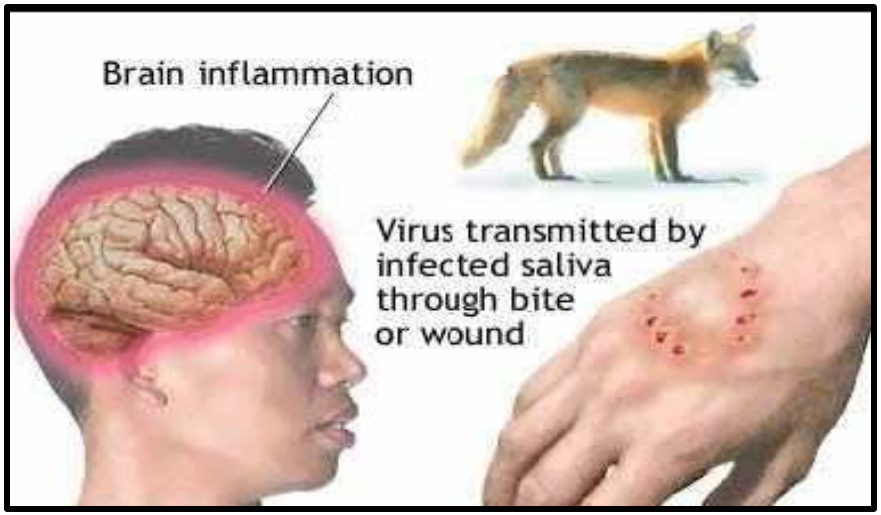
RabiMabs
A novel monoclonal antibody cocktail for post-bite prophylaxis against Rabies virus

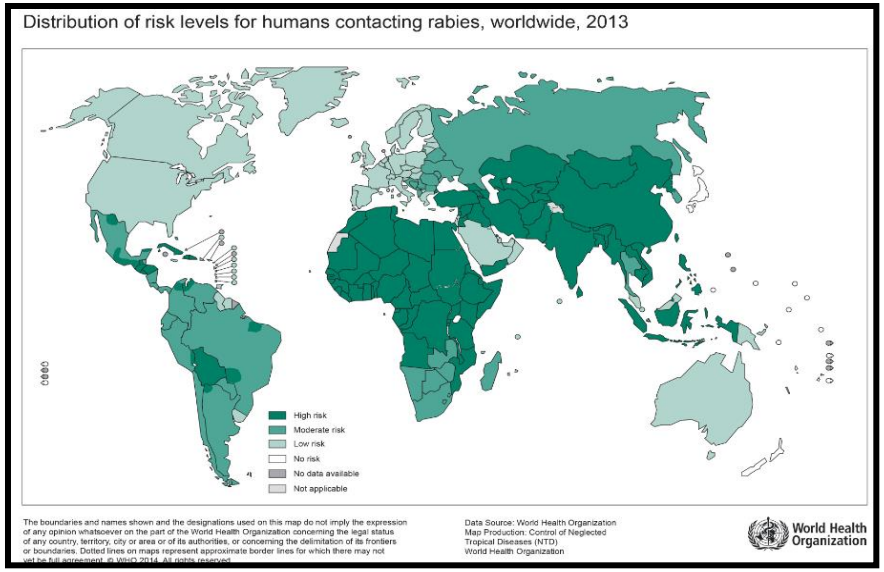
Cadila Healthcare Ltd. in collaboration with WHO

Zydus
dedicated to life

Introduction: Rabies

- Acute viral encephalomyelitis of humans and other warm-blooded vertebrates.
- Caused by a member of the genus *Lyssavirus* of the Rhabdoviridae family.
- Disease in humans characterised by anxiety, hydrophobia, aerophobia, seizures, paresis or paralysis, coma and death.
- Once clinical signs manifest the disease is almost invariably 100% fatal.
- After entering the human body, the rabies virus progresses from the subcutaneous tissue, or from the muscle, into peripheral nerves. The virus migrates along nerves to the spinal cord and brain.
- 16 million bites p.a. worldwide; many deaths



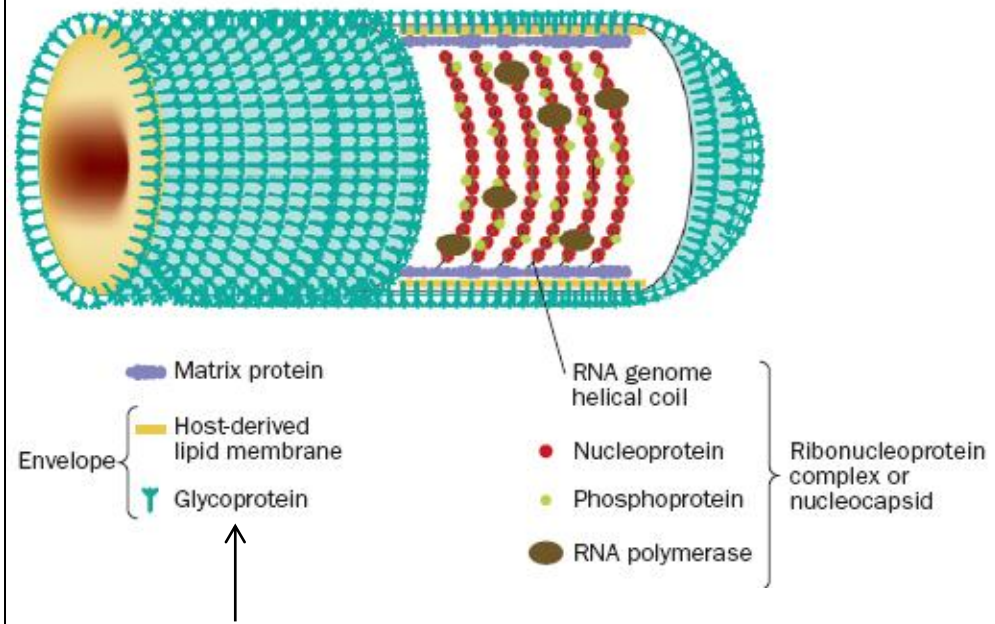


WHO Guideline for Treating a Category 3 Exposure

Immediate washing of the wound followed by administration of a rabies post-exposure prophylaxis (PEP) comprising of both rabies vaccine and rabies-immunoglobulin (RIG).

Two types of RIGs (ERIG and HRIG) are available. However they have the following drawbacks:

- Human RIG : Risk of infections. Very expensive and available in confidential quantities.
- Equine RIG : Risk of zoonotic infections. Production largely discontinued due to animal protection groups.



Unmet Need - Requirement of anti-rabies monoclonal antibodies

RabiMabs – Salient Features - 1

• Novel cocktail of two murine monoclonal antibodies produced by hybridomas Sourced from WHO partnering centers: CDC, Atlanta, USA and ADRI, Nepean, Canada -

- **M777-16-3** (IgG1) - Binds to site II on G protein of rabies virus envelope
- **62-71-3** (IgG2b) - Binds to site III on G protein of rabies virus envelope

• **Risk mitigation** : The binding of RabiMabs product to two distinct antigenic sites provides adequate protection against a mutated rabies virus that has lost an epitope due to a mutation.

RabiMabs – Salient Features - 2

- **Breadth of rabies virus neutralization :**
  - Extensive in vitro and in vivo virus neutralization studies conducted at WHO collaborating laboratories –
    - FLI, Germany
    - CDC Atlanta, USA
    - Wusterheusen, Canada
    - NIMHANS, Bangalore, India
  - Monoclonal antibodies have been tested for neutralization of viruses isolated from domestic and wild animals from a variety of countries e.g., dogs from India, Turkey, Ethiopia, Mexico, Nepal etc.; fox from Europe, Eastern Europe, Polar fox; Wolf from Sarajevo; Bat from Europe; variety of animals from US; etc.

In vivo potency studies conducted so far - 1

Experiment Conducted By	Animal model	Challenge virus	Group	Dose (i.m. route)	Survival	% survival
CDC Expt # 1201	Hamsters	Thai (2006) canine RABV variant (i.m. route)	62-71-3 / 62-71-3	50µL (400IU/mL)	5/9	55.5%
			Negative control (PBS)	50µL	0/9	0%
			62-713/1112-1	50µL (1:1 combination of each antibody totaling 400IU/mL)	7/9	77.7%
			62-713/E559		6/9	66.6%
			62-713/M727		6/9	66.6%
			62-71-3/M777-16-3		**9/9**	**100%**
			62-71-3 only	50µL (200IU/mL)	1/9	11%
			HRIG positive control group	50µL (150IU/mL)	**5/9**	**55.5%**
CDC Expt # 1226	Hamsters	Mexican (2004) canine RABV variant (i.m. route)	62-71-3 / 62-71-3	50µL (400IU/mL)	9/9	100%
			Negative control (PBS)	50µL	3/9	33.33%
			62-71-3/1112-1	50µL (1:1 combination of each antibody totaling 400IU/mL)	9/9	100%
			62-71-3/E559		8/9	88.88%
			62-71-3/M727		8/9	88.88%
			62-71-3/M777-16-3		**9/9**	**100%**
			62-71-3 only	50µL (200IU/mL)	9/9	100%
			HRIG positive control group	50µL (150IU/mL)	**4/9**	**44.44%**

Equipotent combination of 62-71-3 and M777-16-3 was found to be efficacious in hamsters challenged with lethal dose of rabies virus

In vivo potency studies conducted so far - 2

Experiment Conducted By	Animal model	Challenge virus	Group	Dose (i.m. route)	Survival	% survival
CDC IER/PTT, CDC IAA# CI12-026	Hamsters	Texas fox 393 (i.m. route)	Control group (PBS)	50µL	0/9	0%
			Vaccine only	50µL	0/9	0%
			HRIG	50µL (20IU/kg)	7/9	77.8%
			Vaccine* + HRIG	50µL + 50µL (20IU/kg)	**7/9**	**77.8%**
			Rabimabs	50µL (20IU/kg)	6/9	66.7%
			Vaccine* + Rabimabs	50µL + 50µL (20IU/kg)	**8/9**	**88.9%**

*-Vaccine was administered i.m. in the left gastrocnemius muscles in volumes of 50µl on days 0, 3, 7, 14 and 28

Rabimabs in conjunction with vaccine was found to be highly efficacious in hamsters challenged with lethal dose of rabies virus

In vivo potency studies conducted so far - 3

Experiment Conducted By	Animal model	Virus strain	% survival				
			Rabimabs		HRIG 0.2 IU/ mice	ERIG 0.4 IU/ mice	Placebo
			0.2 IU/ mice	0.4 IU/ mice			
NIMHANS India SOP/NIMH/NV/ RAB 005	Mice	CVS	100	100	100	100	0
		SV1	100	100	100	100	10
		SV2	100	100	100	100	10
		SV3	100	100	100	100	0
		SV4	100	100	100	100	20
		SV5	100	100	100	100	0
		SV6	100	100	100	100	0
		SV7	100	100	100	100	10
		SV8	100	100	100	100	10
		SV9	100	100	100	100	0
		SV10	100	100	100	100	0

Rabimabs was found to be equipotent to both HRIG and ERIG in mice challenged with lethal dose of 11 different street isolates of rabies virus

In vivo potency studies conducted so far - 4

Experiment Conducted By	Animal model	Challenge virus	Group (Drug administered 6 hours after virus challenge)	Dose (i.m. route)	Survival	% survival
Cadila Healthcare P/EX-WHO BT-0006/BT/002-00	Hamsters	CVS-11 (i.m. route)	Standard (HRIG)	100µL (15IU)	10/10	100%
			Test (Rabimabs)	100µL (15IU)	10/10	100%

Experiment Conducted By	Animal model	Challenge virus	Group (Drug administered 24 hours after virus challenge)	Dose (i.m. route)	Survival	% survival
Cadila Healthcare P/EX-WHO BT-0006/BT/002-00	Hamsters	CVS-11 (i.m. route)	Control	100µL	4/10	40%
			Standard (HRIG)	100µL (15IU)	8/10	80%
			Test (Rabimabs)	100µL (15IU)	7/10	70%

Rabimabs in was found to be highly efficacious in hamsters challenged with lethal dose of rabies virus

RabiMabs – Salient Features - 3

- **Rabimabs virus neutralization activity** : The product is formulated to contain an equipotent mix of each antibody which is determined using a standard pharmacopeial assay (in comparison to 'Anti-rabies Immunoglobulin, Human WHO International Standard' (RAI) by undertaking a virus neutralization RFFIT assay using CVS-11 virus)
- **Hygiene :** Highly purified. Much lesser protein per dose (lower hypersensitivity risk). Can be produced in scalable quantities like any monoclonal antibody.

Drug Product Composition - Equipotent Mix of Two Monoclonals

Strength - 3000 IU in 10 mL	
Ingredients	Quantity per mL
Active ingredients	
Monoclonal antibodies* (M777-16-3 and 62-71-3)	300 IU (150 IU each)
Inactive ingredients	
Sodium citrate dihydrate (IP / USP)	5.12 mg
Citric acid (IP / USP)	0.5 mg
Sodium chloride (IP / USP)	5.84 mg
Sodium hydroxide (IP / NF)	q.s. to pH 6.0
Polysorbate 80 (IP / NF)	0.1 mg
Water for Injection (IP / USP)	q.s.
Total Fill volumes	10.5 mL
Extractable volume during administration	10 mL

* - Each strength of drug product preparation is composed of equipotent amounts of M777-16-3 (D8) and 62-71-3 (D2) monoclonal antibodies e.g. for 3000 IU / 10mL – 1500 IU of M777-16-3 (D8) and 1500 IU of 62-71-3 (D2) were mixed together to achieve 3000 IU strength

RabiMabs Drug Product: Stability

Strength - 3000 IU in 10 mL

Real-time storage condition – between +2 °C and +8 °C		
Batch No.	Status	Remarks
CT-105	36 months completed	Stable; Study completed
E15004	6 months completed	Stable; Study ongoing; planned for 36 m
E16004	3 months completed	Stable; Study ongoing; planned for 36 m
Accelerated storage condition – 25 °C ± 2 °C; RH 60% ± 5%		
CT-105	12 months completed	Stable; Study completed
E15004	6 months completed	Stable; Study completed
E16004	3 months completed	Stable; Study ongoing; planned for 6 m

RabiMabs is a stable drug product

Clinical Status - RabiMabs

Indication	Status
Post-bite Prophylaxis	**Phase I study is completed with 10, 20 and 40 IU/kg dose of RabiMabs**
	Phase II study is completed with 40 IU/kg dose of RabiMabs + VaxiRab N (on days 0, 3, 7, 14 and 28)
	Phase III protocol approved by DCGI - "Randomized, Multi-centric, Open-label, Comparator-controlled study to evaluate the efficacy and safety of RabiMabs administered in conjunction with Vaxirab N for Post-exposure prophylaxis in patients following potential rabies exposure"
Total subjects in Phase 1 and 2 studies: 41	

Clinical assay - RFFIT

- For the clinical trials a validated rabies virus neutralizing assay – RFFIT was used
- The potency of the rabies virus neutralizing antibodies of the clinical samples was determined by RFFIT in comparison with an 'Anti-rabies Immunoglobulin, Human WHO International Standard' (RAI)
- RFFIT assays is useful for the determination of antibodies against the rabies virus in both early phase (passive immunization) and the late phase (active immunization) of the clinical trials
- Assay is pharmacopeial
- Assay is used by industry to test potency of ERIG, HRIG and vaccines

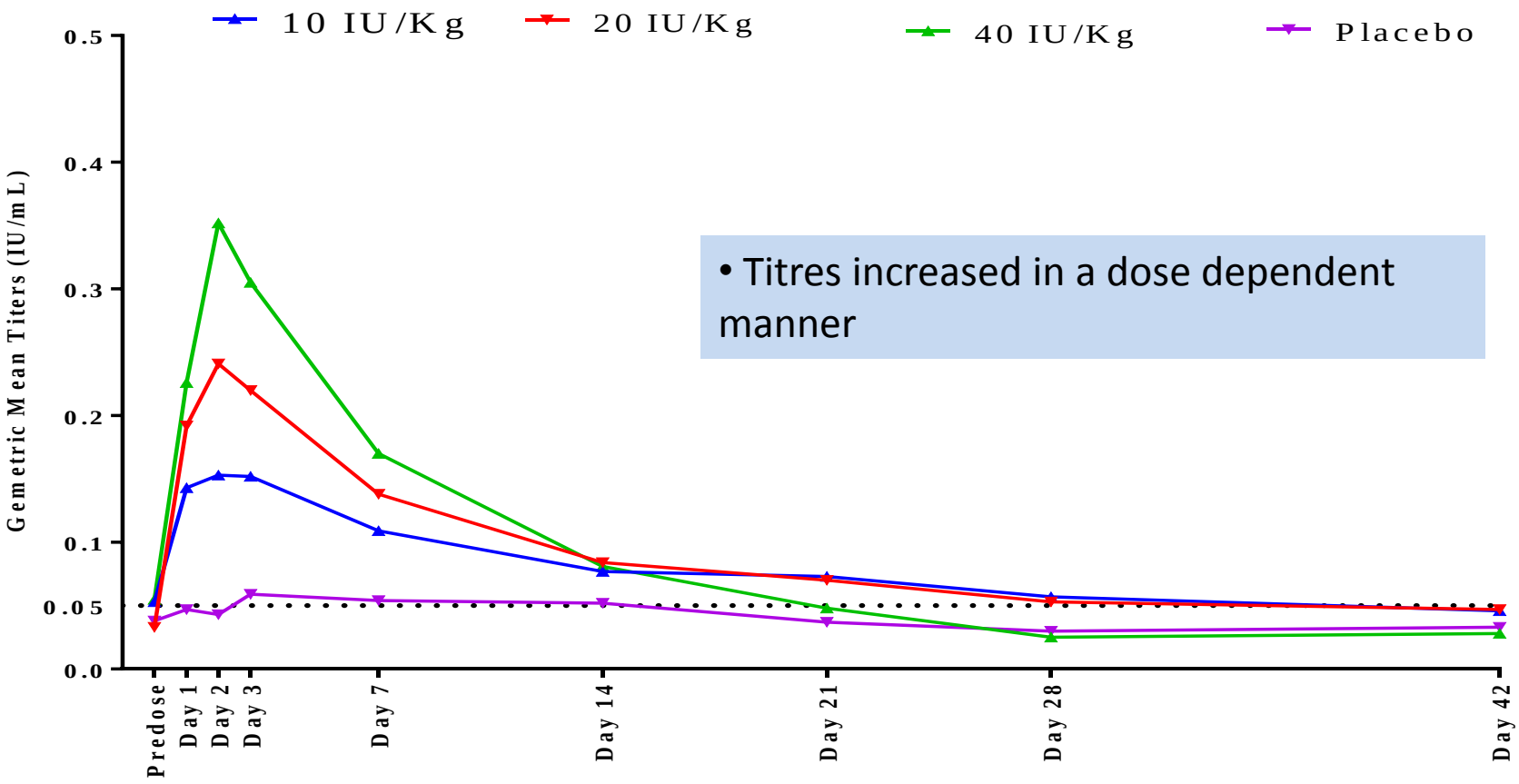
Phase 1 Study – Safety and Tolerability

Objective:

- To evaluate the safety, tolerability and neutralizing activity of RabiMabs against rabies virus in healthy subjects

- Panel 1:
  - 6 healthy Volunteers received 10IU/kg RABIMABS and,
  - 2 Healthy Volunteers received Placebo
- Panel 2:
  - 6 healthy Volunteers received 20IU/kg RABIMABS and,
  - 2 Healthy Volunteers received Placebo
- Panel 3:
  - 6 healthy Volunteers received 40IU/kg RABIMABS
  - 2 Healthy Volunteers received Placebo
- Mode of administration:
  - For 10 & 20 IU/kg a single dose was injected into the lateral thigh muscle. For 40 IU/kg equal volumes of two injections were administered into the right and left lateral thigh muscles.

Phase 1: Geometric Mean Titres (without error bars)



- Titres increased in a dose dependent manner

Note: * Data are geometric means and 95% confidence intervals. Values below the limit of 0.05 IU/mL were set to half of the limit (i.e., 0.025).

Phase 1: Summary of Adverse Events and ADA

Categories	Placebo	Rabimabs 10 IU/Kg	Rabimabs 20 IU/Kg	Rabimabs 40 IU/Kg
	n (%)	n (%)	n (%)	n (%)
Adverse events	None			

	M62-71-3	M777-16-3
ADA-positive at baseline (Pre-dose)	all negative	all negative
ADA-positive from day 01 to day 07	all negative	all negative
ADA-positive from day 14 to day 42	00	02

Phase 2 Study – Combination with vaccine

Study Design

- 12 healthy volunteers received RabiMabs (40 IU/kg) on day 0 plus five doses of vaccine (Vaxirab N) on days 0, 3, 7, 14 and 28.

- 6 healthy volunteers received placebo on day 0 plus five doses of vaccine (Vaxirab N) on days 0, 3, 7, 14 and 28.

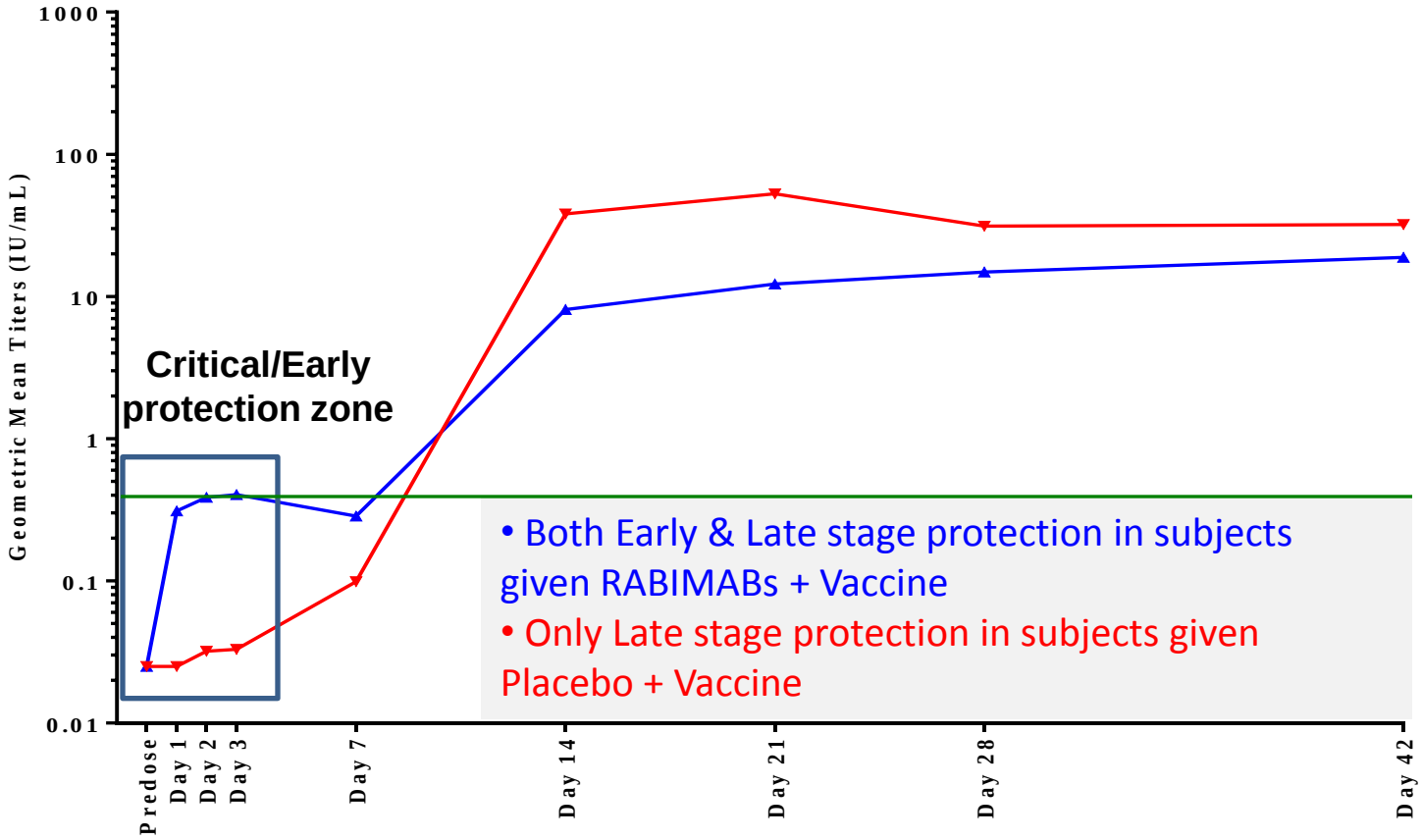
Phase 2 Study – Combination with vaccine

Vaccine administration:

- One milliliter of Zydus rabies vaccine (Vaxirab) was injected into the deltoid muscles alternately as mentioned below.

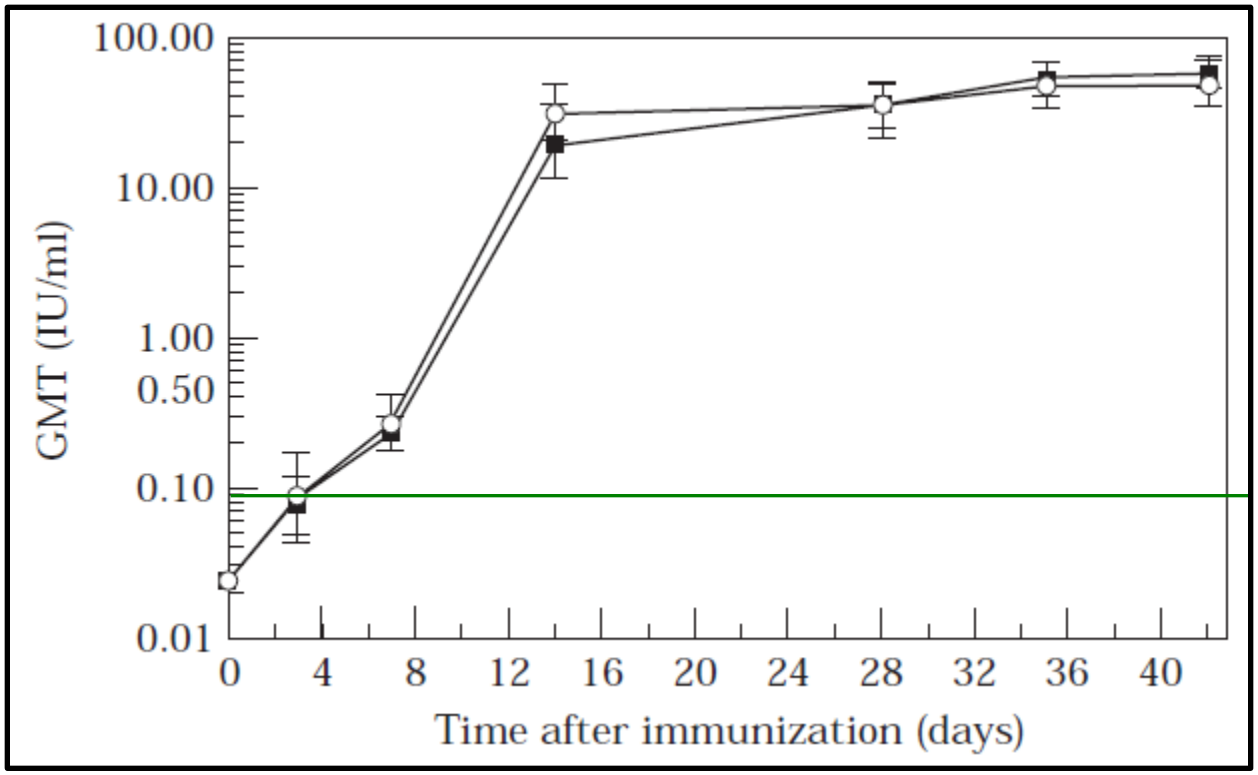
Day	Either	or
0	Right deltoid muscle	Left deltoid muscle
3	Left deltoid muscle	Right deltoid muscle
7	Right deltoid muscle	Left deltoid muscle
14	Left deltoid muscle	Right deltoid muscle
28	Right deltoid muscle	Left deltoid muscle

Phase 2 Clinical Trial Data – Geometric Mean RVNA Titers (Semi-log with error bars)



- Product provides significantly better protection (at least about 3x) against currently available RIGs when it is most needed

Rabies virus neutralizing antibody data with IMOGAM (HRIG)



Rabies antibody titres (mean and 95% confidence interval, log-linear scale) after administration of HRIG/HDCV (o, n=16) and HTRIG*/HDCV (■, n=16)

***IMOGAM (HRIG heat treated at 60°C)**

Evaluation of the Safety and Immunogenicity of a New, Heat-treated Human Rabies Immune Globulin Using a Sham, Post-exposure Prophylaxis of Rabies. J.Lang et al Biologicals (1998) 26, 7–15

Rabies virus neutralizing antibody data with ERIG

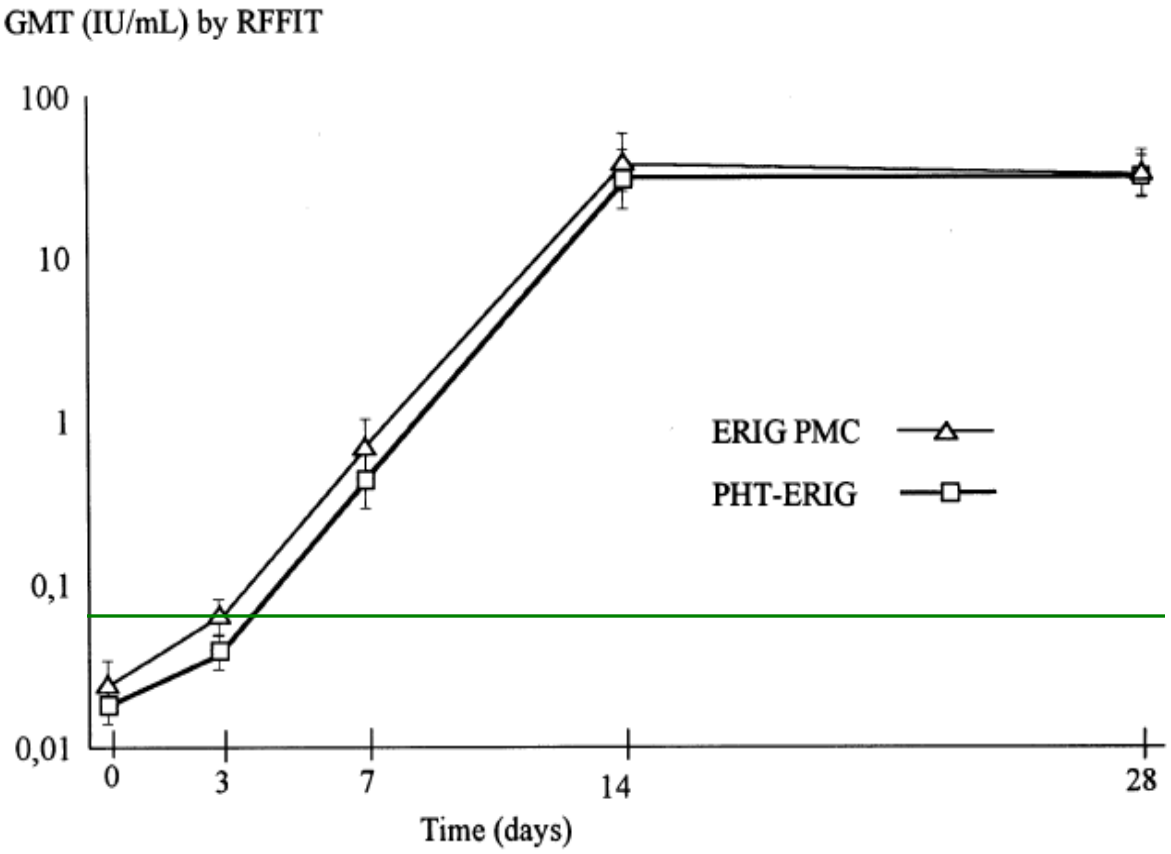


Fig. 2. Evolution of the dose-normalised geometric mean titre (GMT) following the intramuscular administration of a single 40 IU kg^{-1} dose of Erig PMC or PHT-Erig and five doses of Vero-cell rabies vaccine (PVRV) on D0, 3, 7, 14 and 28 (Study 2).

Evaluation of the safety, immunogenicity, and pharmacokinetic profile of a new, highly purified, heat-treated equine rabies immunoglobulin, administered either alone or in association with a purified, Vero-cell rabies vaccine. J Lang et al. Acta Tropica 70 (1998) 317–333

Phase 2: Summary of Adverse Events and ADA

	Placebo	40 IU/Kg
	N(e)	N(e)
Total no. of subjects given investigational products	n=06	n=11
Adverse events in no of subjects	-	2(3)
Fever	-	1(1)
Fever, burning micturation	-	1(1)
Skin lesions and pain	-	1(1)
N (e)	-	2(3)

	M62-71-3	M777-16-3
ADA-positive at baseline (Pre-dose)	all negative	all negative
ADA-positive from day 01 to day 07	all negative	all negative
ADA-positive from day 14 to day 42	5	4

Almost all subjects (6 out of 7) showed a reduced to nil ADA response by day 42

Phase 3 Study

Phase III study	
Title	Randomized, Multi-centric, Open-label, Comparator-controlled Study to evaluate the efficacy and safety of RABIMABs administered in conjunction with Vaxirab N for Post-exposure Prophylaxis in Patients following Potential Rabies Exposure.
Objective	**Primary Objectives:** Proportion of subjects with RFFIT titre more than or equal to 0.5 IU/ml on Days 14 who receiving RABIMABs + Vaxirab N and Immunoglobulins (Imogam®) + Vaxirab N. **Secondary Objectives:** a. Proportion of subjects with RFFIT titre more than or equal to 0.5 IU/ml on Days 28, 42 and 84 b. Proportion of subjects with RFFIT titre more than or equal to 0.1 IU/ml on Days 03 and 07 who receiving RABIMABs + Vaxirab N and Immunoglobulins (Imogam®) + Vaxirab N. c. Incidence of local and systemic reactions up to Day 7 for RABIMABs and Imogam® d. Incidence of adverse events and serious adverse events during the study participation e. Proportion of subjects with Immunogenicity of RABIMABs on Day 14, 42 and 84

Phase 3 Study

Phase III study cont.	
Treatment	Treatment arm A: RABIMABs (40 IU/Kg) + Vaxirab N (1 mL) on day 0, 3, 7, 14 and 28. Treatment arm B: Rabies Immunoglobulins (Imogam®20 IU/Kg) + Vaxirab N(1 mL) on day 0, 3, 7, 14 and 28
Participants	WHO Category III exposure(s) by a suspected rabid animal
No. of subjects	A total 308 subjects including 20% dropout, will be enrolled in a ratio of 1:1 to have 124 subjects in each group i.e., RABIMABs (40 IU/Kg) + Vaxirab N (124) : Rabies Immunoglobulin (Imogam®) + Vaxirab N (124)

Conclusion

- The test product Rabimabs of M/s. Cadila Healthcare Limited, Ahmedabad, India, has been found **safe and well tolerated** when administered as a single intramuscular dose upto 40 IU/kg in healthy subjects as well as 40 IU/kg in conjunction with VaxiRab N (Day 0, 3, 7, 14 and 28).
- The pharmacokinetic evaluations indicated that the active drug is well absorbed on intramuscular administration in healthy subjects in dose related manner. **RVNA in Phase 2 suggests that timely administration of Rabimabs dose will provide better early protection after animal bite.**
- VaxiRab N was not significantly neutralized by Rabimabs at a dose of 40 IU/kg as the vaccine was still able to give **titers well above the WHO recommendation of >0.5 IU/mL after vaccination.**
- For better assessment of efficacy and safety a Phase 3 study will be conducted in category 3 animal bite subjects.

Thank you