# Vi-CRM$_{197}$ conjugate vaccine against typhoid fever: development and early clinical testing

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8th International Typhoid Fever and Invasive Salmonelloses – Dhaka, Bangladesh

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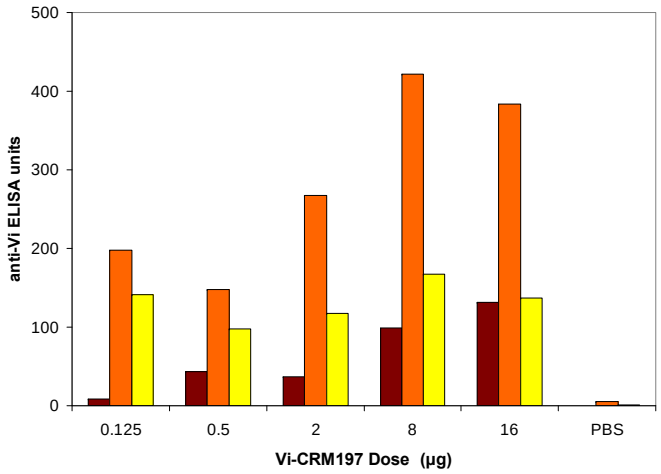
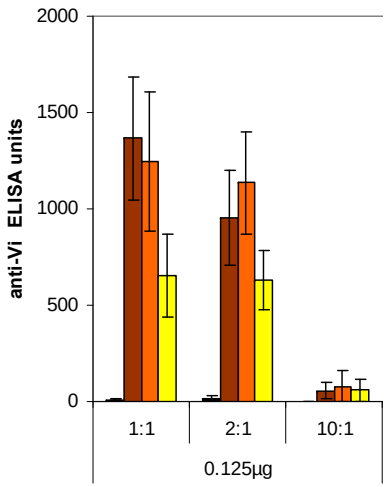
# Agenda

- Status of project as presented in Kilifi
- Clinical plan overview
- Phase 1 & dose ranging studies
- Phase 2 studies in endemic countries
- Proposed basis for pre-qualification
- Next steps
- Acknowledgements

# Vi-$CRM_{197}$: Laboratory proof of concept presented in Kilifi (Laura Martin | January 2009)

- Immunogenic and well tolerated
  - Antibody response is dose dependent
  - 1:1 or 2:1 weight ratio Vi:$CRM_{197}$ superior to 10:1 ratio




- anti-Vi antibody levels comparable to other Vi-conjugates
  - Analysis of sera supplied by NIH
  - Using $CRM_{197}$, TT conjugates made with Vi obtained from NIH



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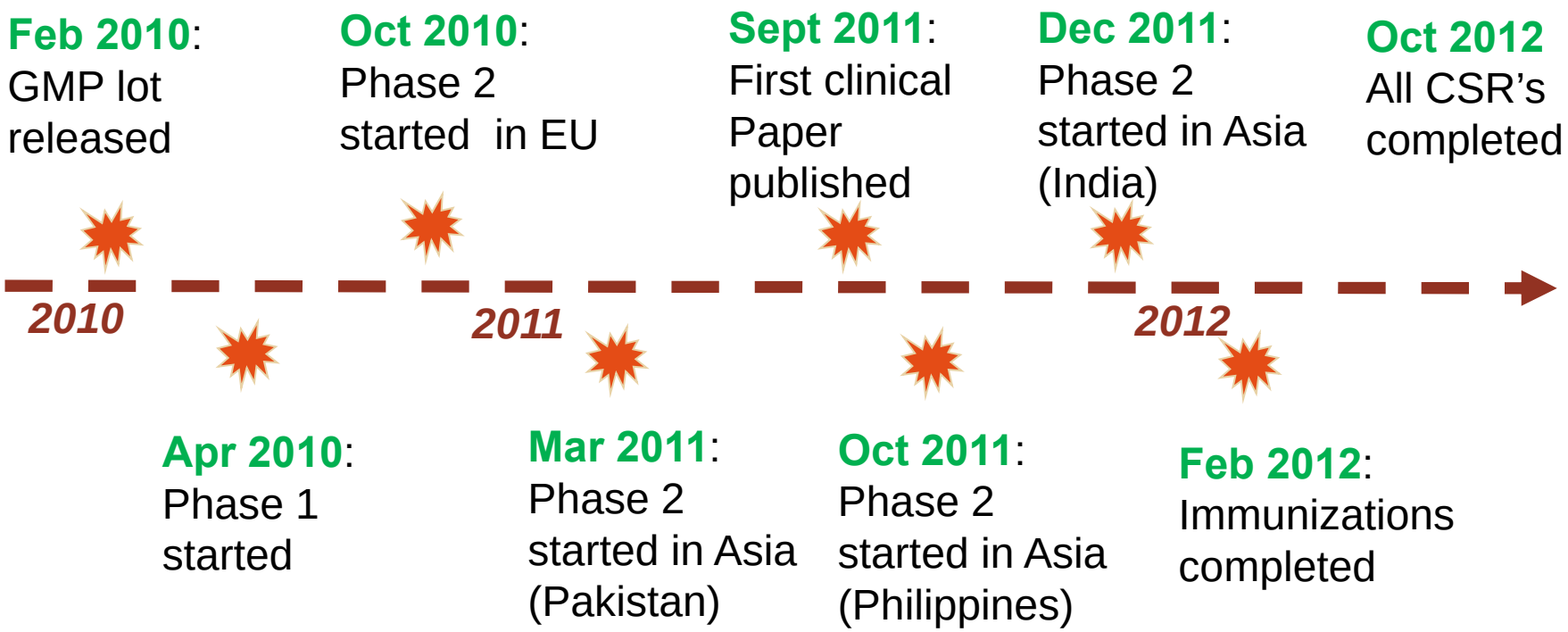
# Vi-CRM$_{197}$ – Clinical development overview

*A 30 month journey: key milestones*



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# Phase 1 & dose ranging studies in EU adults (1)

*Study design*

| First in Man Trial | |
|---|---|
| **Group** | **Vaccine** |
| A | Vi-$CRM_{197}$ conjugate (25.0 µg/dose) |
| B | Typherix (25.0 µg/dose) |

Clinical Site:

Center for Evaluation of Vaccines
University of Antwerp – Belgium

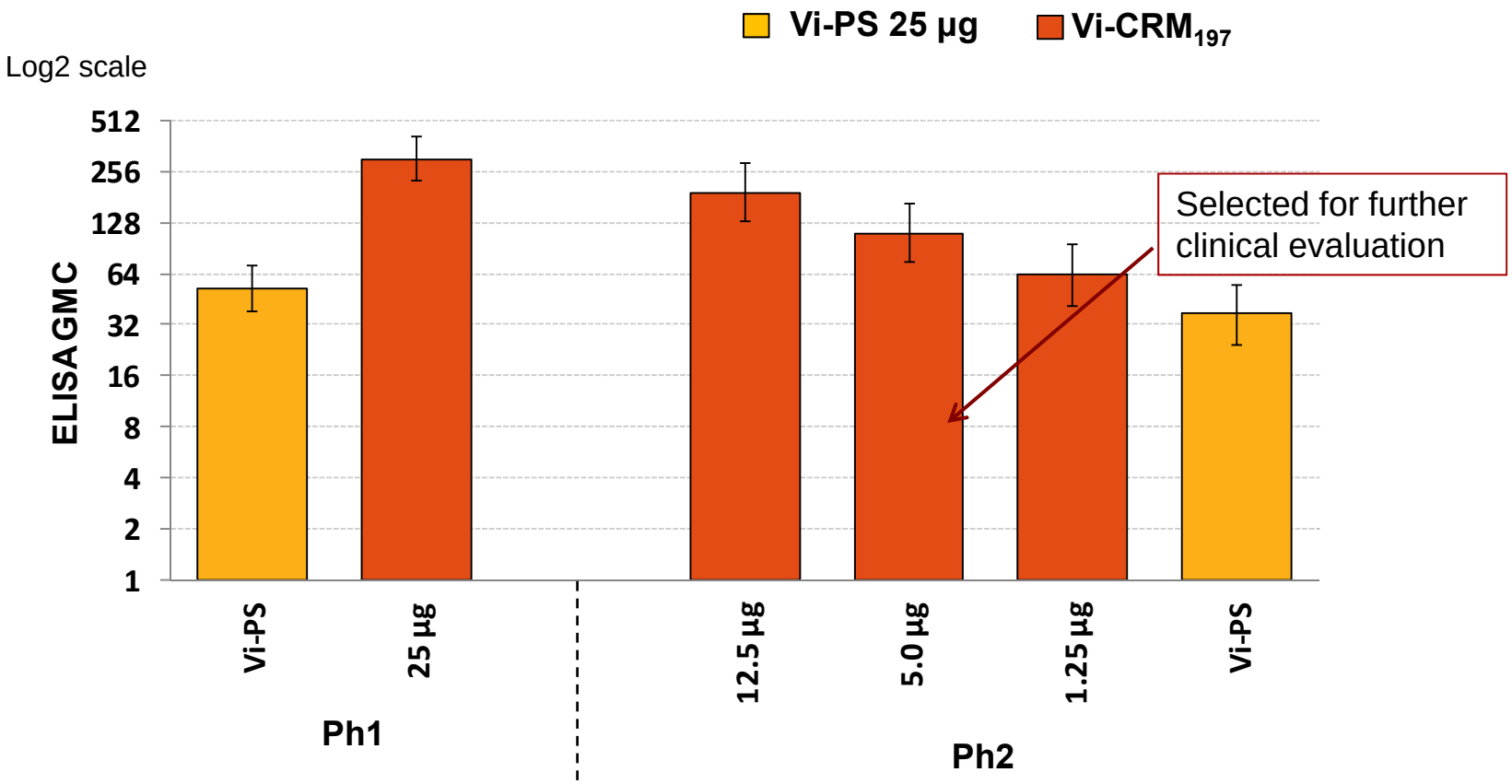
PI: Prof. Pierre Van Damme

| Dose Ranging trial | |
|---|---|
| **Group** | **Vaccine** |
| A | Vi-$CRM_{197}$ conjugate (12.5 µg/dose) |
| B | Vi-$CRM_{197}$ conjugate (5.0 µg/dose) |
| C | Vi-$CRM_{197}$ conjugate (1.25 µg/dose) |
| D | Typherix (25.0 µg/dose) |

***Source: Van Damme et al. PLoS ONE 2011; 6 (9): e25398 doi; 10.1371***

# Phase 1 & dose ranging studies in EU adults (2)

*Anti-Vi serum IgG 28 days after vaccination*




***Source: Van Damme et al. PLoS ONE 2011; 6 (9): e25398 doi; 10.1371***



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# Phase 2 clinical studies in endemic countries (1)

*Study Design*

| | 1° dose | 2° dose | 3° dose |
|---|---|---|---|
| Adults 18-45 y | Vi-CRM | | |
| | Vi-PS | | |
| DSMB | | | |
| Children 24-59 mo * | Vi-CRM | Vi-CRM | |
| | Vi-PS | Prevenar | |
| DSMB | | | |
| Older Infants 9 mo * | Vi-CRM + EPI | Vi-CRM | |
| | Prevenar + EPI | Prevenar | |
| DSMB | | | |
| Infants 6 wks ** | Vi-CRM + EPI | Vi-CRM + EPI | Vi-CRM + EPI |
| | Prevenar+EPI | Prevenar+EPI | Prevenar+EPI |

* **Doses 8 weeks apart in children & and older infants** ** **Doses 4 weeks apart in infants**

# Phase 2 clinical studies in endemic countries (2)

*Clinical Sites and population enrolled*

| PAKISTAN | INDIA | PHILIPPINES |
|---|---|---|
| **Aga Khan University Karachi, Pakistan**<br><br>**PI: Prof Zulfiqar Buttha**<br>**Prof Sajid Soofi** | **KEM Hospital Pune, India**<br><br>**PI: Prof Ashish Bavdekar** | **Research Institute for Tropical Medicine Manila, Philippines**<br>**PI: Prof Rose Capeding** |
| **Adults 18-45 years** | **Adults 18-45 years** | |
| **Children 24-59 months** | | **Children 24-59 months** |
| **Older Infants 9 months** | | **Older Infants 9 months** |
| **Infants 6 weeks** | | **Infants 6 weeks** |

# Overall safety profile in endemic countries trials

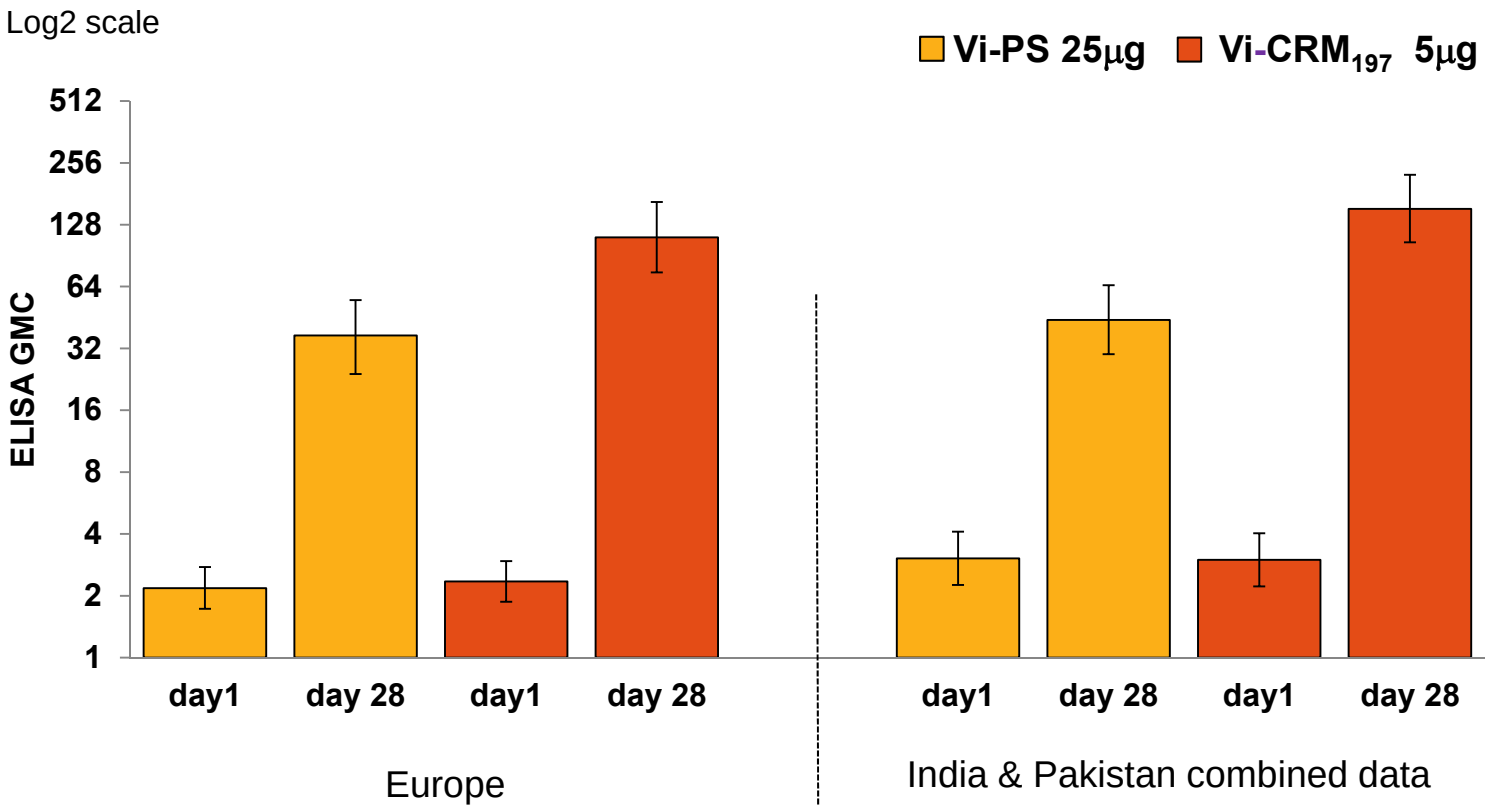
*Pakistan, India & Philippines, combined data*

| Vaccine | # subjects | # doses | Any death | Any SAE* | Any Local | Any systemic |
|---|---|---|---|---|---|---|
| $Vi\text{-}CRM_{197}$ | 40 adults | 40 | 0 | 0 | 19 (48%) | 20 (50%) |
| | 40 children | 80 | 0 | 2 (5%) | 23 (58%) | 16 (40%) |
| | 40 older infants | 80 | 0 | 4 (10%) | 9 (23%) | 18 (45%) |
| | 40 infants | 120 | 0 | 5 (13%) | 34 (85%) | 33 (83%) |
| Control | 40 adults | 40 | 0 | 0 | 20 (50%) | 20 (50%) |
| | 40 children | 80 | 0 | 2 (5%) | 22 (55%) | 18 (45%) |
| | 40 older infants | 80 | 0 | 5 (13%) | 21 (53%) | 29 (73%) |
| | 39 infants | 117 | 0 | 4 (10%) | 31 (79%) | 28 (72%) |

* No Serious Adverse Event was vaccine related

# Immunogenicity in Adults is similar in Europe and Asia

*Anti-Vi serum IgG 28 days after vaccination*



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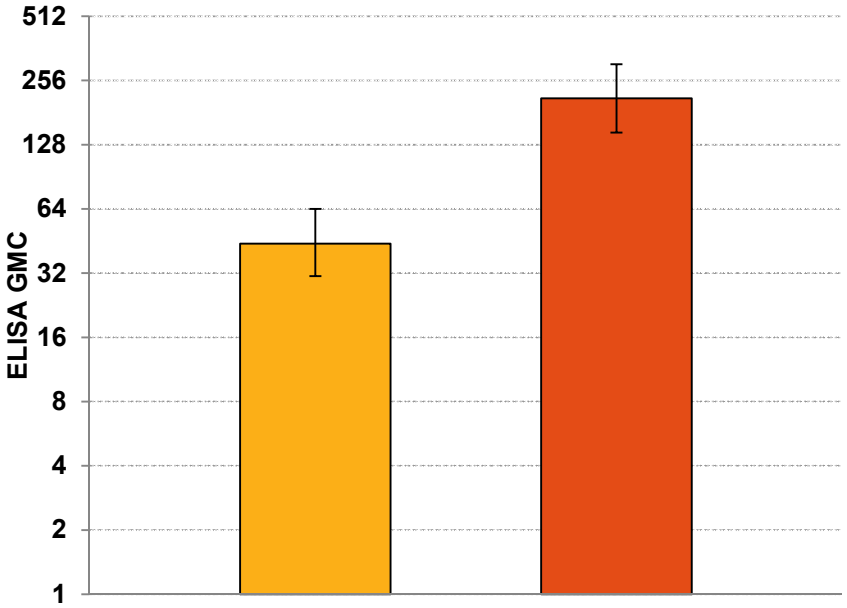
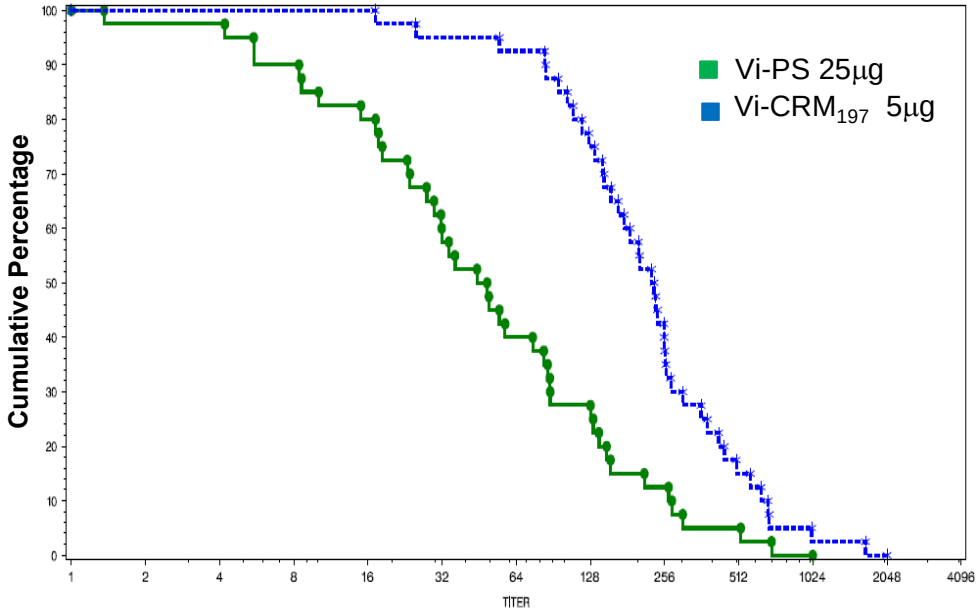
# Vi-CRM197 (5µg) in 9 month infants vs. Vi-PS (25µg) in adults

*Anti-Vi serum IgG 28 days after vaccination*




**Vi-PS: All adults from NVGH studies in endemic countries combined**

**Vi-CRM$_{197}$: Older infants from NVGH studies in endemic countries combined**



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# NVGH proposed basis for WHO pre-qualification

- Field trials with the Vi-PS vaccines and Vi-rEPA have consistently shown that anti-Vi IgG serum antibodies confer protection against typhoid fever.
- The investigators of the Vi-rEPA efficacy trial defined serological correlates of protection (i.e., threshold of anti-Vi antibody levels which correlates with clinical protection)
- Therefore, the prequalification of ViCP-CV could be based on immunogenicity data (i.e., without a pre-licensure efficacy trial with clinical endpoints)
- Regulatory wise, two approaches should be considered:
  - ViCP-CV induce protective titers in children <2 years. Sero-protection rates can be calculated by correlating the manufacturer's ELISA data with the NIH ELISA data used to define serological correlates of protection in the Vietnamese efficacy trial
  - Immunogenicity of ViCP-CV in <2 years is not inferior than that of the licensed Vi-PS in >2 years (i.e., age groups where the clinical efficacy of Vi-PS was shown and the vaccine is licensed)
- Following registration and pre-qualification, larger post marketing surveillance studies should be undertaken to further assess vaccine effectiveness and long term safety

# Conclusions

- NVGH studies show that Vi-$CRM_{197}$ is a safe and well tolerated vaccine in all age groups
- NVGH studies show that Vi-$CRM_{197}$ is immunogenic in infants and inclusion of a typhoid vaccine into WHO EPI schedules is a concrete possibility
- NVGH is ready to pass the baton to an Asian manufacturer to complete development, obtain licensure, achieve WHO pre-qualification and start distribution

# Acknowledgements


All study participants of clinical studies and their families

Aga Khan Clinical Team
Zulfiqar Buttha
Sajid Soofi
Atif Habib
Shabina Ariff
Noshad Ali

RITM Manila Clinical Team
Maria Rosario Capeding
Edison Alberto
Nelia Malubay

KEM Clinical Team
Ashish Bavdekar
Sanjay Juvekar
Anand Kawade

NVGH Development Project Team
Laura Martin & all of NVGH

Vi-CRM$_{197}$ DSMB
Steven Black
Dipika Sur
Sajid Maqbool
Lulu Bravo
Juhani Eskola

Antwerp CEV Clinical Team
Pierre Van Damme
Froukjie Kafeja
Ilse De Coster

Funding
SVA
FMdP
RT




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