

Development of CL184 human monoclonal antibody cocktail for rabies post-exposure prophylaxis, update on clinical evaluation

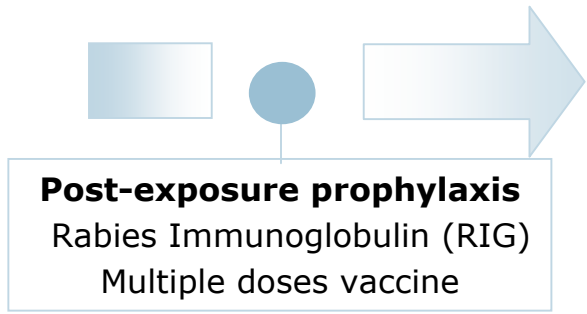
XIX RITA , 1st October 2008, Atlanta

C.P. Python on behalf of the study team

Crucell



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



Patient with rabies

Two types of RIG preparations

Human (HRIG)

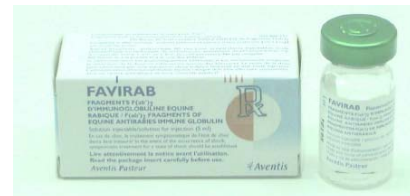


HyperRab
(Talecris)



Imogam Rabies HT
(sanofi pasteur)

Equine (ERIG)



Favirab (F(ab)'2)
(sanofi pasteur)

National productions
Endemic area

CL184: Pre-clinical and clinical data

- 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
- CL184 neutralized all rabies street viruses tested (>42 strains)
- In the hamster model, CL184 protected, in combination with rabies vaccine, against challenge by rabies virus at least as well as HRIG
- In 2 Phase I studies (US and India), CL184 was safe, well tolerated and demonstrated the expected rabies virus neutralizing activity (manuscript in publication)
- CL184 has been granted Fast Track status by US FDA

Development and commercialization partnership with sanofi pasteur as of January 2008

sanofi pasteur

The vaccines business of sanofi-aventis Group

- Crucell will continue to drive the CL184 development and will be responsible for manufacturing of the product
- sanofi pasteur will commercialize CL184 globally
- Crucell retains co-exclusive distribution rights in China, exclusive rights in Europe and the right to sell CL184 to supranational organizations

Press Releases

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Crucell Enters Agreement with Sanofi Pasteur for Next-generation Biologicals against Rabies

Exclusive agreement for rabies monoclonal antibodies to fight fatal disease

Leiden, The Netherlands, 3 January 2008 - Dutch biotechnology company Crucell N.V. (Euronext, NASDAQ: CRXL, Swiss Exchange: CRX) today announced that it has signed an exclusive collaboration and commercialization agreement with sanofi pasteur, the vaccines division of sanofi-aventis Group, for Crucell's rabies monoclonal antibodies, the next-generation rabies biologicals to be used in association with rabies vaccine for post-exposure prophylaxis against this fatal disease.

Under the terms of the agreement, Crucell will continue to perform the development activities. Crucell will be responsible for the manufacturing of the final product and will retain exclusive distribution rights in Europe, co-exclusive distribution rights in China and the rights to sell to supranational organizations such as UNICEF. Crucell will receive a payment of € 10 million following the execution of the agreement and will be eligible for milestone payments of up to € 66.5 million.

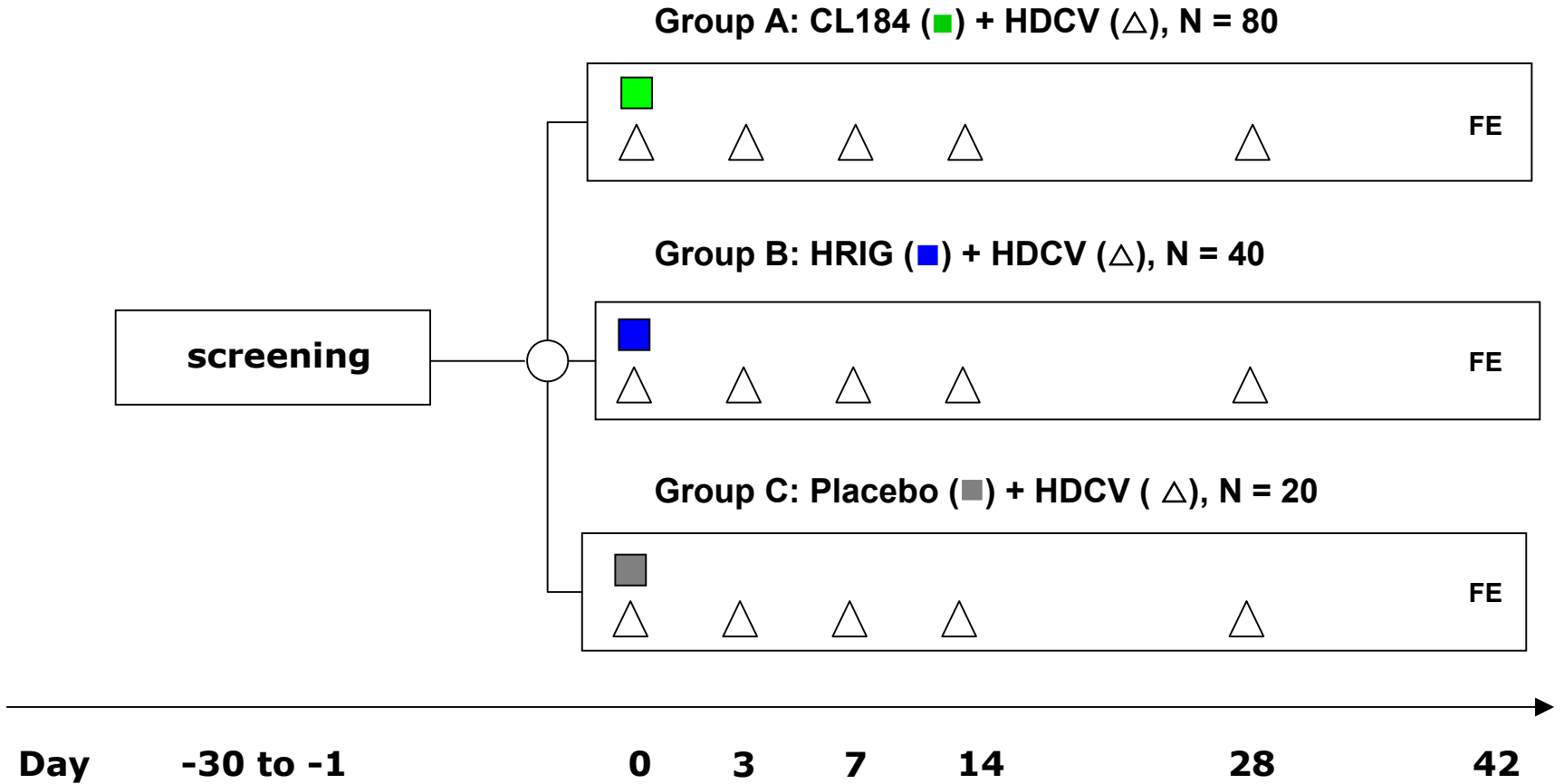
RAB-M-A003: Study design

- Design: randomized, single-blind (subjects blinded), controlled, monocentric
- Objective: safety and neutralizing activity
- Simulated rabies post-exposure prophylaxis
- 140 healthy adults
- Treatments:
 - CL184 20 IU/kg i.m.
 - HRIG (Imogam Rabies HT™) 20 IU/kg i.m.
 - CL184 Placebo i.m.

} + HDCV
(Imovax™) i.m.

Potency: 2.6 IU/dose

Study design II



Study parameters

- Safety parameters:
 - Unsolicited adverse events (AE)
 - Solicited adverse events
 - redness, swelling, induration, pain, bruising, fever
 - Laboratory safety panel
 - Blood chemistry, hematology, urine analysis
 - Vital signs
 - ECG
 - Human anti-human antibodies against CL184
- Effect parameters:
 - Rabies virus neutralizing activity (RVNA) measured by RFFIT at Kansas State University
 - CR57 and CR4098 Pharmacokinetics (PK subset)

Subject disposition

	CL184 + HDCV	HRIG + HDCV	Placebo + HDCV
Randomized	80	40	20
Received study treatment	80	40	20
Completed study	80	40	20
RVNA quantifiable at pre-dose	4	0	1

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RVNA quantifiable at pre-dose	4	0	1

Excluded from ATP

Safety

Subjects (%) with	CL184 + HDCV N= 80	HRIG + HDCV N=40	Placebo + HDCV N=20
≥ 1 AE (solicited + unsolicited)	51 (63.8)	30 (75.0)	13 (65.0)
≥ 1 AE (unsolicited)	50 (62.5)	21 (52.5)	10 (50.0)
≥ 1 AE (unsolicited) related to IMP	18 (22.5)	11 (27.5)	4 (20.0)
≥ 1 severe AE (unsolicited)	1 (1.3)	0 (0.0)	0 (0.0)
≥ 1 SAE (any)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)

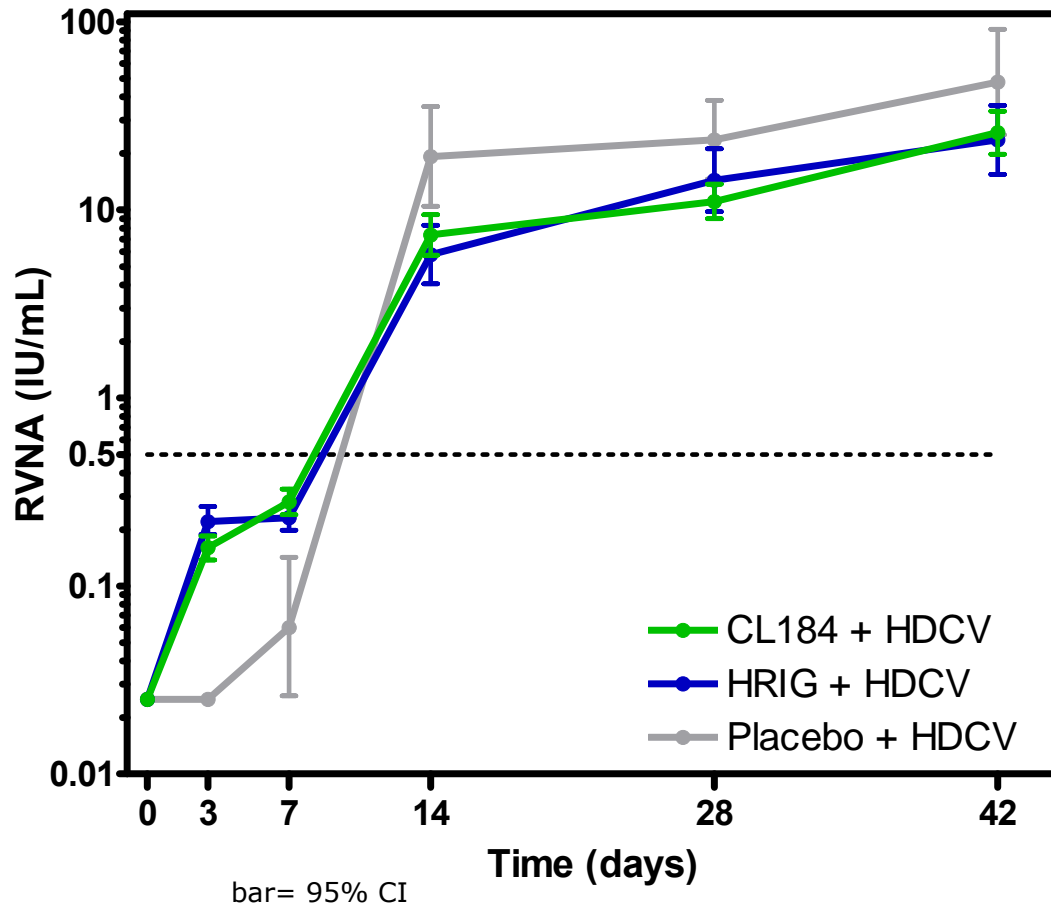
Safety

Subjects (%) with	CL184 + HDCV N= 80	HRIG + HDCV N=40	Placebo + HDCV N=20
≥ 1 AE (solicited + unsolicited)	51 (63.8)	30 (75.0)	13 (65.0)
≥ 1 AE (unsolicited)	29 (36.2)	21 (52.5)	10 (50.0)
≥ 1 AE (unsolicited related to IMP)	5 (6.25) # 129: headache, started 10 h after dosing, duration 2 h	11 (27.5)	4 (20.0)
≥ 1 severe AE (unsolicited)	1 (1.3)	0 (0.0)	0 (0.0)
≥ 1 SAE (any)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)

Solicited AEs

Subjects (%) with	CL184 + HDCV N= 80	HRIG + HDCV N=40	Placebo + HDCV N=20
Any CL184/HRIG injection site reaction	10 (12.5)	26 (65.0)	6 (30.0)
Redness	1 (1.3)	4 (10.0)	3 (15.0)
Swelling	1 (1.3)	4 (10.0)	0 (0.0)
Induration	2 (2.5)	3 (7.5)	0 (0.0)
Pain	9 (11.3)	21 (52.5)	3 (15.0)
Bruising	2 (2.5)	6 (15.0)	3 (15.0)
Fever	2 (2.5)	0 (0.0)	0 (0.0)

Rabies virus neutralizing activity (RVNA) (ATP)

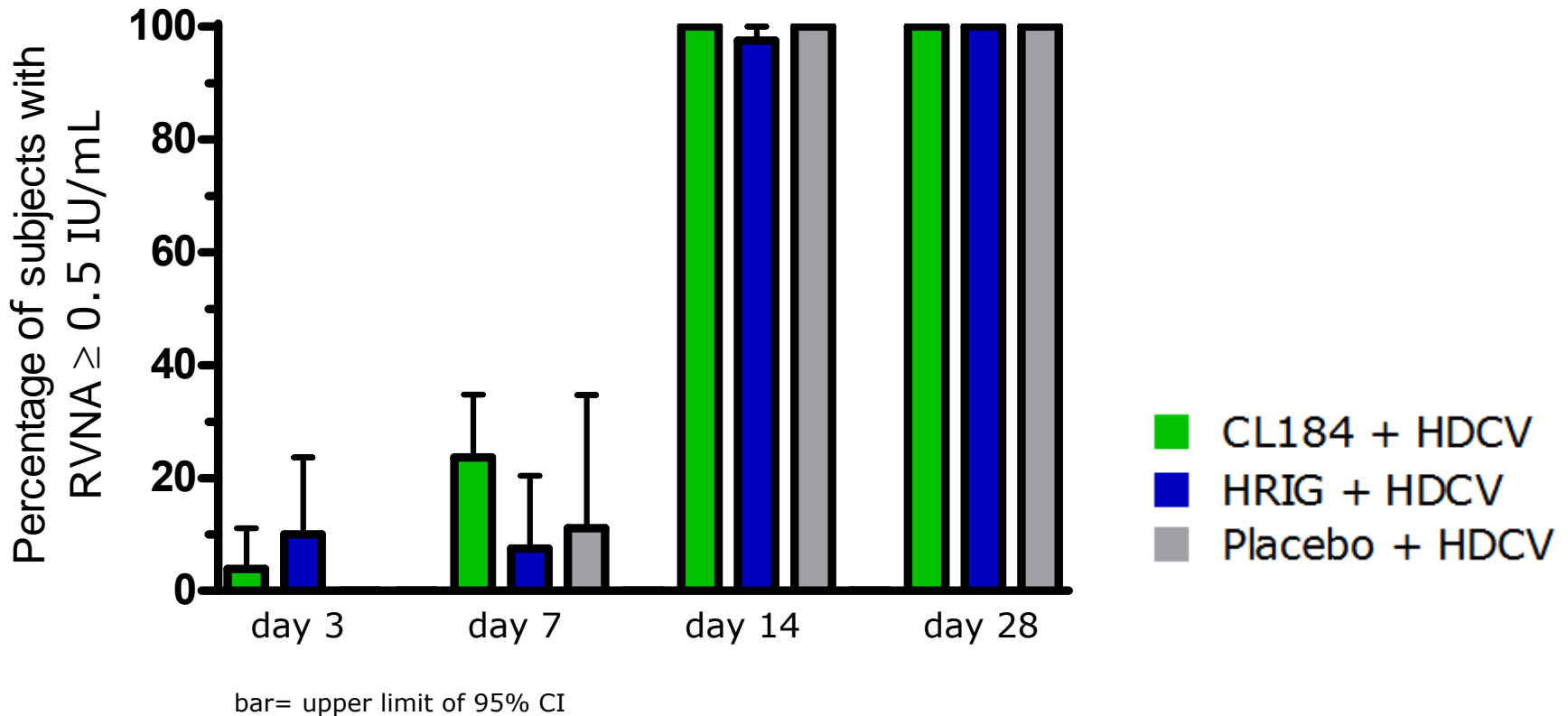


0.5 IU/mL= RVNA considered adequate by WHO/ACIP

CL184, HRIG or Placebo administered at D0
HDCV administered at D0, 3, 7, 14 & 28



Percentage of subjects with RVNA \geq 0.5 IU/mL (ATP)



**CL184, HRIG or placebo administered at D0
HDCV administered at D0, 3, 7, 14 & 28**

0.5 IU/mL= RVNA considered adequate
by WHO/ACIP

Summary

Safety

- CL184 was safe and well tolerated

Neutralizing activity

- Neutralizing activity after administration of CL184 in combination with rabies vaccine was comparable to HRIG combined with rabies vaccine
- Passive immunization with CL184 or HRIG slightly decreased the immune response to rabies vaccine. The decrease was comparable between CL184 and HRIG
- Within 14 days, all subjects administered CL184 plus rabies vaccine reached immunity levels considered adequate by WHO/ACIP

 **Preliminary RAB-M-A003 data confirms and extends safety and neutralizing activity data and supports further development of CL184**

Collaborating institutions

- Crucell, Leiden/Berne, The Netherlands/Switzerland
- sanofi pasteur, Lyon, France
- Dr CJ Kissling (PI) and colleagues at MDS Pharma Services, Lincoln, Nebraska, USA
- Dr Susan Moore and colleagues at Kansas State University for RFFIT