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

2.6.7 毒性試験概要表

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2.6.7　毒性試験の概要表

1.　毒性試験：一覧表

					Test Article: RM-1929		
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dose**	**Dose (mg/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Single-Dose Toxicity	Rat / Sprague Dawley	Intravenous	Single dose bolus	0, 2.6, 7.8, and 26 mg/kg IR 700-CO_2	No	Explora Biolabs	EB10-039-016C /MC13B-0228
	Rat / Sprague Dawley	Intravenous	Single dose bolus	0 (PBS), 10, 30, 100 mg/kg IR 700-CO_2	Yes	Charles River Laboratories	20065734/ASPY-0927A
	Monkey / Cynomolgus	Intravenous	Single dose infusion over 1.8 hrs	0, 32 mg/kg cetuximab 32 (35) mg/kg[1] RM-1929[2]	No	Xenometrics	11108
	Monkey / Cynomolgus	Intravenous	Single dose infusion over 2 hrs	0 (PBS), 16 mg/kg cetuximab 40, 80 mg/kg RM-1929	Yes	Xenometrics	11286
Repeat-Dose Toxicity: No studies were conducted.							

IR 700-CO_2 = Carboxylate IR 700 which is the free form of the dye.
[1] Value in parentheses indicates the actual dose of RM-1929 administered based on the dose formulation analysis completed after dosing.
[2] To model the potential presence of free dye in circulation, 4.1% of free dye (as IR 700-CO_2) was added to the final dose of RM-1929 just prior to the injection.

2.6.7 毒性試験の概要表

					Test Article: IR 700-CO_2		
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dose**	**Dose (mg/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Genotoxicity: Ames Bacterial Reverse Mutation Assay	Four tester strains of *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and 1 *Escherichia coli strain* (WP2 *uvrA*) Range-finding assay, strains TA100 and WP2 *uvrA*: 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate Mutagenicity assay without light activation: 100, 250, 500, 1000, 2500, and 5000 µg/plate Mutagenicity assay with light activation: 2.5, 5.0, 10, 25, 50, 100, 250, and 500 µg/plate	N/A	N/A	Range-finding assay, strains TA100 and WP2 *uvrA*: 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate Mutagenicity assay without light activation: 100, 250, 500, 1000, 2500, and 5000 µg/plate Mutagenicity assay with light activation: 2.5, 5.0, 10, 25, 50, 100, 250, and 500 µg/plate	Yes	Charles River Laboratories	01302001

2.6.7 毒性試験の概要表

					Test Article: IR 700-CO_2		
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dose**	**Dose (mg/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Genotoxicity: Micronucleus Assay	Cultured Human Peripheral Blood Lymphocytes	N/A	N/A	120, 250 and 500 µg/mL	Yes	Charles River Laboratories	01302002
Genotoxicity: *In Vivo* Micronucleus Assay	Rat / Sprague Dawley	Intravenous	Single dose bolus, two consecutive days	20, 40 and 80 mg/kg	Yes	Charles River Laboratories	01302003
Carcinogenicity: No studies were conducted.							
Reproductive and Developmental Toxicity: No studies were conducted.							
Local Tolerance: No studies were conducted.							
					Test Article: ASP-1929 + Omicron Laserage; PIT690.4-2500		
Other Toxicity Studies: Skin Phototoxicity	Monkey / Cynomolgus	Intravenous	Single dose infusion over 2 hrs	40	Yes	Charles River Laboratories (formerly Citoxlab)	1119-5883

2.6.7 毒性試験の概要表

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

Section 2.6.6.2 参照

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

Section 2.6.6.2 参照

4. 毒性試験：被験物質（バッチ毎）一覧

				Test Article: RM-1929				
Batch No.	Purity (%)			Specified Impurity (%)			Study Number	Type of Study
	Purity by SEC-HPLC (A_{690})	Purity by SDS-PAGE, Reduced, Coomassie	Purity by SDS-PAGE, Non-reduced, Coomassie	High molecular weight antibody fragments	Low molecular weight antibody fragments	Free dye		
PROPOSED SPECIFICATION[1]	≥ 90.0 %	≥ 90.0 %	≥ 90.0 %	≤ 5.0 %	≤ 5.0 %	≤ 7.0 %		
[redacted]	98.6	78.6	87.2	1.3	0	4.1	11108	Single-dose toxicity
[redacted]	97.8	99.7	99	0.45	0	1.7	11286	Single-dose toxicity
				Test Article: ASP-1929				
ASP-1929 lot [redacted]	97.0	97.2	98.3	3.0	<LOQ	0.2	1119-5883	Single-dose toxicity

[1] Proposed specification for final Drug Product for clinical trials.

5. 単回投与毒性試験：重要な試験以外の試験

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat / Sprague Dawley	Intravenous bolus injection	0, 2.6, 7.8, 26 mg/kg IR 700-CO_2	Control: 2M Treatments: 6M	Not observed	IR 700-CO_2 was well tolerated at all dose tested. No clinical signs of toxicity observed or unscheduled deaths. No skin color changes in any of the low-dose animals (2.6 mg/kg). Within 10 minutes after the completion of dosing, all rats in the mid- and high- dose groups (7.8 and 26 mg/kg, respectively) temporarily exhibited moderate to severe blue-greenish/gray coloring of various areas of exposed skin, respectively. Since the skin color for all animals returned to normal (pre-study), the transient blue-green coloration of the skin was not considered adverse. A transient green coloration of the urine and feces was observed in all IR 700-CO_2-treated animals within a few hours after dosing. Coloration of the urine and feces returned to normal by one day after dosing; therefore, not considered adverse. Minimal to mild microscopic findings were observed in the kidney and the live in control and all IR 700-CO_2 dose groups. The renal changes included renal tubule degeneration and collecting duct casts, and the liver findings included hydropic degeneration of hepatocytes and biliary hyperplasia. The microscopic changes observed in the kidney and liver, however, were consistent with those typically observed in the young rat or associated with an indwelling-catheter, and therefore, these changes were not attributed to treatment with IR 700-CO_2.	EB10-039-016C
Monkey / Cynomolgus	Intravenous infusion over 1.8 hr	0, 32 mg/kg cetuximab	2M	Not observed	No unscheduled deaths. No treatment-related effects on clinical signs/neurological evaluations, food consumption,	11108

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
		32 (35)[1] of RM-1929[2]			body weights, clinical pathology, organ weights or histopathology. A slight green color of the urine observed in the RM-1929-treated animals throughout dose administration had changed back to normal 3 hrs after completion of the infusion; therefore, not considered adverse. With the exception of the slightly green urine, there were no effects associated with RM-1929 observed in comparison to animals administered cetuximab alone.	

IR 700-CO_2 = Carboxylate IR 700 which is the free form of the dye.

[1] Value in parentheses indicates the actual dose of RM-1929 administered based on the dose formulation analysis completed after dosing.

[2] To model the potential presence of free dye in circulation, 4.1% of free dye (as IR 700-CO_2) was added to the final dose of RM-1929 just prior to the injection.

6. 単回投与毒性試験：重要な試験

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat / Sprague Dawley	Intravenous bolus injection	0, 10, 100 mg/kg IR 700-CO_2	10M/10F	30 mg/kg	Animals died (n=2) or euthanized (n=1) in moribund condition in the high dose group; histopathology could not determine cause of death or moribundity for these animals. Treatment-related clinical signs were observed in all dose groups, which included pale, blue, and/or green skin and blue urine; the blue coloration of the skin and urine partially or completely recovered by Day 15; the skin coloration had no microscopic correlates; therefore, not considered adverse. Animals in the high dose group exhibited decreased activity/uncoordinated movement, which completely recovered by Day 15. Clinical pathology changes were limited to increases in ALT and AST in the high dose group on Day 3, which recovered by Day 15. No evidence of a treatment-related effect on the skin was noted in any animal in clinical observations or macroscopically or microscopically. Histopathological changes were observed only in the high dose males and females, which consisted of mild to marked Harderian gland inflammation and necrosis, minimal to mild retrobulbar muscle inflammation and degeneration, minimal to mild brown adipose tissue degeneration, moderate pulmonary vein inflammation and minimal to mild myocardial inflammation and degeneration; these histopathologic changes were recovered by Day 15, with observations being limited to Harderian gland regeneration.	20065734 /ASPY-0927A

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Monkey / Cynomolgus [1, 2]	Intravenous infusion over 1.8 hr	0 (PBS), 16 mg/kg cetuximab 40, 80 mg/kg RM-1929	Toxicology animals: 2 males/2 females in 40 mg/kg group terminated on Day 3; 3 males/3 females per group terminated on Day 15; 2 males/2 females in control and 80 mg/kg groups terminated on Day 28.	80 mg/kg	No treatment-related changes were observed for any of the in-life parameters assessed. No treatment-related gross lesions observed at necropsy or changes in terminal body weight. No treatment-related effects on electrocardiograms, respiratory rate, or behavior/activity levels. A difference in absolute and relative heart weights was observed in females administered 80 mg/kg terminated on Day 15 (higher than vehicle control). A difference in absolute and relative heart weights was also observed in cetuximab-treated females (higher than vehicle control), but not cetuximab-treated males. This difference in heart weight did not have any correlative histopathological findings and was not observed in low dose animals, high-dose males, or recovery animals; thus, this difference in relative and absolute heart weights were considered to be likely incidental rather than directly related to treatment. There were no other changes in any other organ weights considered related to RM-1929 or cetuximab. No microscopic changes considered related to RM-1929 or cetuximab were observed, and there was no evidence of toxicity in dermal observations (clinical, macroscopic, or microscopic). Note: since no treatment-relate microscopic changes were noted in the 80 mg/kg RM-1929 group, tissues from the 40 mg/kg RM-1929 or recovery animals were not examined.	11286

ALT = alanine transaminase; AST = aspartate transaminase; IR 700-CO_2 = Carboxylate IR 700 which is the free form of the dye; PBS = phosphate buffered saline; TK = Toxicokinetic; Eos = Eosinophils; Neu = Neutrophils; Bas = Basophils; Lymph = Lymphocytes; LUC = Large Unclassified Cells; Mono = Monocytes (relative); Glob = Globulin, calculated; A/G = Albumin/Globulin Ratio

[1] Biodistribution of RM-1929 was also evaluated in this study; See Module 2, Section 2.6.5.

[2] Safety pharmacology parameters were incorporated into this study (electrocardiograms, respiratory rate, and neurobehavioral based on cageside observations); See Module 2, Section 2.6.3.

7. 反復投与毒性試験

RM-1929 の反復投与毒性試験は実施していない。

8. *In vitro* 遺伝毒性試験

Type of Study	Species/ Strain	Method of Administration	Duration of Dosing	Doses	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Genotoxicity: Ames Bacterial Reverse Mutation Assay	Four tester strains of *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and 1 *Escherichia coli* strain (WP2 *uvrA*) Range-finding assay, strains TA100 and WP2 *uvrA*: 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate Mutagenicity assay without light activation:	N/A	N/A	Range-finding assay, strains TA100 and WP2 *uvrA*: 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate Mutagenicity assay without light activation: 100, 250, 500, 1000, 2500, and 5000 µg/plate Mutagenicity assay with light activation: 2.5, 5.0, 10, 25, 50, 100, 250, and 500 µg/plate	N/A	The data of this study support the conclusion that IR700-CO_2 is negative for mutagenic activity in the *Salmonella* strains TA1537, TA98, TA100, and TA1535 and in the *E. coli* strain WP2 *uvrA*, with and without metabolic activation, under the conditions of this assay.	01302001

Type of Study	Species/ Strain	Method of Administration	Duration of Dosing	Doses	NOAEL (mg/kg)	Noteworthy Findings	Study Number
	100, 250, 500, 1000, 2500, and 5000 µg/plate						
Genotoxicity: Micronucleus Assay	Cultured Human Peripheral Blood Lymphocytes	N/A	N/A	125, 250 and 500 µg/mL	N/A	IR 700-CO_2 was considered negative for inducing micronuclei in human peripheral blood lymphocytes with and without metabolic activation under the conditions of the test system used for this study.	01302002

IR 700-CO_2 = Carboxylate IR 700 which is the free form of the dye

9. *In vivo* 遺伝毒性試験

Type of Study	Species / Strain	Method of Administration	Duration of Dosing	Doses	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Genotoxicity: *In Vivo* Micronucleus Assay	Rat / Sprague Dawley	Once daily intravenous	Single dose bolus, two consecutive days	20, 40 and 80 mg/kg/day of IR 700-CO_2	N/A	The data of this study support the conclusion that administration of IR 700 by once daily intravenous (slow bolus) injection to Sprague Dawley rats at dose levels of 20, 40, and 80 mg/kg/day for 2 consecutive days was negative for clastogenic activity and/or disruption of the mitotic apparatus under the conditions of this assay, and resulted in a negative response for induction of bone marrow micronuclei at all dose levels	01302003

IR 700-CO_2 = Carboxylate IR 700 which is the free form of the dye

10. がん原性試験

RM-1929 のがん原性試験は実施していない。

11. 生殖発生毒性試験

RM-1929 の生殖発生毒性試験は実施していない。

12. 新生児を用いた試験

RM-1929 の幼若動物試験は実施していない。

13. 局所刺激性試験

RM-1029 の局所刺激性試験は実施していない。

14. その他の毒性試験：光毒性試験

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Monkey / Cynomolgus	Intravenous infusion over 2 hr	40 mg/kg ASP-1929	4M	N/A	There were no test article-related effects on body weight, food consumption, ophthalmology exams, urinalysis parameters, or coagulation parameters. Minimal to moderate non-adverse changes in hematology (Eos, Neu, Bas, Lymph, LUC, and Mono counts) and clinical chemistry (AST, CK, Glob, and A/G) parameters were noted with most relatively close to or within historical control ranges. Test article-related clinical observations included slight edema and erythema at the dose site on all animals up to Days 13 and 8, respectively. No gross lesions were noted at either of the skin biopsy sites (light-exposed and non light-exposed). ASP-1929-related microscopic findings at the light-exposed skin biopsy site included minimal single cell necrosis of the epidermis and/or hair follicle epithelium, with mild epidermal hyperplasia in one monkey that was considered to likely correspond with a scab noted in-life at the light-exposed biopsy site.	1119-5883