC-15 (human squamous cell carcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P007	4.2.1.1-7
RM-1929 mediated PIT: dependence on dye:antibody ratio (DAR)	A431 cells (human epidermoid carcinoma), BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P008	4.2.1.1-8
Overview			Test Article: RM-1929		

2.6.3 薬理試験の概要表

Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location
RM-1929 binding Kd to human and monkey EGFR	Recombinant human and Rhesus monkey EGFR (extracellular domain)	*In vitro*	Aragen Biosciences, Inc	SR-RM1929-P009	4.2.1.1-9
RM-1929 activation of ADCC activity	A431 cells (human epidermoid carcinoma)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P010	4.2.1.1-10
RM-1929 inhibition of EGFR mediated cell proliferation	FaDu (human hypopharyngeal tumor cells)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P011	4.2.1.1-11
RM-1929 inhibition of EGFR signaling	A431 cells (human epidermoid carcinoma), FaDu (human hypopharyngeal tumor cells)	*In vitro*	Aspyrian Therapeutics, Inc.	SR-RM1929-P012	4.2.1.1-12
RM-1929 mediated PIT: anticancer activity in mouse Xenografts	*In vivo*, orthotopic, pancreas, mouse Xenograft BxPC3 (human pancreas adenocarcinoma)	IV injection as solution in PBS	Anticancer, Inc.	SR-RM1929-P013	4.2.1.1-13
RM-1929 mediated PIT as adjuvant to surgery in mouse Xenografts	*In vivo*, orthotopic, pancreas, mouse Xenograft BxPC3 (human pancreas adenocarcinoma)	IV injection as solution in PBS	Anticancer, Inc.	SR-RM1929-P014	4.2.1.1-14
RM-1929 mediated PIT utilizing the clinical laser (ML7710-690-ASP): anticancer activity in mouse Xenografts	*In vivo*, subcutaneous, pancreas, mouse Xenograft BxPC3 (human pancreas adenocarcinoma)	IV injection as solution in PBS	Anticancer, Inc.	SR-RM1929-P015	4.2.1.1-15
Evaluation of 690 nm light penetration through “phantom” tissue	Phantom Tissues	NA	Aspyrian Therapeutics, Inc.	SR-RM1929-P016	4.2.1.1-16
副次的薬理試験：実施していない					
安全性薬理試験					
Single-dose toxicology study with safety pharmacology endpoints incorporated	Cynomolgus Monkey GLP Toxicology	2-hour intravenous infusion	Xenometrics, LLC	11286	4.2.3.1-1
薬力学的薬物相互作用試験：実施していない					

2. 効力を裏付ける試験

				Test Article: RM-1929		
Type of Study	Species/Strain	Method of Admin.	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
ELISA binding assay human EGFR	Human recombinant EGFR	*In vitro*	Multiple, dose escalation	NA	Binding properties of RM-1929 on human EGFR by ELISA are virtually identical to the native antibody Cetuximab.	SR-RM1929-P001
Microscopic observation of PIT killing with RM-1929	A431 cells (human epidermoid carcinoma) NIH/3T3 mouse embryo fibroblast cell line	*In vitro*	10 µg/mL of RM-1929 27 J/cm^2 of 690 nm	NA	RM-1929 mediated PIT cell killing is highly specific. Only cells expressing the EGFR antigen bind to RM-1929 and undergo cell death upon PIT. PIT causes membrane integrity destruction within 1.5 h.	SR-RM1929-P002
RM-1929 interaction with EGFR in cells	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	1 µg/mL of RM-1929 16 J/cm^2 of 690 nm	NA	Binding of RM-1929 to cell surface EGFR is required for PIT induced killing of cancer cells.	SR-RM1929-P003
PIT therapeutic window: RM-1929 bound and unbound to cellular EGFR	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Multiple, dose escalation 16 J/cm^2 and 32 J/cm^2 of 690 nm	NA	More than four logs concentration difference between cell surface antigen bound vs unbound RM-1929 to induce cell killing.	SR-RM1929-P004
RM-1929 mediated PIT: dose dependence on light fluence and power	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	10 µg/mL of RM-1929 690 nm dose escalation with multiple fluences	NA	PIT induced cell killing is light energy dose dependent (J/cm^2), but is not dependent on light power density (mW/cm^2).	SR-RM1929-P005
RM-1929 mediated PIT: dose dependence on light energy and drug concentration	BxPC3 (human pancreas adenocarcinoma)	*In vitro*	Multiple, dose escalation 8 J/cm^2 and 32 J/cm^2 of 690 nm	NA	The light fluence needed to induce RM-1929 mediated PIT-cell killing varies with antibody concentration. Light fluence and antibody concentration needed to induce RM-1929 mediated PIT cell killing are interdependent.	SR-RM1929-P006

2.6.3 薬理試験の概要表

				Test Article: RM-1929		
Type of Study	Species/Strain	Method of Admin.	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
RM-1929 mediated PIT: dependence on antigen levels and cell killing of head and neck cancer cells	A431 cells (human epidermoid carcinoma) BxPC3 (human pancreas adenocarcinoma) FaDu (human hypopharyngeal tumor cells) SCC-15 (human squamous cell carcinoma)	*In vitro*	10 µg/mL of RM-1929 690 nm dose escalation with multiple fluences	NA	The light fluence needed to induce RM-1929 mediated PIT-killing is dependent on antigen expression levels. More light sensitivity when antigen levels are higher. RM-1929 can induce complete killing of human head and neck cancer cells.	SR-RM1929-P007
RM-1929 mediated PIT: dependence on dye:antibody ratio (DAR)	A431 cells (human epidermoid carcinoma) BxPC3 (human pancreas adenocarcinoma)	*In vitro*	10 µg/mL of RM-1929 690 nm dose escalation with multiple fluences	NA	Saturation of RM-1929 PIT-mediated potency is reached for a DAR between 2 and 3 dyes per antibody. Increasing dye:Ab ratios does not enhance activity. Lower DAR may reduce sensitivity to light.	SR-RM1929-P008
RM-1929 binding Kd to human and monkey EGFR	Recombinant human and Rhesus monkey EGFR	*In vitro*	Multiple, dose escalation	NA	Dye conjugation doesn't disrupt EGFR affinity for antigen binding of the antibody. Affinities (K_d) of RM-1929 to bind human or Rhesus monkey EGFR are virtually identical between batches and very comparable to Cetuximab.	SR-RM1929-P009

RM-1929 activation of ADCC activity	A431 cells (human epidermoid carcinoma)	*In vitro*	Multiple, dose escalation	NA	RM-1929 presents ADCC activity with potency comparable to Cetuximab but lower maximal response.	SR-RM1929-P010
				Test Article: RM-1929		
Type of Study	Species/Strain	Method of Admin.	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
RM-1929 inhibition of EGFR mediated cell proliferation	FaDu (human hypopharyngeal tumor cells)	*In vitro*	Multiple, dose escalation	NA	RM-1929 inhibits EGFR mediated cell proliferation of cancer cells with potency and efficacy virtually identical to Cetuximab.	SR-RM1929-P011
RM-1929 inhibition of EGFR signaling	A431 cells (human epidermoid carcinoma) FaDu (human hypopharyngeal tumor cells)	*In vitro*	Multiple, dose escalation	NA	RM-1929 inhibits EGFR receptor signaling with potency and efficacy virtually identical to Cetuximab.	SR-RM1929-P012
RM-1929 mediated PIT: anticancer activity in mouse Xenografts	*In vivo*, orthotopic, pancreas, mouse Xenograft nu/nu and the strain is BALB/c BxPC3 (human pancreas adenocarcinoma)	IV bolus, tail injection, RM-1929 in PBS solution Frontal light illumina-tion with 690 nm	100 µg per mice of RM-1929 250 J/cm^2 of 690 nm light	Males N = 5	One PIT treatment using RM-1929 causes significant tumor killing and reduces tumor progression.	SR-RM1929-P013

				Test Article: RM-1929		
Type of Study	Species/Strain	Method of Admin.	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
RM-1929 mediated PIT as adjuvant to surgery in mouse Xenografts	*In vivo*, orthotopic, pancreas, mouse Xenograft nu/nu and the strain is BALB/c BxPC3 (human pancreas adenocarcinoma)	IV bolus, tail injection, RM-1929 in PBS solution Frontal light illumina-tion with 690 nm	50 µg per mice of RM-1929 250 J/cm^2 of 690 nm light	Males N = 10	One PIT treatment using RM-1929 as adjuvant to surgical resection of the tumor reduces dramatically the number of tumor relapses after surgery, indicating that RM-1929 mediated PIT eradicated residual cancer cells remaining after surgery.	SR-RM1929-P014
RM-1929 mediated PIT utilizing the clinical laser (ML7710-690-ASP): anticancer activity in mouse Xenografts	*In vivo*, subcutaneous, pancreas, mouse Xenograft nu/nu and the strain is BxPC3 (human pancreas adenocarcinoma)	IV bolus, RM-1929 in PBS solution Cylindri-cal light illumina-tion with 690 nm	100 µg per mice of RM-1929 100 J/cm, 300 J/cm of 690 nm light	Males N = 3-4	One PIT treatment using RM-1929 elicits robust tumor destruction within 3 days post treatment. Histology analysis shows extensive tumor destruction with broad necrosis and high specificity so that surrounding non-cancerous tissue (skin and muscle) are not affected upon PIT treatment.	SR-RM1929-P015
Evaluation of 690 nm light penetration through “phantom” tissue	NA	NA	NA	NA	690 nm can achieve about 6-8% linear light transmission through 1 cm of phantom tissue samples.	SR-RM1929-P016

3. 副次的薬理試験

RM-1929 の副次的薬理試験は実施していない。

4. 安全性薬理試験

				Test Article: RM-1929			
Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses	Gender and No. per Group	Noteworthy Findings	GLP	Study Number
Single-dose toxicology study with safety pharmacology endpoints incorporated (visual respiratory rate, electrocardiograms, and neurobehavioral changes (e.g., cageside observations of activity, behavior, etc.)	Cynomolgus Monkey	2-hour intravenous infusion	Phosphate buffered saline (vehicle control) or RM-1929 at 40 or 80 mg/kg or Cetuximab at 16 mg/kg	3 males/3 females per group Phosphate buffered saline (vehicle control) or RM-1929 at 40 or 80 mg/kg or Cetuximab at 16 mg/kg terminated on Day 15 (main study); 2 males/2 females control and 80 mg/kg terminated on Day 28 (recovery)	None - no evidence of a treatment-related effect on respiratory rate, electrocardiograms or neurobehavioral function/activity (e.g., cageside observations of activity, behavior, etc.)	Yes	11286

5. 薬力学的薬物相互作用試験

RM-1929 の薬力学的薬物相互作用試験は実施していない。