

Evaluation of the safety and neutralizing activity of CL184, a monoclonal antibody cocktail against rabies virus, in a Phase II study in healthy adolescents and children

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on behalf of the study team

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Post exposure prophylaxis

100 % effective in preventing rabies



Bite by rabid dog



PEP

**Administration of
Rabies Immune Globulin
and multiple doses of rabies vaccine
blocks infection and prevents rabies**



Patient with fatal rabies



Blood-derived products

Advantages of monoclonals vs blood-derived immune globulins

Human Rabies Immune Globulin (**HRIG**)

Equine Rabies Immune Globulin (**ERIG**)



(Talecris)



(sanofi-pasteur)



(sanofi-pasteur)

**(HRIG & ERIG)
Asia and South
America**

(National productions)

- Expand product availability
- Improve production flexibility
- Increase product concentration

- Heterogeneous product quality: avoid the risk of adventitious agents
- Avoid unsafe plasma sources
- Improve production consistency and flexibility
- Expand product availability
- Increase product concentration



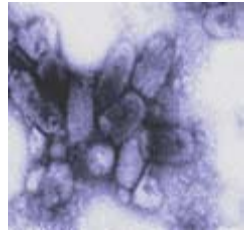
Human monoclonal antibodies

highly suitable to replace HRIG and ERIG

- Available in quantities able to answer endemic area needs
- Consistent potency combined with high specific activity
- Concentrated product to better address bite wound infiltration
 - Reduce administration of excess volume at distant i.m. site



CL184: a combination of two human neutralizing anti-rabies mAbs (CR57 and CR4098) as the next generation of RIG



- Human mAb sequences derived from B cell repertoire from rabies vaccinated donors
- CR57 and CR4098 mAbs bind to distinct non-overlapping epitopes on rabies virus glycoprotein
- CL184 provides good coverage of natural rabies virus isolates (N=43)
- CL184 provides equal *in vivo* efficacy as compared to HRIG in relevant animal model
- In three Phase I/II studies (US and India, all adult population), CL184 was well tolerated and demonstrated the expected rabies virus neutralizing activity



Study design of RAB-M-A004

- Design: randomized, single-blind (subjects blinded), controlled, monocentric
 - Objectives: safety and rabies virus neutralizing activity
 - Simulated rabies post-exposure prophylaxis
 - 48 healthy adolescents and children (age staggered)
 - Study site: Research Institute for Tropical Medicine (RITM), Metro Manila, Philippines
 - Treatments:
 - CL184 20 IU/kg i.m.
 - HRIG (Imogam Rabies HT™) 20 IU/kg i.m. } + PVRV i.m.
(Verorab™)
- PVRV Potency: 8.0 IU/dose



Study chart and endpoints

	<i>D0</i>	<i>D3</i>	<i>D7</i>	<i>D14</i>	<i>D28</i>	<i>D42</i>
	PVRV	PVRV	PVRV	PVRV	PVRV	
16 Ado (12-18 years)	CL184					
8 Ado (12-18 years)	HRIG					
↓						
16 Child. (5-11 years)	CL184					
8 Child. (5-11 years)	HRIG					
BS for RFFIT	X	X		X		X
BS for safety	X			X		

- **Primary endpoint: safety**

- Adverse events
- Laboratory safety panel
- Injection site reactions
- Body temperature
- Human anti-human antibodies

- **Secondary endpoint: efficacy**

- Rabies virus neutralizing activity (RFFIT)



Subject disposition

	CL184 + PVRV	HRIG + PVRV
Randomized	33	15
Received study treatment	33	15
Completed study	33	15
Major protocol violation	1	1



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No Day3 PVRV dose, subject completed the study but was excluded from the According To Protocol population (ATP)



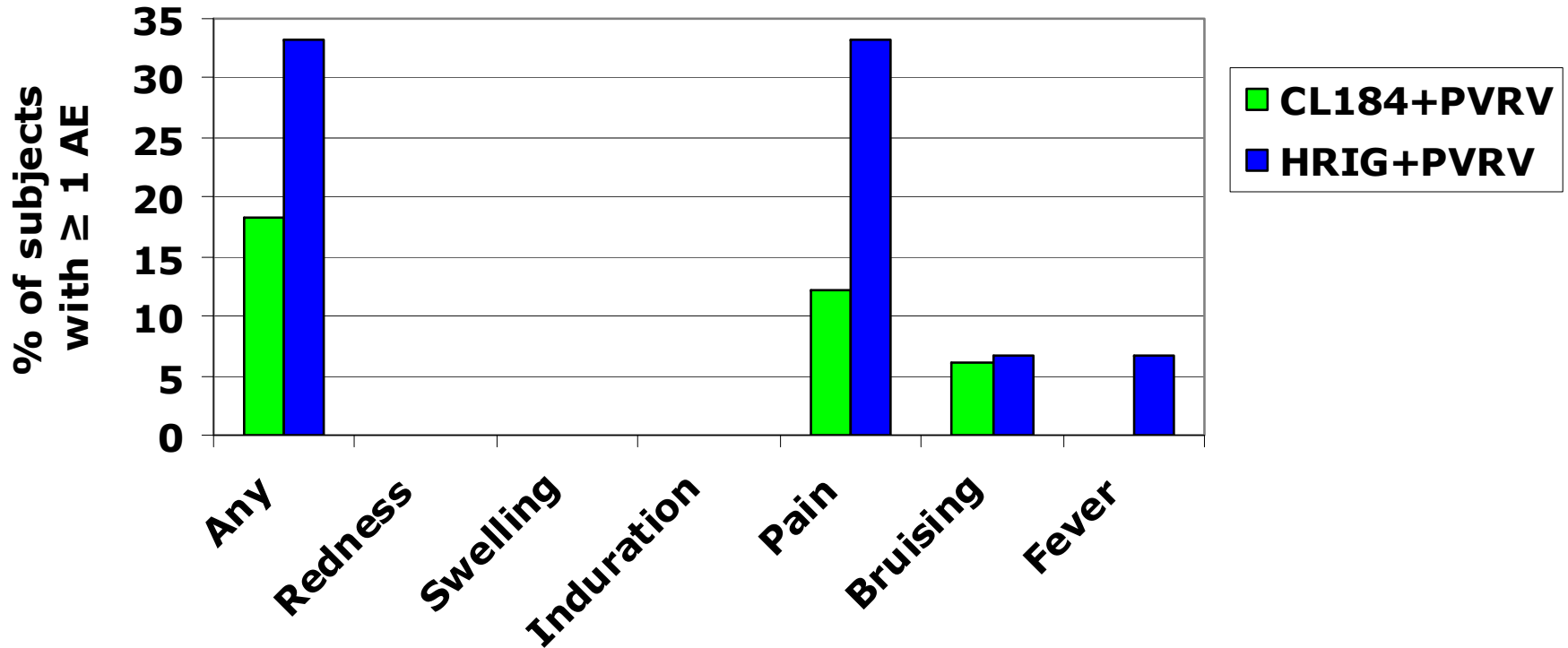
Demography

	CL184 + PVRV N=33	HRIG + PVRV N=15
Male/Female (%)	54.5	53.3
Mean age (year)	11.44	12.79
≥5- <12 years	7.82	9.34
≥12- <18 years	15.29	15.8
Age range (year)	5.1- 18.0	5.7- 17.5
≥5- <12 years	5.1- 11.7	5.7- 11.2
≥12- <18 years	12.3- 18.0	12.5- 17.5



Solicited adverse events

Safety population



Solicited adverse event
local reactions at CL184/HRIG injection site(s) and
fever (body temperature $\geq 38^{\circ}\text{C}$)



Unsolicited adverse events

safety population

Subjects (%) with	Adolescents		Children		Total	
	CL184 + PVRV N= 16	HRIG + PVRV N= 8	CL184 + PVRV N= 17	HRIG + PVRV N= 7	CL184 + PVRV N= 33	HRIG + PVRV N= 15
≥ 1 AE	7 (43.8)	5 (62.5)	15 (88.2)	5 (71.4)	22 (66.7)	10 (66.7)
≥ 1 AE related to IMP	0 (0)	0 (0)	1 (5.9)	0 (0)	1 (3.0)	0 (0)
≥ 1 SAE	0 (0)	0 (0)	3 (17.6)	0 (0)	3 (9.1)	0 (0)
AEs leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)



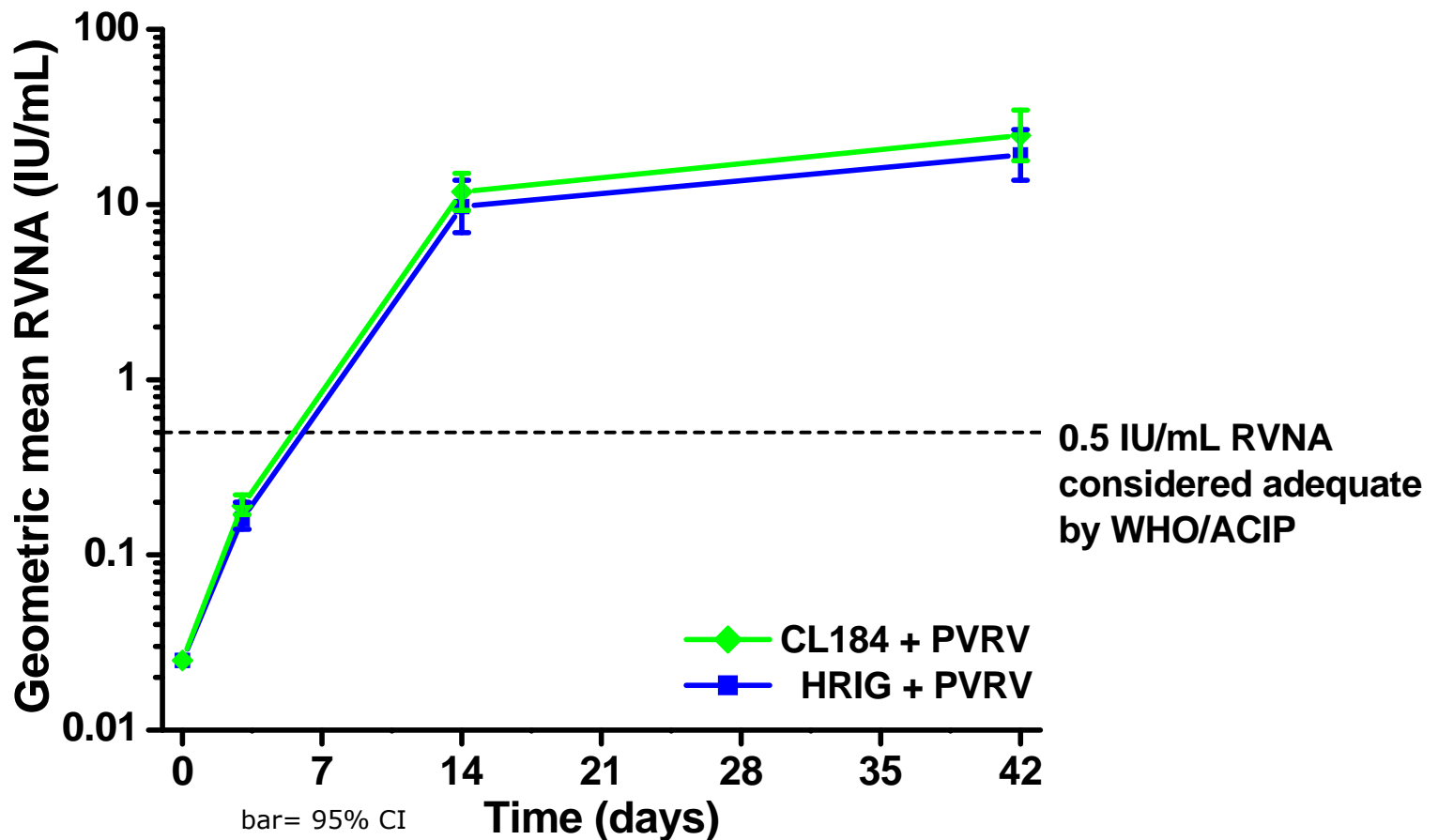
RAB-M-A004: SAEs

- In the frame of the routine safety laboratory investigations, Troponin I and CKMB were assessed at Days 0 & 14 in case of CK elevation (results available only after dosing)
- 4 children administered CL184 had slight troponin I elevations, 3 from 4 already pre-dose
- Based on those elevations and the absence of acute symptoms, 3 subjects were diagnosed with “possible subclinical myocarditis” (SAE). 1 subject was not reported as AE due to decreasing troponin I values already at post-dose
- All 4 children were well and asymptomatic during the study and up to 12 months after the trial
- Retention sample analysis of troponin T revealed no abnormalities. US FDA recently warned about false-positive troponin elevations, especially at low troponin values. Hypothesis is that the initial troponin I elevations might have been false positive results.



Rabies virus neutralizing activity

ATP



CL184, or HRIG administered at D0

PVRV administered at D0, 3, 7, 14 & 28

Data pooled from adolescent and children cohort

Similar data in the Intent-to-Treat population



Summary

- Safety
 - CL184 was safe and well tolerated in adolescents and children
 - Favorable local tolerability compared with HRIG
- Neutralizing activity
 - Neutralizing activity after administration of CL184 in combination with rabies vaccine was comparable to HRIG combined with rabies vaccine
 - Within 14 days, all subjects administered CL184 plus rabies vaccine reached immunity levels considered adequate by WHO/ACIP
 - RVNA levels were comparable to those reached in adults and there was no apparent difference between children and adolescents
- 1 (3 %) subject displayed specific and treatment-emergent human anti-human antibody against CL184 (not shown). There was no apparent impact on safety or rabies virus neutralizing activity



Conclusion

Initial Phase I and Phase II clinical evaluation supports further development of CL184, including in the pediatric population

- ✓ Phase I (US) (study completed)
 - ✓ Healthy volunteers
- ✓ Phase I (India) (study completed)
 - ✓ Healthy volunteers
- Phase II (ongoing)
 - ✓ US, healthy volunteers (study completed)
 - ✓ Philippines, healthy adolescents and children (study completed)
 - India, healthy volunteers (planned)
- Phase III (planning ongoing)
 - Exposed adults and children in endemic areas



Collaborating institutions

- Research Institute for Tropical Medicine, Manila, Philippines
- Crucell, Leiden, The Netherlands/Bern, Switzerland
- sanofi pasteur, Lyon, France
- Kansas State University, Kansas, US for RFFIT
- BioAnaLab, Cambridge, UK for HAHA

