2 SYNOPSIS

Company: Crucell Holland B.V. **Name of finished product:** CL184 **Name of active ingredient:** CR57/CR4098	**Summary table referring to Module 5 of the dossier** **Volume:** **Page:**	*(For national authority use only)*

Title:
A single-blind, randomized, monocentric Phase II trial to explore[1] the safety and rabies-neutralizing activity of combined administration of CL184 and rabies vaccine versus human rabies immune globulin plus rabies vaccine in simulated rabies post-exposure prophylaxis in children and adolescents

Study code: RAB-M-A004

Clinical phase: Phase II

Start date: 12-May-2008 (first subject first visit)

End date: 20-Oct-2008 (last subject last visit)

Main investigator(s) and center(s):
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Publication (reference):
Not applicable

Objectives:
Primary:

To explore[1] the safety and local tolerability of CL184 in combination with rabies vaccine as compared with human rabies immune globulin (HRIG) in combination with rabies vaccine in children and adolescents.

Secondary:

To explore[1] the rabies virus neutralizing activity (RVNA) after administration of CL184 and rabies vaccine, compared with HRIG and rabies vaccine.

Methods:
The first part of the study included only adolescents (aged ≥12 to <18 years); the second part included children (aged ≥5 to <12 years) and was only started after Day 14 safety data for all adolescent subjects had been reviewed by the Independent Safety Monitoring Committee and had raised no concern.[2]

After screening, eligible subjects were randomized 2:1 (stratified according to gender) to receive either CL184 and purified vero cell rabies vaccine (PVRV) or HRIG and PVRV.[2] Baseline assessments, administration of CL184 or HRIG (investigational medicinal product [IMP]) and administration of the 1st dose of PVRV took place at Day 0. Subjects were closely observed for at least 1 hour after dosing. A Subject Diary to record solicited local (reactions at the IMP injection site) and systemic (body temperature) adverse events (AEs) for 4 days were provided.

[1] Changed from "evaluate" to "explore" in Version 2.0 of the Study Protocol.
[2] Two-step procedure, stratification according to gender, and different type of vaccine (PVRV instead of purified chick embryo cell culture rabies vaccine [PCECV]) were specified in Version 3.0 of the Study Protocol.

Further single doses of PVRV were administered on Days 3, 7, 14, and 28; a final visit took place on Day 42.

Unsolicited AEs were recorded on every visit from Day 0 onwards. Blood samples for determination of human-anti-human antibodies (HAHA)[3] were taken on Days 0 and 42; blood samples for routine safety laboratory were collected on Days 0 and 14. Blood samples for RVNA (detected with the rapid fluorescent focus inhibition test [RFFIT]) were taken on Days 0 (pre-dose), 3, 14, and 42.

Number of subjects total and for each treatment (planned and analyzed):
As planned, 48 subjects were included in the present study. The actual numbers for each population and treatment group are shown below:

Group		Randomized	Safety	ITT	ATP
A (CL184+PVRV)	All ages	33	33	33	32
	Adolescents (≥12 to <18 y)	16	16	16	16
	Children (≥5 to <12 y)	17	17	17	16
B (HRIG+PVRV)	All ages	15	15	15	14
	Adolescents (≥12 to <18 y)	8	8	8	8
	Children (≥5 to <12 y)	7	7	7	6

ATP = according-to-protocol; HRIG = human rabies immune globulin (Imogam Rabies-HT); ITT = intention-to-treat; purified PVRV = vero cell rabies vaccine (Verorab)

Diagnosis and main criteria for inclusion and exclusion:
Male or female subject aged ≥5 to <18 years were included if they were free of obvious health-problems as established by medical history, physical examination, and clinical judgment of the investigator, if they were living, studying, or working close to the study referral site, and if the parent or legal representative signed the written informed consent; in addition an assent form had to be signed by subjects ≥12 years.

The main exclusion criteria were prior history of rabies exposure or immunization, acute infection or disease within the last 2 weeks, pregnancy or lactation, history and/or family history of immunodeficiency or auto-immune disease, and history of known or suspected anaphylaxis or hypersensitivity reaction.

Test and reference product(s) (dose, route of administration, batch number):
Test IMP: CL184 (a 1:1 equipotent mixture of CR57 and CR4098), 500 IU/mL; Dose: 20 IU/kg; administered intramuscularly (i.m.) into the anterolateral thigh (*M. vastus lateralis*); 1 dose on Day 0 given as 1 injection; Lot no.: 07M00/02

Comparator IMP: Commercially available HRIG (Imogam Rabies-HT), 150 IU/mL; Dose: 20 IU/kg; administered i.m. into the anterolateral thigh (*M. vastus lateralis*); 1 dose on Day 0 given as 1 to 2 injections; Lot no.: A0315-9

Rabies vaccine: Commercially available PVRV (Verorab).[4] Administration of 0.5 mL i.m. into the deltoid. 1 dose on Days 0, 3, 7, 14, and 28 (Essen regimen); Lot no.: B0422-4

Duration of treatment:
During the 42-Day study period, 1 dose of IMP was administered on Day 0 given as 1 or more injections (depending on body weight). PVRV was administered according to the Essen regimen: 1 dose on Days 0, 3, 7, 14, and 28.

[3] Blood sampling for HAHA was added in Version 3.0 of the Study Protocol
[4] Rabies vaccine was changed from the PCECV Rabipur to the PVRV Verorab in Version 3.0 of the Study Protocol.

Criteria for evaluation:

Primary endpoint: [5]

- Safety as assessed by recording unsolicited AEs throughout the study; solicited local and systemic AEs from Day 0 to Day 3; routine safety laboratory on Days 0 and 14, as well as HAHA determination on Days 0 and 42

Secondary endpoints:[5]

- Proportion of subjects with RVNA ≥0.5 IU/mL on Day 14
- Proportion of subjects with detectable RVNA on Day 3
- Geometric mean of RVNA on Days 3, 14, and 42
- Area under the curve (AUC) for RVNA (Day 0 to Day 14 and Day 0 to Day 42)

Statistical methods:

No formal sample size calculation was performed. A total of 48 subjects randomized in a 2:1 ratio was considered sufficient to explore the safety and local tolerability of CL184 in combination with rabies vaccine as compared with HRIG in combination with rabies vaccine in children and adolescents. No formal hypothesis testing was performed. All variables were analyzed descriptively.

SUMMARY OF RESULTS – CONCLUSIONS

Subject disposition, demography and baseline characteristics:

All 48 randomized subjects received IMP and completed the study; 2 subjects (1 in the CL184 20 IU/kg+PVRV and 1 in the HRIG 20 IU/kg+PVRV group) were excluded from the ATP population because they did not receive rabies vaccination at Day 3. All other subjects received the full course (5 doses) of rabies vaccination.

Demographic data at Day 0 (safety, ITT)

		CL184 20 IU/kg+PVRV (N = 33)	HRIG 20 IU/kg+PVRV (N = 15)	Total (N = 48)
Gender [n (%)]	Female	15 (45.5)	7 (46.7)	22 (45.8)
	Male	18 (54.5)	8 (53.3)	26 (54.2)
Race [n (%)]	Asian	33 (100)	15 (100)	48 (100)
Age group [n (%)]	≥5 to <12 years	17 (51.5)	7 (46.7)	24 (50)
	≥12 to <18 years	16 (48.5)	8 (53.3)	24 (50)
Age [years]	Median (min, max)	11.73 (5.1, 18.0)	12.54 (5.7, 17.5)	12.01 (5.1, 18.0)
	Mean ± SD	11.44 ± 4.228	12.79 ± 3.788	11.86 ± 4.104
Height [cm]	Mean ± SD	138.1 ± 20.85	143.1 ± 16.71	139.7 ± 19.62
Weight [kg]	Mean ± SD	34.64 ± 14.441	40.33 ± 16.369	36.42 ± 15.130
BMI [kg/m^2]	Mean ± SD	17.29 ± 3.390	18.89 ± 4.488	17.79 ± 3.792

Percentages are based on N (= number of subjects in group).
BMI = body mass index; HRIG = human rabies immune globulin (Imogam Rabies-HT); n = number of subjects in specified category; PVRV = purified vero cell rabies vaccine (Verorab); SD = standard deviation.

All subjects were Asian. The median age was 12.01 years (safety and ITT population); subjects in the CL184 20 IU/kg+PVRV group were slightly younger and height, weight, and BMI were slightly lower than in the HRIG 20 IU/kg+PVRV group.

[5] Both primary and secondary endpoints were extended in Version 3.0 of the Study Protocol.

Efficacy:
In the present study, all efficacy variables were analyzed as secondary variables. Results are summarized for the ATP analysis; the ITT analysis showed similar results.

Proportion of subjects with RVNA ≥0.5 IU/mL

RVNA did not reach 0.5 IU/mL in any subject at baseline or at Day 3, neither in the CL184 20 IU/kg+PVRV group nor in the HRIG 20 IU/kg+PVRV group. From Day 14 onwards, all subjects in both treatment groups had RVNA levels ≥0.5 IU/mL.

Proportion of subjects with RVNA ≥0.5 IU/mL (ATP)

	CL184 20 IU/kg+PVRV		HRIG 20 IU/kg+PVRV	
	n/n'	% (95%CI)	n/n'	% (95%CI)
Day 0	0/32	0 (0.0, 10.9)	0/14	0 (0.0, 23.2)
Day 3	0/32	0 (0.0, 10.9)	0/14	0 (0.0, 23.2)
Day 14	32/32	100 (89.1, 100.0)	14/14	100 (76.8, 100.0)
Day 42	32/32	100 (89.1, 100.0)	14/14	100 (76.8, 100.0)

RVNA was detected with the RFFIT. Percentages are based on n' (=number of subjects with observations).
ATP = according to protocol; CI = confidence interval (Pearson-Clopper); HRIG = human rabies immune globulin (Imogam Rabies-HT); n = number of subjects with RVNA ≥0.5 IU/mL; PVRV = purified vero cell rabies vaccine (Verorab); RFFIT = rapid fluorescent focus inhibition test; RVNA = rabies virus neutralizing activity

Proportion of subjects with detectable RVNA

At baseline, RVNA was below the detection limit in all subjects. From Day 3 onwards, RVNA was detectable in the serum of all subjects (lower limit of quantitation [LLOQ] of the assay = 0.1 IU/mL).

Geometric mean RVNA

The geometric mean RVNA was slightly higher in the CL184 20 IU/kg+PVRV group than in the HRIG 20 IU/kg+PVRV group at all time points. Geometric mean RVNA ranged from 0.16 IU/mL with HRIG 20 IU/kg+PVRV to 0.19 IU/mL with CL184 20 IU/kg+PVRV at Day 3. From Day 14 onwards, considerably higher levels were seen in both groups in response to rabies vaccination; geometric means at Day 42 reached 19.18 IU/mL with HRIG 20 IU/kg+PVRV and 24.77 IU/mL with CL184 20 IU/kg+PVRV. The subgroup analysis according to age showed that geometric mean RVNA in adolescents and children was similar.

AUC of RVNA

AUC of RVNA was slightly higher in the CL184 20 IU/kg+PVRV group than in the HRIG 20 IU/kg+PVRV group. The subgroup analysis according to age did not reveal major differences in AUC of RVNA between adolescents and children.

Safety:
An overview of AEs is provided in the table below:

Number (%) of subjects with adverse events (safety)

	CL184 20 IU/kg+PVRV (N = 33)		HRIG 20 IU/kg+PVRV (N = 15)	
Subjects with ≥1 AE	**n**	**(%)**	**n**	**(%)**
AEs (unsolicited and solicited)	23	(69.7)	11	(73.3)
AEs (unsolicited and solicited) related to IMP	7	(21.2)	5	(33.3)
Unsolicited AEs	22	(66.7)	10	(66.7)
Solicited local AEs (IMP injection site)	6	(18.2)	5	(33.3)
- Bruising	2	(6.1)	1	(6.7)
- Redness	0	(0)	0	(0)
- Induration	0	(0)	0	(0)
- Pain	4	(12.1)	5	(33.3)
- Swelling	0	(0)	0	(0)
Solicited systemic AE (fever [a])	0	(0)	1	(6.7)
AEs leading to discontinuation	0	(0)	0	(0)
SAEs	3	(9.1)	0	(0)

[a] Fever was defined as body temperature ≥38 °C.
Percentages are based on N (= number of subjects in group)
AE = adverse event; HRIG = human rabies immune globulin (Imogam Rabies-HT), IMP = investigational medicinal product; n = number of subjects with specified events; PVRV = purified vero cell rabies vaccine (Verorab); SAE = serious AE.

Overall incidence rates of AEs (unsolicited and solicited)

The incidence rate of AEs was similar in the CL184 20 IU/kg+PVRV group (23 [69.7%] subjects) and in the HRIG 20 IU/kg+PVRV group (11 [73.3%] subjects).

The most common AEs reported in the CL184 20 IU/kg+PVRV group were upper respiratory tract infection (10 [30.3%] subjects), pain at the CL184 injection site[6] (4 [12.1%] subjects), and possible subclinical myocarditis[7] (3 [9.1%] subjects). Upper respiratory tract infection and injection site pain were also reported in the HRIG 20 IU/kg+PVRV group (6 [40.0%] and 5 [33.3%] subjects, respectively); possible subclinical myocarditis was not reported after administration of HRIG 20 IU/kg+PVRV.

Significant and serious AEs

There were no discontinuations due to AEs.

Possible subclinical myocarditis was diagnosed based on elevated CK and troponin I levels and classified as serious AE (SAE) in 3 children (Subjects [redacted] [male, 6.9 years], [redacted] [male, 6.3 years], [redacted] [female, 6.8 years]) in the CL184 20 IU/kg+PVRV group. The SAE in Subject [redacted] was assessed as related to the IMP by the investigator and thus was classified as a suspected unexpected serious adverse reaction (SUSAR). All 3 events were of mild intensity, and were ongoing at study end (Day 42). During the active study phase and 6 months of follow-up all 3 children showed no clinical signs and symptoms of cardiac disorders; there were no findings with respect to health status, the electrocardiogram (ECG) showed no abnormalities or only transient changes, and chest X-ray was normal. The SAEs in Subjects [redacted] and [redacted] were assessed as resolved by the investigator after the 6-month follow-up; the SAE in Subject [redacted] was judged as resolved after 12 months of follow up. All 3 cases were thoroughly examined by expert cardiologists and, to date, have not indicated a safety concern. The retrospective troponin T analysis did not reveal abnormalities in any of these

[6] Solicited local AE.
[7] Coded as myocarditis (MedDRA preferred term).

subjects. A reanalysis of the retention samples of Day 0 (pre-dose) and Day 14 for Subjects [redacted], and [redacted] at a different laboratory in [redacted] resulted in troponin I values within normal range (<0.040 ng/mL) at both time-points. However, it cannot be excluded that troponin I had degraded during storage of the samples.

Solicited AEs (bruising, redness, induration, pain, swelling, fever)

Local reactions at the IMP injection site were more frequent after administration of HRIG 20 IU/kg (5 [33.3%] subjects) than after administration of CL184 20 IU/kg (6 [18.2%] subjects). This was also true, when local reactions in relation to the number of injections[8] were compared (30.4% at the HRIG injection site *vs*. 18.2% at the CL184 injection site). The observed difference was mainly due to a higher incidence rate of pain at the injection site. Injection site bruising occurred with similar incidence rates in both treatment groups. Redness, induration, and swelling at the IMP injection site were not reported at all.

Pain at the injection site was graded as mild for 3 out of 4 subjects in the CL184 20 IU/kg+PVRV group and for 5 out of 5 subjects in the HRIG 20 IU/kg+PVRV group. One subject in the CL184 20 IU/kg+PVRV group experienced moderate pain at the IMP injection site.[9]

The duration of pain at the injection site ranged from 1 to 2 days in both treatment groups; bruising lasted up to 3 days in both groups.

Fever (body temperature ≥38 °C; solicited systemic AE) was reported by 1 subject in the HRIG 20 IU/kg+PVRV group (38.4 °C on Day 1). The AE was assessed as related to the IMP and resolved within 1 day without sequelae.

Unsolicited AEs

In both treatment groups, the majority of subjects with unsolicited AEs reported mild symptoms; severe symptoms did not occur. The average duration of unsolicited AEs was slightly longer with CL184 20 IU/kg+PVRV (mean 9.8 days) than with HRIG 20 IU/kg+PVRV (mean 6.9 days).

AEs assessed as related to the IMP

In addition to all solicited local AEs at the IMP injection site (considered as causally related by definition), the reported case of fever (solicited systemic AE) in the HRIG 20 IU/kg+PVRV group was assessed as related to the IMP. Among the unsolicited AEs, 1 case of possible subclinical myocarditis (Subject [redacted]) in the CL184 20 IU/kg+PVRV group was assessed as related to the IMP by the investigator.

Subgroup analysis of AE in children and adolescents

The incidence rate of both unsolicited and solicited AEs was higher in children (≥5 to <12 years) than in adolescents (≥12 to <18 years) in both treatment groups.

Routine safety laboratory

In both treatment groups, minor changes in mean values of hematology and serum biochemistry parameters were observed. All out-of-range values of routine safety laboratory parameters were assessed as not clinically significant by the investigator except for abnormalities in creatine kinase (CK), and troponin I observed in Subjects [redacted] and [redacted] (both reported as SAE possible subclinical myocarditis).[10] In addition, Subject [redacted] had elevated CK and

[8] The volume and number of injections needed to achieve 20 IU/kg was higher with HRIG than with CL184.
[9] No severity grading was performed for bruising.
[10] Elevations in LDH (not part of the routine safety laboratory panel but measured to further investigate the cases of possible subclinical myocarditis) were considered as clinically significant by the investigator as well.

troponin I levels at Days 0 and 14, which were originally not assessed as clinically significant but later possible subclinical myocarditis was diagnosed and classified as SAE. A retrospective analysis of troponin T in serum samples of all enrolled subjects did not reveal any abnormalities. Subject [redacted] had elevated amylase at Day 14 (>5 x ULN, corresponding to Toxicity Grade 4) which was reported as non-serious AE and attributed to the non-fasting state at measurement.

HAHA

A CR4098-specific, treatment-emergent HAHA response was observed in 1 subject ([redacted], female, aged 14.5 years). This subject did not report any AE.

Conclusions:

Overall, CL184 administered as a single dose of 20 IU/kg together with 5 doses of PVRV rabies vaccine (Essen regimen) in a simulated PEP setting was well tolerated in children and adolescents. There were no discontinuations due to AEs. Assessment of solicited AEs showed a favorable tolerability of CL184 compared with HRIG. There were no clinically significant abnormalities of routine safety laboratory parameters except for elevated levels of CK, and troponin I, which led to the diagnosis of possible subclinical myocarditis reported as SAEs in 3 children. Thorough examination and up to 12 months follow-up of these cases did not indicate a safety concern. A retrospective analysis of troponin T in serum samples of all enrolled subjects did not reveal any abnormalities. A treatment-emergent mAb-specific HAHA response was observed in 1 adolescent subject; this subject did not report any AE.

RVNA was detectable in all subjects from Day 3 onwards; by Day 14, all subjects had achieved the expected RVNA level of ≥0.5 IU/mL. There was no apparent difference in RVNA response between children and adolescents and RVNA levels were comparable to those achieved in adults in earlier studies with CL184.

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