

# A Phase Ib Study with Monoclonal Antibody Cocktail in Simulated Rabies Post-exposure Prophylaxis in Healthy Asian Subjects

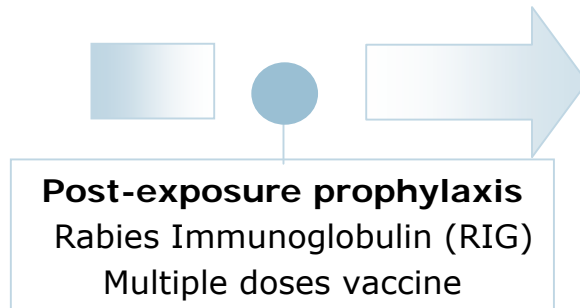
JITMM Bangkok, 30th November 2007

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Crucell

# Post-exposure Prophylaxis (PEP) can be 100% effective in preventing rabies



Patient with rabies

## Two types of RIG preparations

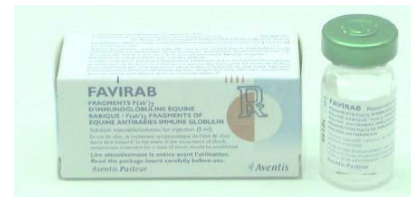
### Human (HRIG)



HyperRab  
(Talecris)



Imogam Rabies HT  
(Sanofi-Aventis)



Favirab (Fab2)  
Sanofi-Aventis)

### Equine (ERIG)

National productions  
Asia and South America

# Drug product CL184

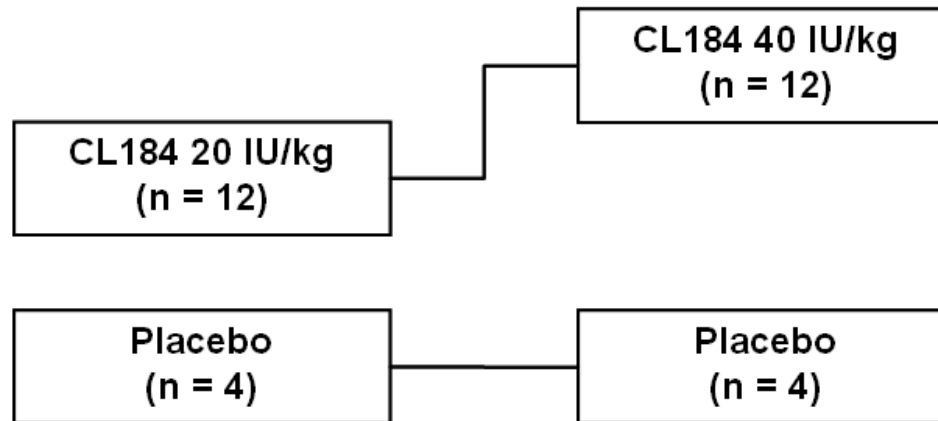
- CL184 is a 1:1 equipotent mixture of two human monoclonal antibodies (CR57 and CR4098), each directed against a distinct, non-overlapping rabies virus epitope
- The cell substrate utilized to generate CL184 is the human fetal PER.C6<sup>®</sup> cell line
- CL184 neutralized all rabies street viruses tested (>42 strains from all continents)
- In the hamster model, CL184 in combination with rabies vaccine protected against challenge by rabies virus at least as well as HRIG (Gold Standard)

# Phase I Clinical Trials

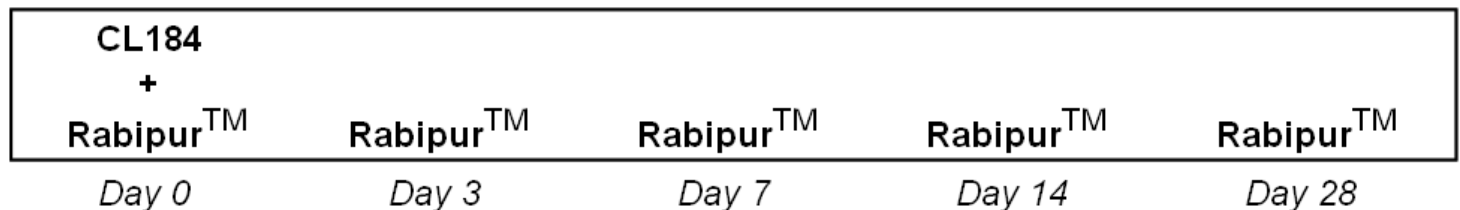
- RAB-M-A001 First-in-Human study performed in US in healthy subjects (Dec06-May07)
  - CL184 was safe, well tolerated and demonstrated rabies virus neutralizing activity
- RAB-M-A002 Phase I study was designed to generate safety data in Asian subjects
  - RAB-M-A002 was performed in a Phase I unit in Mumbai (India) from April to July 2007
  - Healthy male and female subjects were enrolled (18-55 years)

# Study design

- Part 1: Randomized, double-blind, placebo-controlled study in healthy volunteers, CL184 dose escalation



- Part 2: Open, non-controlled administration of CL184 in combination with PCEC vaccine in healthy volunteers



# Study Parameters

- Safety:
  - Unsolicited Adverse Events
  - Solicited local reactions
    - redness, swelling, induration, pain
  - Laboratory safety panel
    - Blood chemistry, hematology and urine analysis
  - Vital signs and physical findings
  - ECG
  - Human anti-human antibodies (HAHA) against CL184
- Effect parameters:
  - Rabies virus neutralizing activity (RVNA) measured by RFFIT (cell based neutralization assay)

# Subject disposition

|  | Part 1  |                   |                   | Part 2            |
|--|---------|-------------------|-------------------|-------------------|
|  | Placebo | CL184<br>20 IU/kg | CL184<br>40 IU/kg | CL184<br>Rabipur™ |
| Entered                                      | 8       | 12                | 12                | 12                |
| Discontinued<br>before IMP<br>administration | 1       | 0                 | 0                 | 0                 |
| Received study<br>medication                 | 7       | 12                | 12                | 12                |
| Completed<br>study                           | 7       | 12                | 12                | 12                |

# Unsolicited Adverse Events

| Subjects (%)<br>with              | Part 1                             |                                   |                                   | Part 2   |
|-----------------------------------|------------------------------------|-----------------------------------|-----------------------------------|--|
|                                   | Placebo<br>(pooled)<br><br>(N = 7) | CL184<br>20 IU/kg<br><br>(N = 12) | CL184<br>40 IU/kg<br><br>(N = 12) | CL184<br>20 IU/kg<br>+<br>Rabipur™<br>(N = 12) |
| ≥ 1 AE                            | 2 (29)                             | 4 (33)                            | 8 (67)                            | 3 (25)   |
| ≥ 1 AE<br>related to IMP          | 1 (14)                             | 4 (33)                            | 6 (50)                            | 3 (25)   |
| SAE                               | 0 (0)                              | 0 (0)                             | 1 (8)                             | (0)  |
| AEs leading to<br>discontinuation | 0 (0)                              | 0 (0)                             | 0 (0)                             | 0 (0)  |



**No CL184-specific HAHA detected**



**CL184 was safe**

# Solicited adverse reactions

| Subjects (%)<br>with | Part 1                             |                                   |                                   | Part 2   |
|----------------------|------------------------------------|-----------------------------------|-----------------------------------|--|
|                      | Placebo<br>(pooled)<br><br>(N = 7) | CL184<br>20 IU/kg<br><br>(N = 12) | CL184<br>40 IU/kg<br><br>(N = 12) | CL184<br>20 IU/kg<br>+<br>Rabipur™<br>(N = 12) |
| Redness              | 0 (0)                              | 0 (0)                             | 0 (0)                             | 0 (0)  |
| Swelling             | 0 (0)                              | 0 (0)                             | 0 (0)                             | 0 (0)  |
| Induration           | 0 (0)                              | 0 (0)                             | 0 (0)                             | 0 (0)  |
| Pain                 | 0 (0)                              | 2 (17)                            | 0 (0)                             | 0 (0)  |

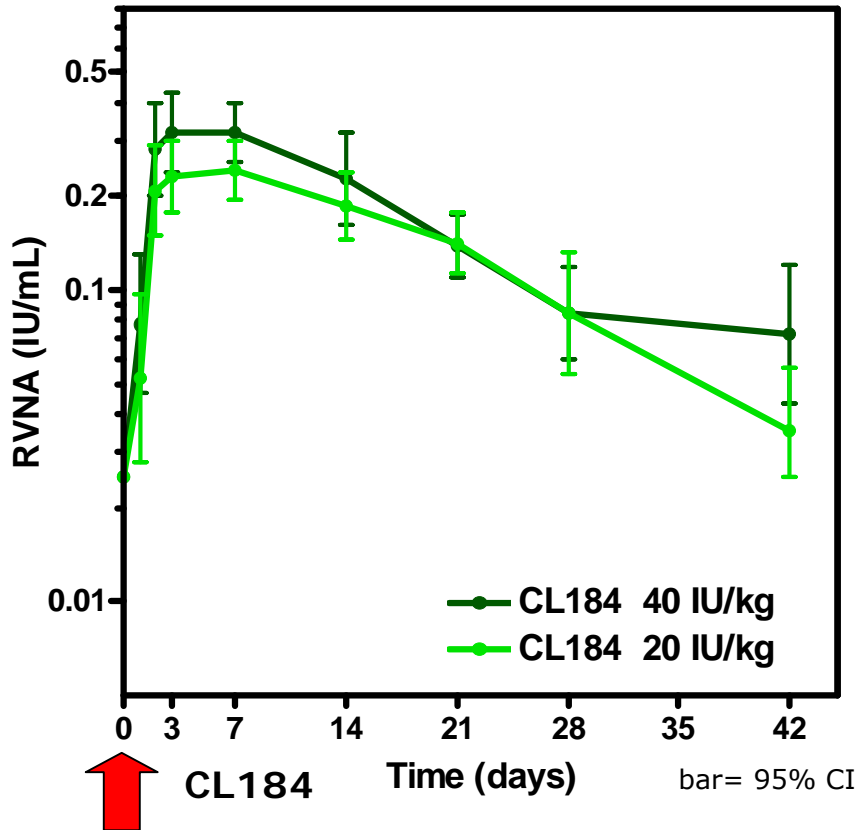


**There was no fever**



**CL184 was well tolerated**

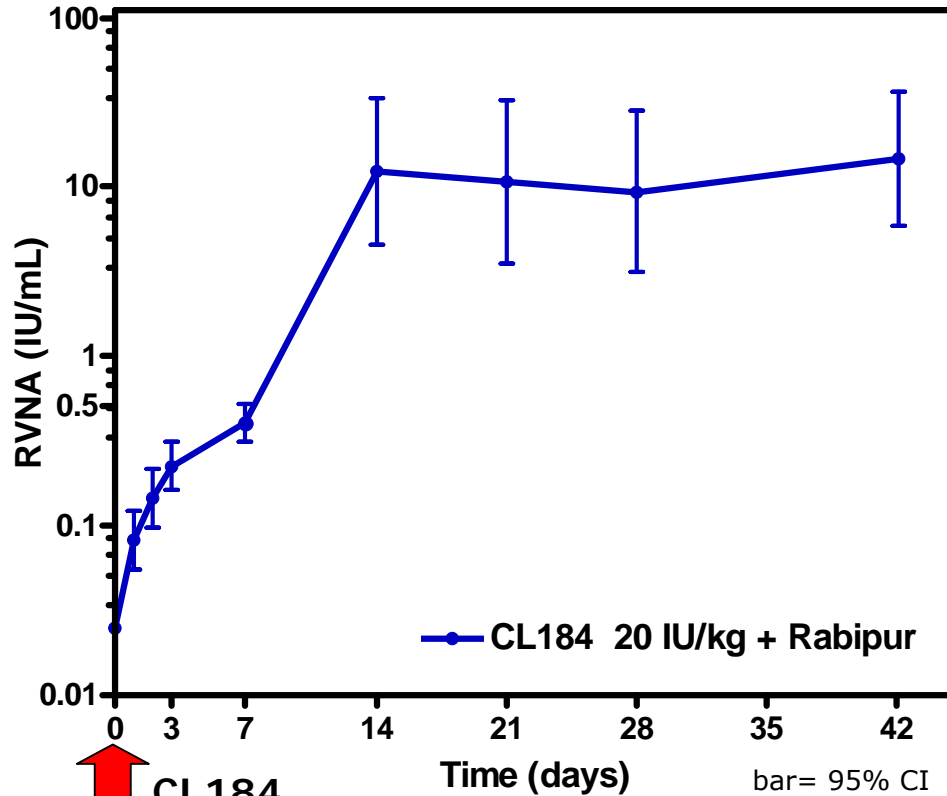
# Part 1: Neutralizing activity in subjects with CL184 mAb cocktail alone



Dose of 20 IU/kg selected to test CL184 in combination with rabies vaccine in Part 2

☞ Neutralizing activity was detected at all doses tested

# Part 2: Neutralizing activity in subjects with CL184 and PCEC vaccine



| Percentage of subjects with RVNA > 0.5 IU/mL |       |
|--|-------|
| Day 7  | 30 %  |
| Day 14                                       | 100 % |

0.5 IU/mL = rabies virus neutralizing activity that is considered to provide protection

↑ CL184

↑ ↑ ↑

↑

↑ PCECV

CL184 combined with PCEC vaccine induces adequate neutralizing activity




# Summary

## Safety

- CL184 was safe and well tolerated

## Efficacy

- When given both alone and in combination with rabies vaccine, neutralizing activity was detected at all mAb dose levels administered
  - In combination with rabies vaccine, all subjects seroconverted at Day 14
  - Neutralizing activity was comparable to historic HRIG data (Gold Standard)
-  **RAB-M-A002 data fully confirms and extends safety and efficacy data obtained in US Phase I study**