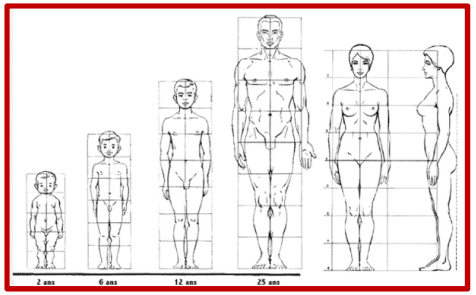
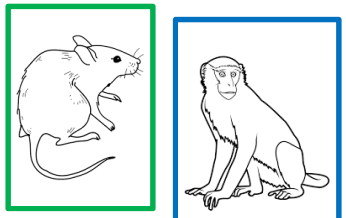
Estimating an effective dose for a repurposed drug to treat Ebola: the case of favipiravir

France Mentré, Anne-Marie Taburet, Jeremie Guedj, Naïm Bouazza, Jean-Marc Treluyer, Xavier Anglaret, Sakoba Keïta, Xavier de Lamballerie, Pierre Frange, Denis Malvy

Outline

- Introduction
- Dose of favipiravir for patients with EVD
- JIKI Clinical trial
  - Design
  - Implementation
- Modelling PKVK
  - Mouse data
  - Next: NHP
- Lessons learnt





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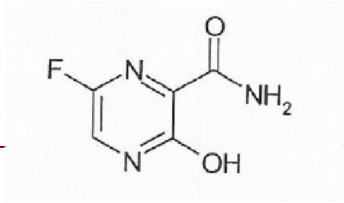
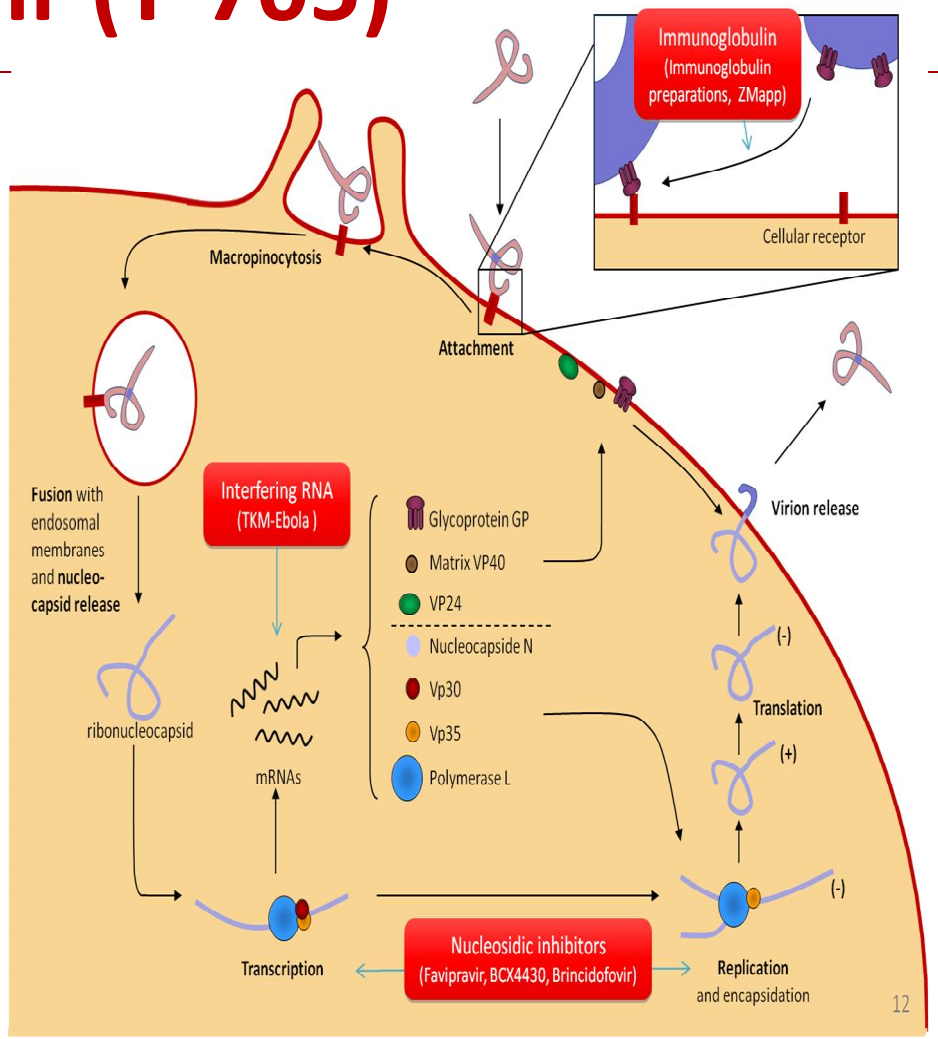


Favipiravir (T-705)

- **Treatment of Ebola Virus Disease**
  - Favipiravir: nucleoside polymerase inhibitor
  - Approved for use in influenza
  - Developed by Toyama Chemicals, Japan
  - Good tolerance
  - Was available in Oct 2014
  - In Ebola infected mice treated with favipiravir: 100% survival (vs 0% untreated)

(*Oesterreich et al, Antivir Res, 2014)*



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Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Short Communication

Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model

Lisa Oestereich [a,b], Anja Lüdtke [a,c], Stephanie Wurr [a,b], Toni Rieger [a,b], César Muñoz-Fontela [a,c], Stephan Günther [a,b,*]

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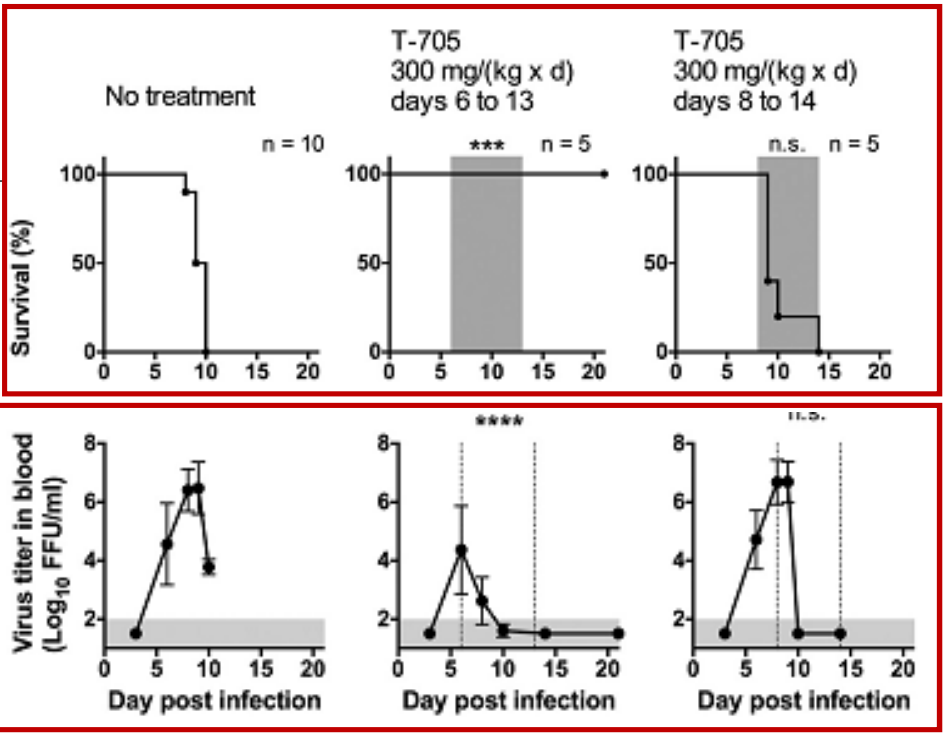
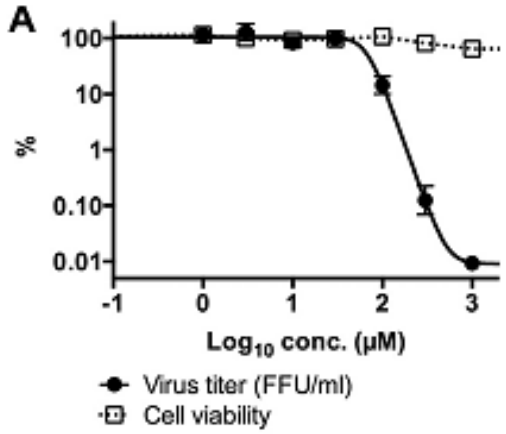
[b] German Centre for Infection Research (DZIF), Partner Site Hamburg, Germany
[c] Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Martinistrasse 52, 20251 Hamburg, Germany





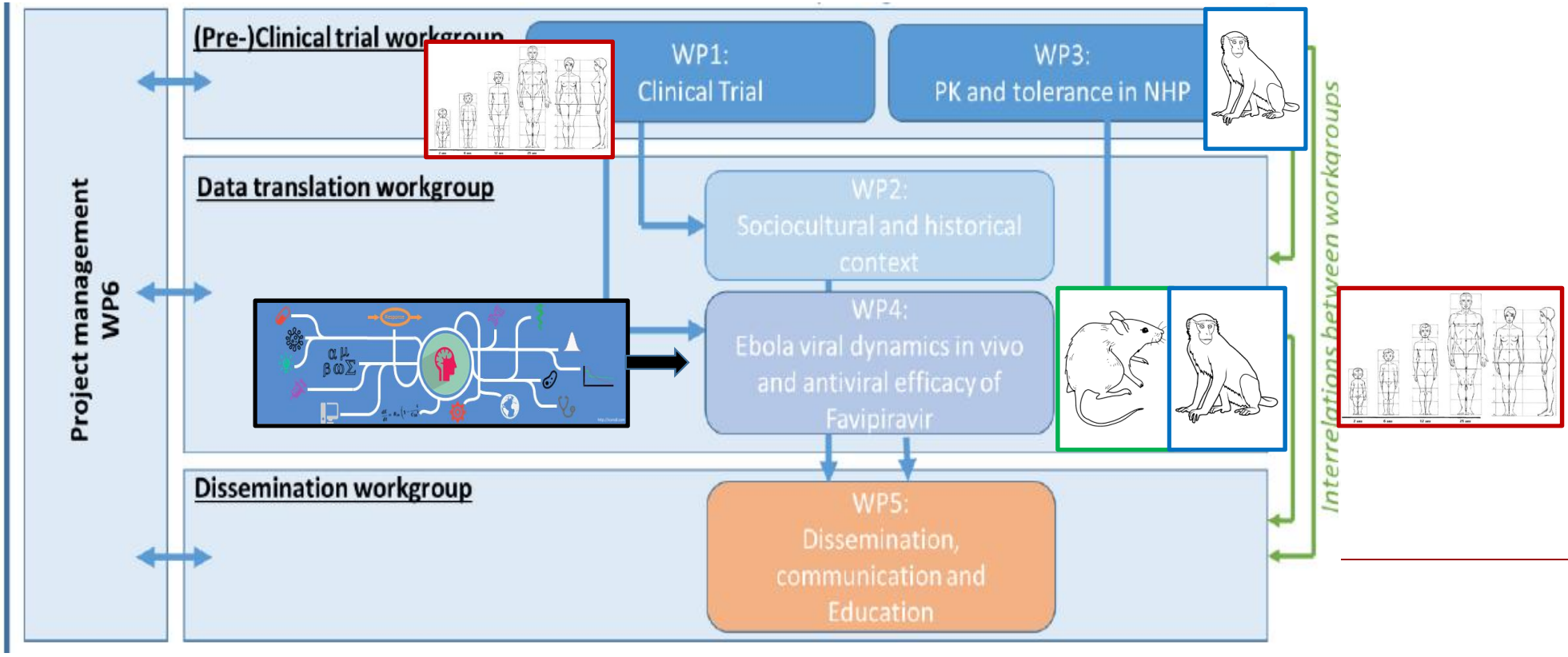
B

		95% CI
IC_{50}	67 µM (10.5 µg/ml)	56 – 75 µM
IC_{90}	110 µM (17 µg/ml)	83 – 143 µM
IC_{99}	186 µM (29 µg/ml)	132 – 265 µM

REACTION!

Evaluation of efficacy and antiviral activity of favipiravir in non-human primates & humans

PI: Hervé Raoul, BSL4, INSERM,France



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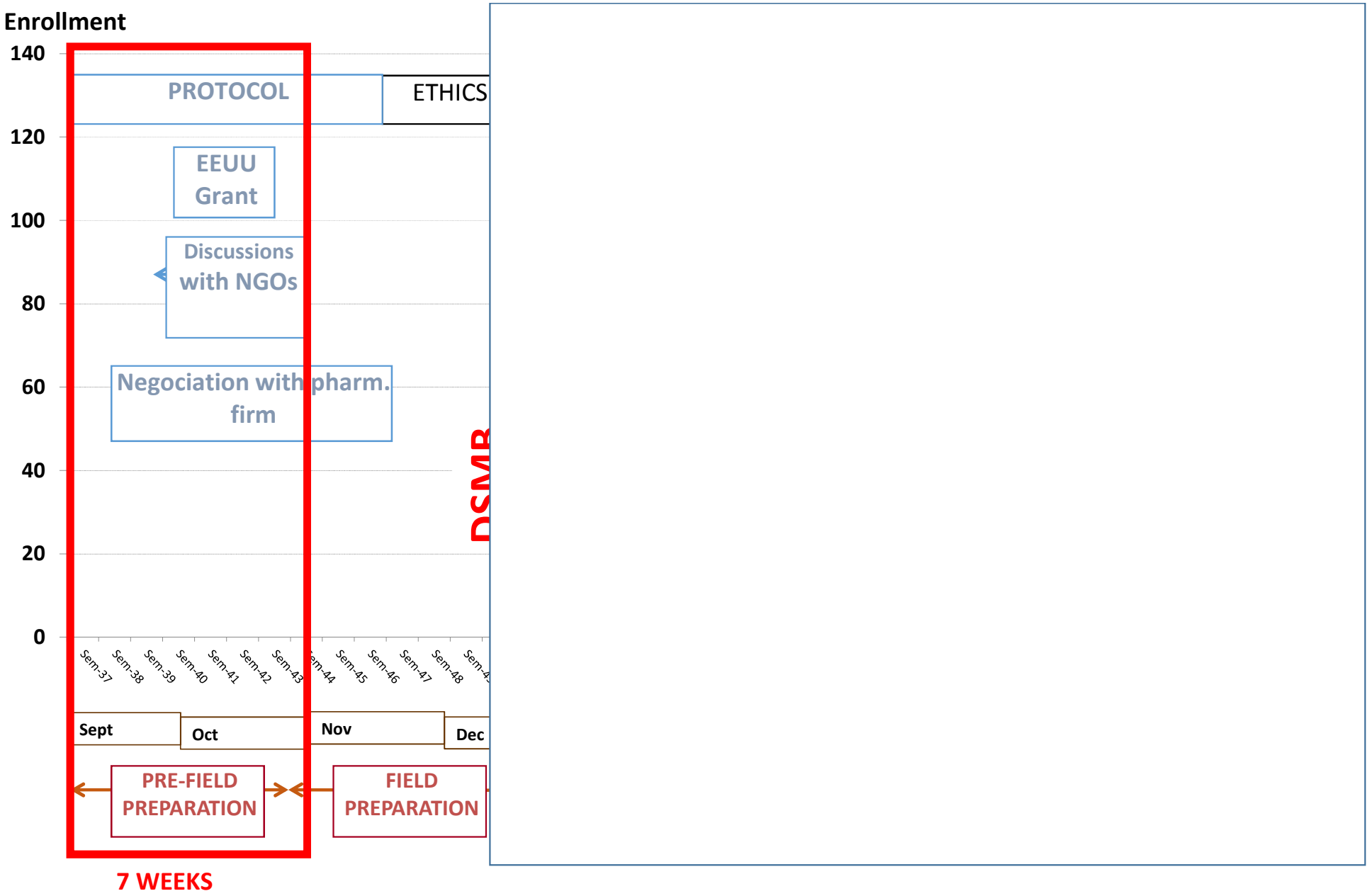
Enrollment
140
120
100
80
60
40
20
0
PROTOCOL
ETHICS
EEUU Grant
Discussions with NGOs
Negociation with pharm. firm
DSMB
Sem-37
Sem-38
Sem-39
Sem-40
Sem-41
Sem-42
Sem-43
Sem-44
Sem-45
Sem-46
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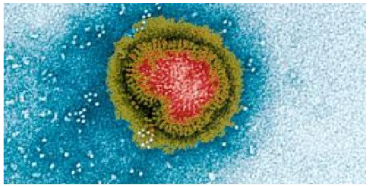
Sem-48
Sept
Oct
Nov
Dec
PRE-FIELD PREPARATION
FIELD PREPARATION
7 WEEKS

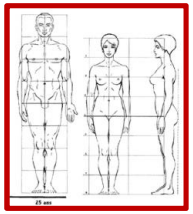
Dose of favipiravir in EVD adult patients?



- Favipiravir in influenza
  - IC50 of favipiravir 1 μg/ml
  - Protein binding 50%
  - Dosage regimen approved in Japan 1600mg/600mg bid for 4 days
  - Dosage regimen for Phase 3 trial in US 1800mg/800mg bid for 4 days
- Higher studied dose in HV
    - Single dose 2400 mg
    - Maintenance dose 600 mg tid

- Favipiravir in Ebola
  - IC50 of favipiravir 10 μg/ml
  - Mice successfully treated with dose of 150 mg/kg bid *per os*

➢ Dosage regimen in adult patients?



- IC50 rule: 10 times higher than for influenza = 8 g?
- Same dose/kg than in mice 150 x 70 = 10.5 g?

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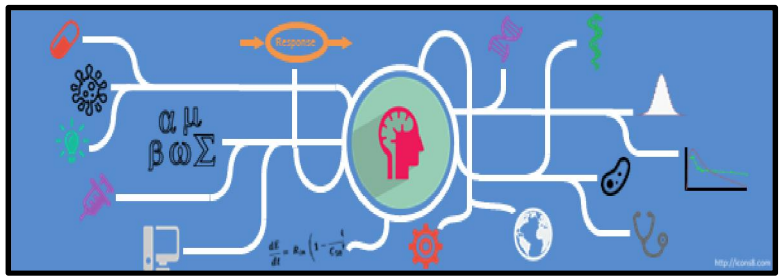
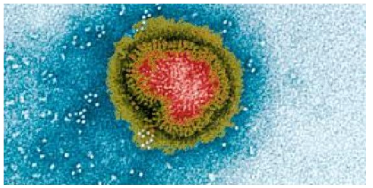
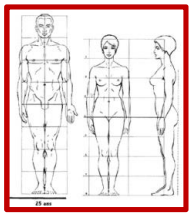
REACTION!

Dose of favipiravir in EVD adult patients?







Additional PK data asked to Toyama Chemicals

Toxicokinetics data in mice with same dose

Population PK in Phase 3 US studies

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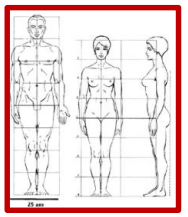
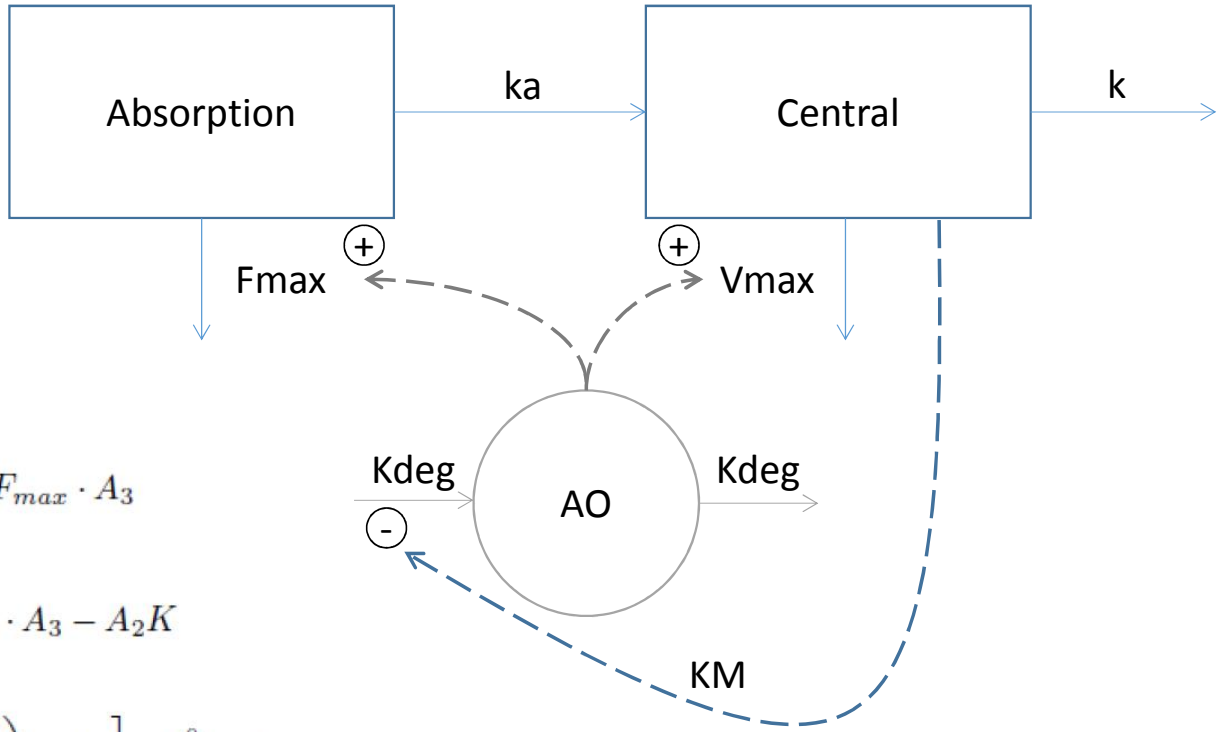
REACTION!

Population PK model (US phase 3 influenza)





$$\frac{dA_1}{dt} = -A_1 K_a - A_1 F_{max} \cdot A_3$$

$$\frac{dA_2}{dt} = A_1 K_a - A_2 V_{max} \cdot A_3 - A_2 K$$

$$\frac{dA_3}{dt} = K_{deg} \cdot \left[1 - \left(\frac{C}{K_M + C}\right) - A_3\right], A_3^{t^0} = 1$$

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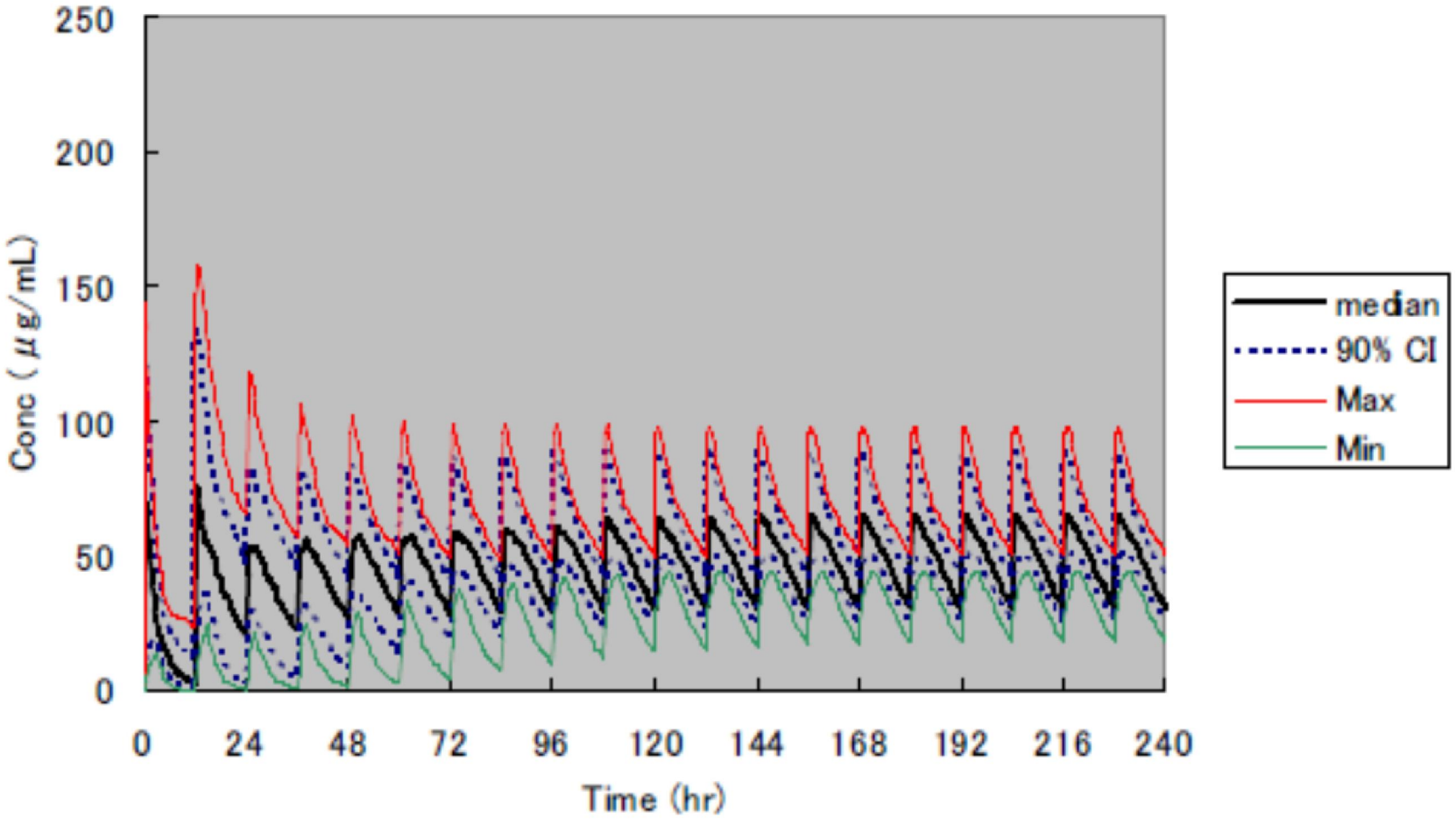
REACTION!

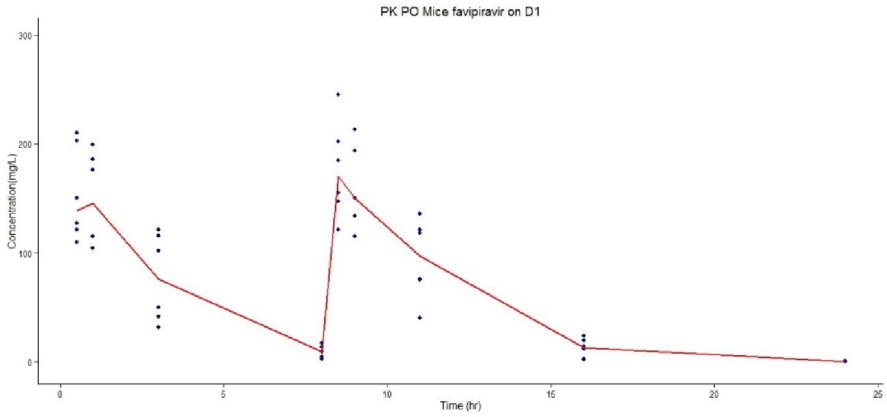
Favipiravir Population Pharmacokinetics Simulation

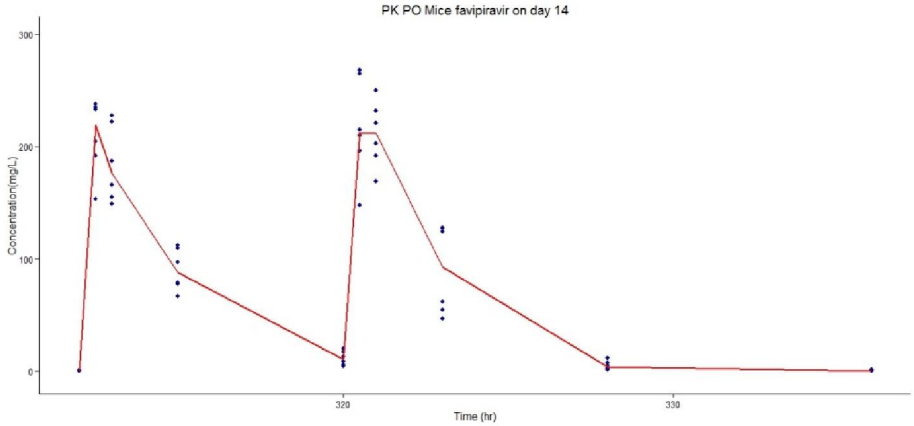
No.1 1800, 1800/ 800, 800 mg
Resource data: PopPK simulation



Favipiravir PK in Mice

- Dosing: 150 mg/kg BID per os (H0 and H8)
- Sampling times (D1, D14): H0.5, 1, 3, 8, 8.5, 9, 11, 16, 24
- 108 mice, one sample per mouse





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REACTION!

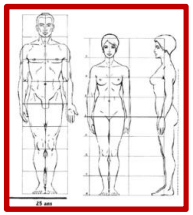
Dose of favipiravir in EVD adult patients (ctd)

- Mice successfully treated with dose of 150 mg/kg bid *per os*
- PK data in mice provided by Toyama

	C_{min} (µg/mL)	C_{ave} (µg/mL)
Free Concentration in mice at steady state	4.5	50
Corresponding total Concentration in humans at steady state	10	113

- Target exposure in humans found by adjusting on protein binding rate
- Population PK data in patients (US Phase 3 study) obtained from Toyama

➢Simulations of various dosage regimens to achieve target exposure



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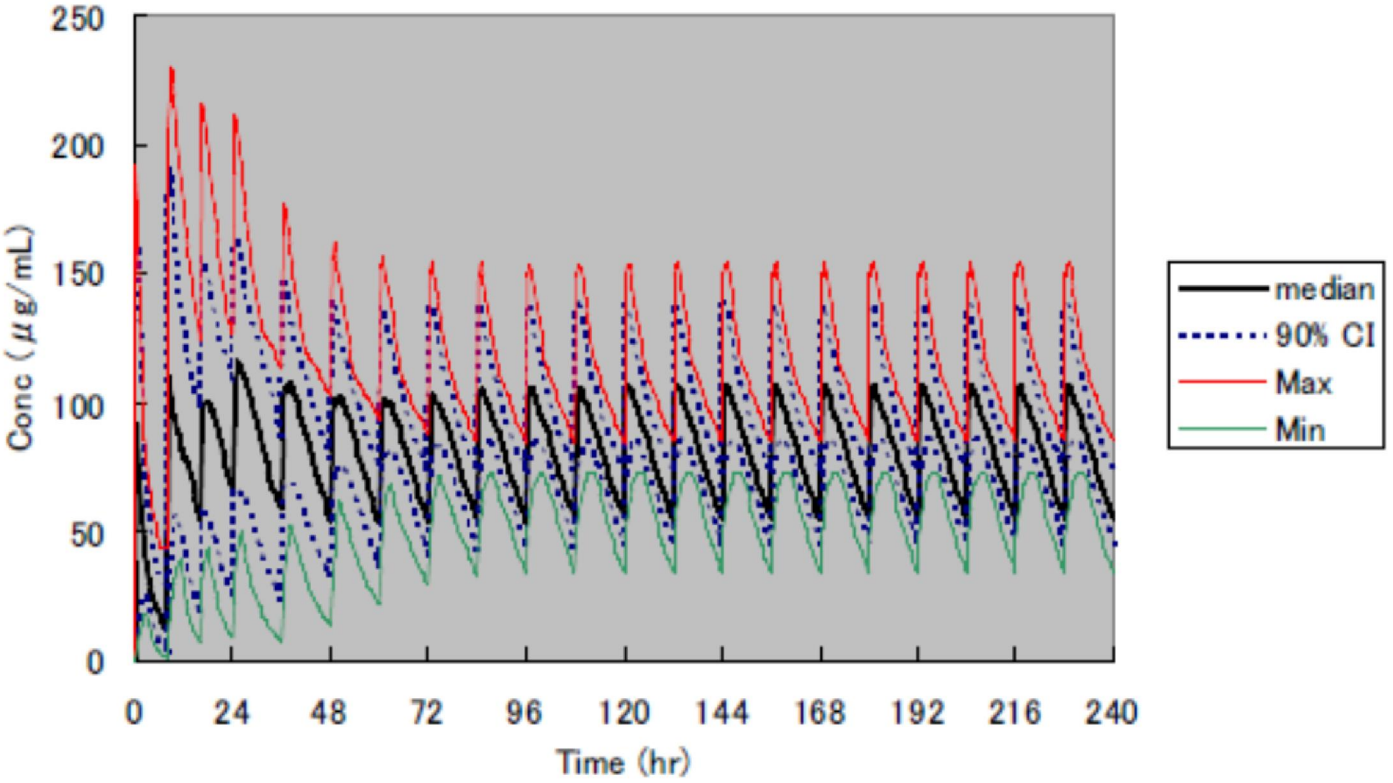
REACTION!

Favipiravir Population Pharmacokinetics Simulation

No.3 2400, 2400, 1200/ 1200, 1200 mg

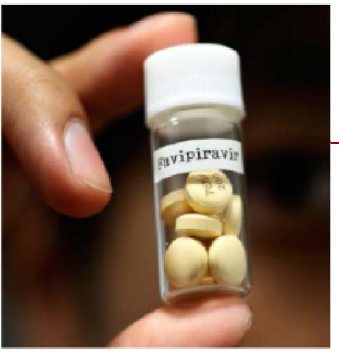
Resource data: PopPK simulation

African American



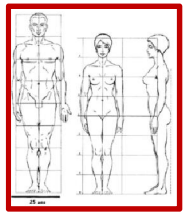
Favipiravir pharmacokinetic concentration-time profiles in 100 subjects for dosing scenario was simulated. (Age 35~60 yr, Body weight 60 kg, Race African American)

7



The drug favipiravir will be tested in clinical trials against Ebola next month.

Dose of favipiravir in EVD adult patients (ctd)



- **Maintenance dose: 1200 mg every twelve hours (10 days)**
- Need to give a loading dose at **day 1** to rapidly achieve high drug concentration: **2400 mg at H0, 2400 mg at H8, 1200 mg at H16**

	C_{min} (µg/mL)	C_{ave} (µg/mL)
Targeted	10	113
Maintenance dose	57	83.3
Day 1	9.8 (8 hours) 45.2 (16 hours)	6.2

Mentré et al., Dose regimen of favipiravir for Ebola virus disease, Lancet Infect Dis (2014)

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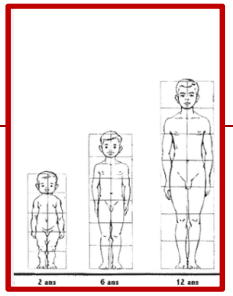
REACTION!

Favipiravir Dose in children



- Collaboration with JM Treluyer and P Frange (Necker, Paris, France)
- Favipiravir never given in children below 12 years
- Aldehyde oxydase involved in degradation of favipiravir mature at 1 year
- Allometric scaling and use of the PK model to get same exposure than in adults

Weight (kg)	First Day (mg)			2^{nd} to 10^{th} day (mg)		
10 - 15	600	600	200	200	200	200
16 - 21	800	800	400	400		400
22 - 35	1200	1200	600	600		600
36 - 45	1600	1600	800	800		800
46 - 55	2000	2000	1000	1000		1000
> 55 (adult)	2400	2400	1200	1200		1200

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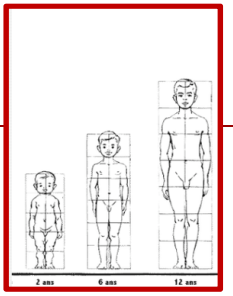
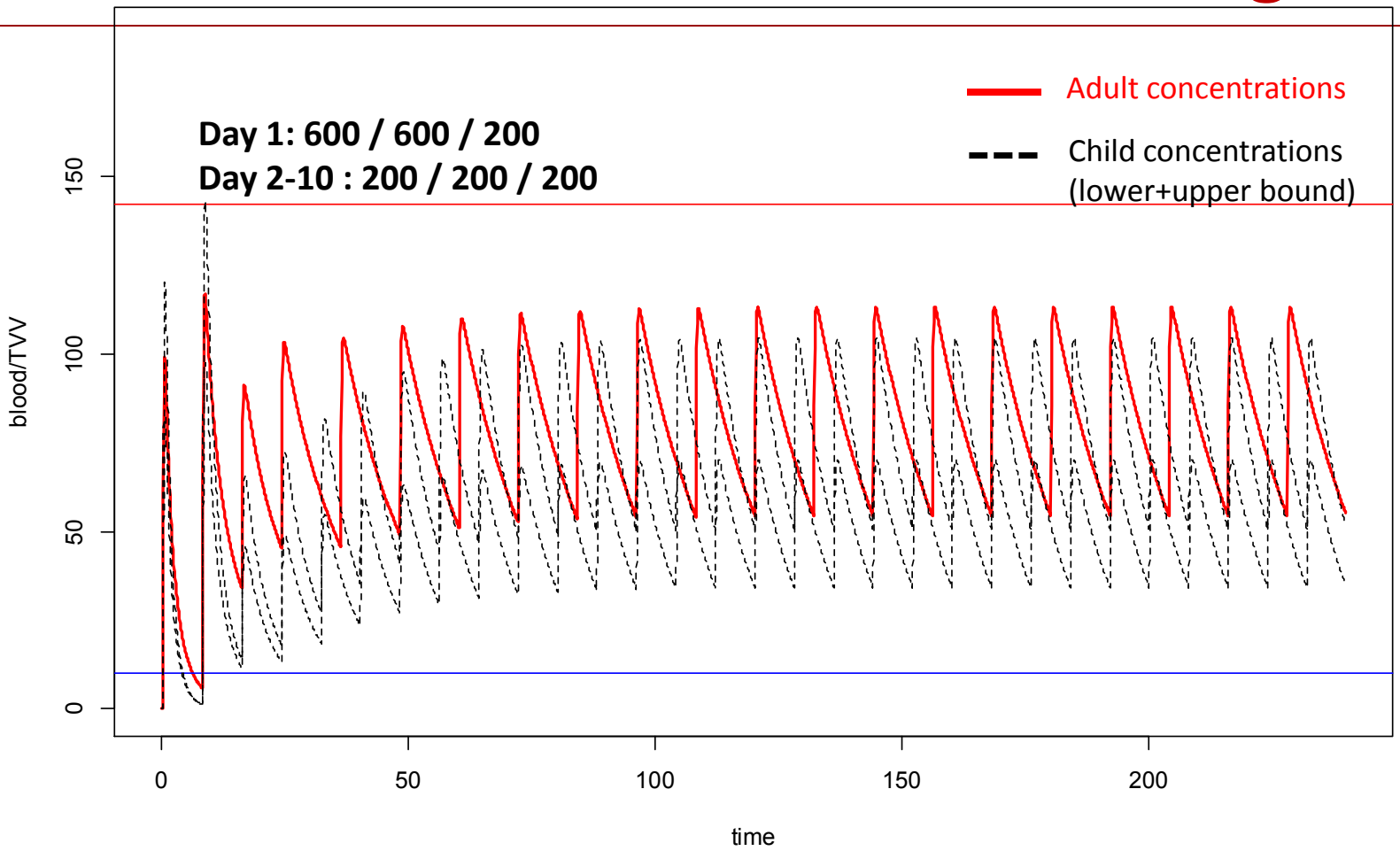
REACTION!

Simulation in children 10 - 15 kg





Frange et al., Favipiravir for Children with Ebola, Lancet (2015)

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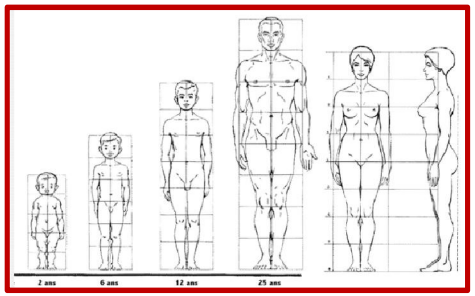
REACTION!

JIKI clinical trial: Favipiravir in patients with Ebola Virus Disease

(Inserm C1463 - EU H2020 666092)

Daouda SISSOKO, Elin FOLKESSON, M'lebing ABDOUL, Abdoul Habib BEAVOGUI, Stephan GUNTHER, Susan SHEPHERD, Christine DANEL, France MENTRE, Xavier ANGLARET, Denis MALVY

Inserm U897, University of Bordeaux, France
Médecins Sans Frontières (MSF), Belgium
Alliance for International Medical Action (ALIMA), France
Centre de Formation et de Recherche en Santé Rurale de Maférinyah, Guinea
Bernhard-Nocht-Institut für Tropenmedizin, Germany
Inserm U1137, Paris Diderot University, France



All authors declared no conflict of interest

The Challenges of Design in Guinea in September 2014

Randomization, while providing the best level of evidence, is not always ethical or possible:

- Ethical arguments should be weighed against the risk/benefit ratio
  - Ebola mortality in Guinea was 60% in adults
  - Favipiravir had an excellent reported safety profile (less than 3% non-severe toxicity)
- RCTs were problematic for the community
  - terrified by the expanding epidemic
  - lacked trust in health-care workers and public authorities
  - informed consent to an RCT was not feasible

Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa?

Simone Lanini, Alimuddin Zumla, John P A Ioannidis, Antonino Di Caro, Sanjeev Krishna, Lawrence Gostin, Enrico Girardi, Michel Pletschette, Gino Strada, Aldo Baritussio, Gina Portella, Giovanni Apolone, Silvio Cavuto, Roberto Satolli, Peter Kremsner, Francesco Vairo, Giuseppe Ippolito

Lancet Infect Dis 2015

Published Online
April 14, 2015
http://dx.doi.org/10.1016/
S1473-3099(15)70106-4

The Ebola outbreak that has devastated parts of west Africa represents an unprecedented challenge for research and ethics. Estimates from the past three decades emphasise that the present effort to contain the epidemic in the three most affected countries (Guinea, Liberia, and Sierra Leone) has been insufficient, with more than 24 900 cases and about 10 300 deaths, as of March 25, 2015. Faced with such an exceptional event and the urgent response it demands, the use of randomised controlled trials (RCT) for Ebola-related research might be both unethical and infeasible and that potential interventions should be assessed in non-randomised studies on the basis of compassionate use. However, non-randomised studies might not yield valid conclusions, leading to large residual uncertainty about how to interpret the results, and can also waste scarce intervention-related resources, making them profoundly unethical. Scientifically sound and rigorous study designs, such as adaptive RCTs, could provide the best way to reduce the time needed to develop new interventions and to obtain valid results on their efficacy and safety while preserving the application of ethical precepts. We present an overview of clinical studies registered at present at the four main international trial registries and provide a simulation on how adaptive RCTs can behave in this context, when mortality varies simultaneously in either the control or the experimental group.

PLOS | MEDICINE

Received: December 3, 2014

Accepted: March 5, 2015

Published: April 14, 2015

RESEARCH ARTICLE

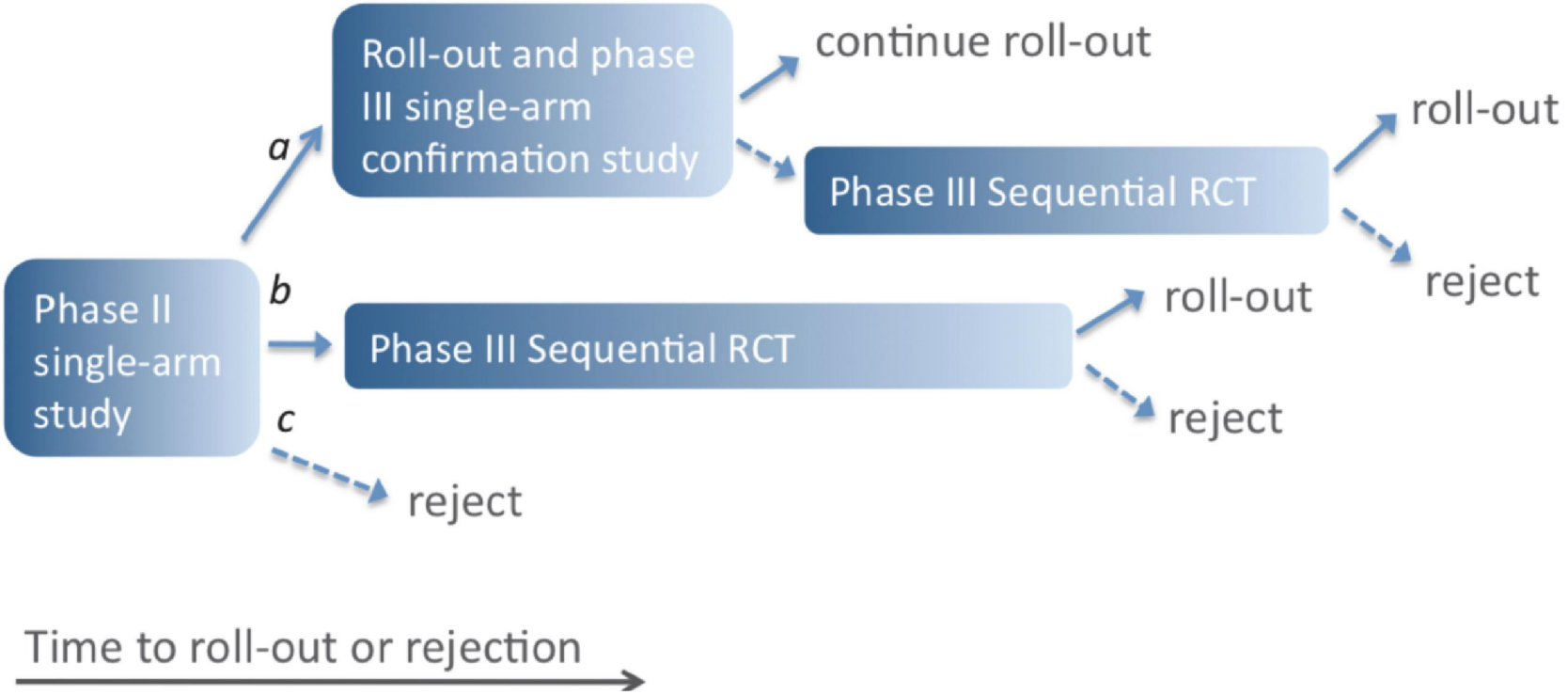
Evaluating Clinical Trial Designs for Investigational Treatments of Ebola Virus Disease

Ben S. Cooper[1,2]*, Maciej F. Boni[2,3], Wirichada Pan-ngum[4], Nicholas P. J. Day[1,2], Peter W. Horby[2], Piero Olliaro[2,5], Trudie Lang[2], Nicholas J. White[1,2], Lisa J. White[1,2], John Whitehead[6]

Design 1. RCT without interim analysis

Design 2. Sequential RCT (up to 20 interim analyses)

Design 3. Multi-stage approach (MSA)



JIKI trial protocol

- **Objective**: assess efficacy of high-dose favipiravir in decreasing mortality in humans with EVD
- **Design**: non-comparative, "proof-of-concept", phase II trial
- **Inclusion criteria:**
  - Age ≥1 year and weight ≥10 kg, informed consent, able to take oral medications
  - Positive EBOV PCR test (RT-PCR, Altona Diagnostics RealStar Ebolavirus RT-PCR Kit 1.0)
    → "cycle threshold"(*Ct*) value is inversely proportional to viral load :
    Ct=20 equivalent to 10^8 copies/ml; +3 cycles equivalent to -1 log
- **Treatment**
  - **Favipiravir**, Toyama Chemical Co., Ltd. Orally administered 200 mg tablets.
  - **Adults** [(1)]*:*
    → Day 0 (inclusion): H0: 2400 mg; H8: 2400 mg; H16: 1200 mg
    → Day 1 to Day 9: 1200 mg bid
  - **Children** [(2)]: according to body weight

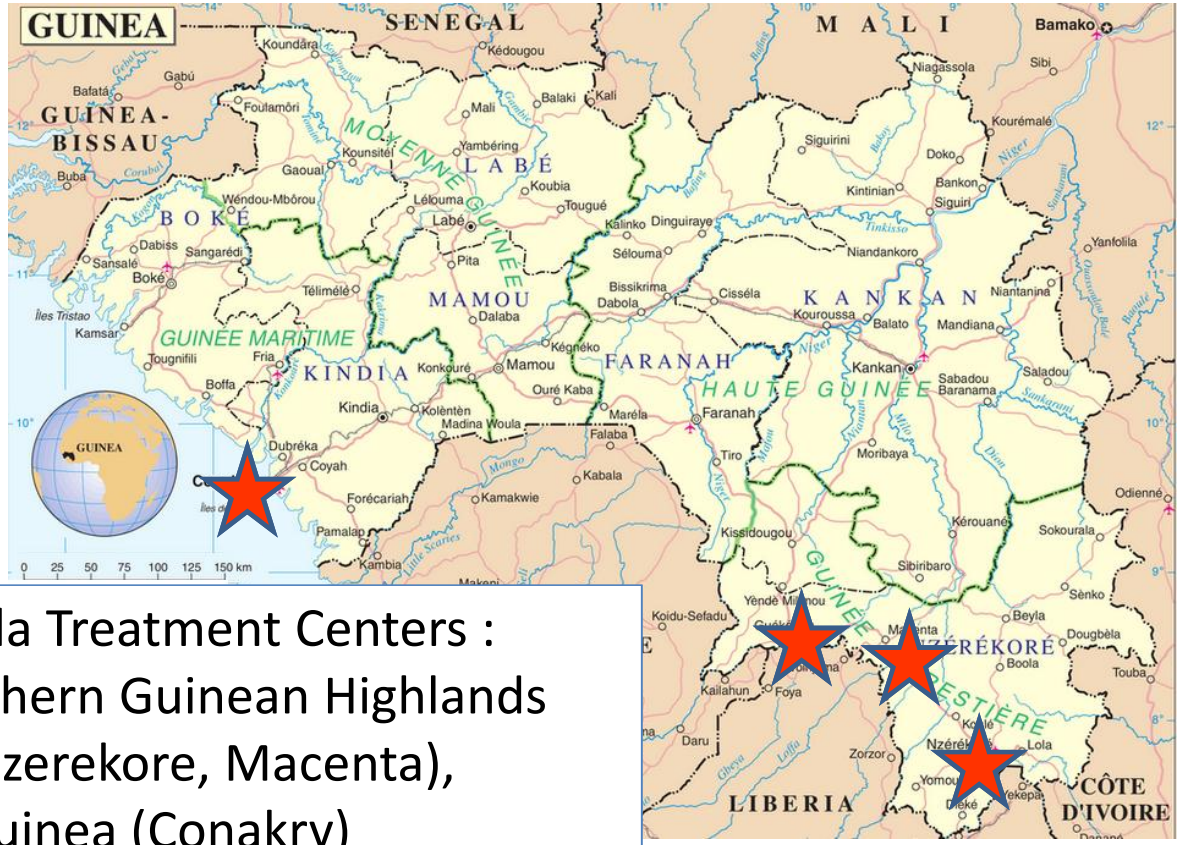
1. Mentre, Lancet Infect Dis 2014 ; 2. Frange, Lancet 2015

JIKI trial protocol

- **Primary outcome**: mortality at Day 14
- **Secondary outcomes**:
  - Evolution of EBOV plasma RNA and infectious loads
  - Grade 3-4 adverse events
  - EBOV genetic micro-diversity (including resistance mutations)
  - Trough concentrations of favipiravir
- **Analysis :**
  - **Reference:** Pre-trial mortality **55%** (MSF/EMLab database, Sept 15- Dec 14, 2015), **with same team, same procedures and same laboratory**
  - **Stratification variables**: Time since symptom onset: < 72h *vs.* ≥ 72h
- **Sample size calculation**:
  - Recruitment continues until 60 participants with <72h symptom duration are included (futility analysis every 20 patients)

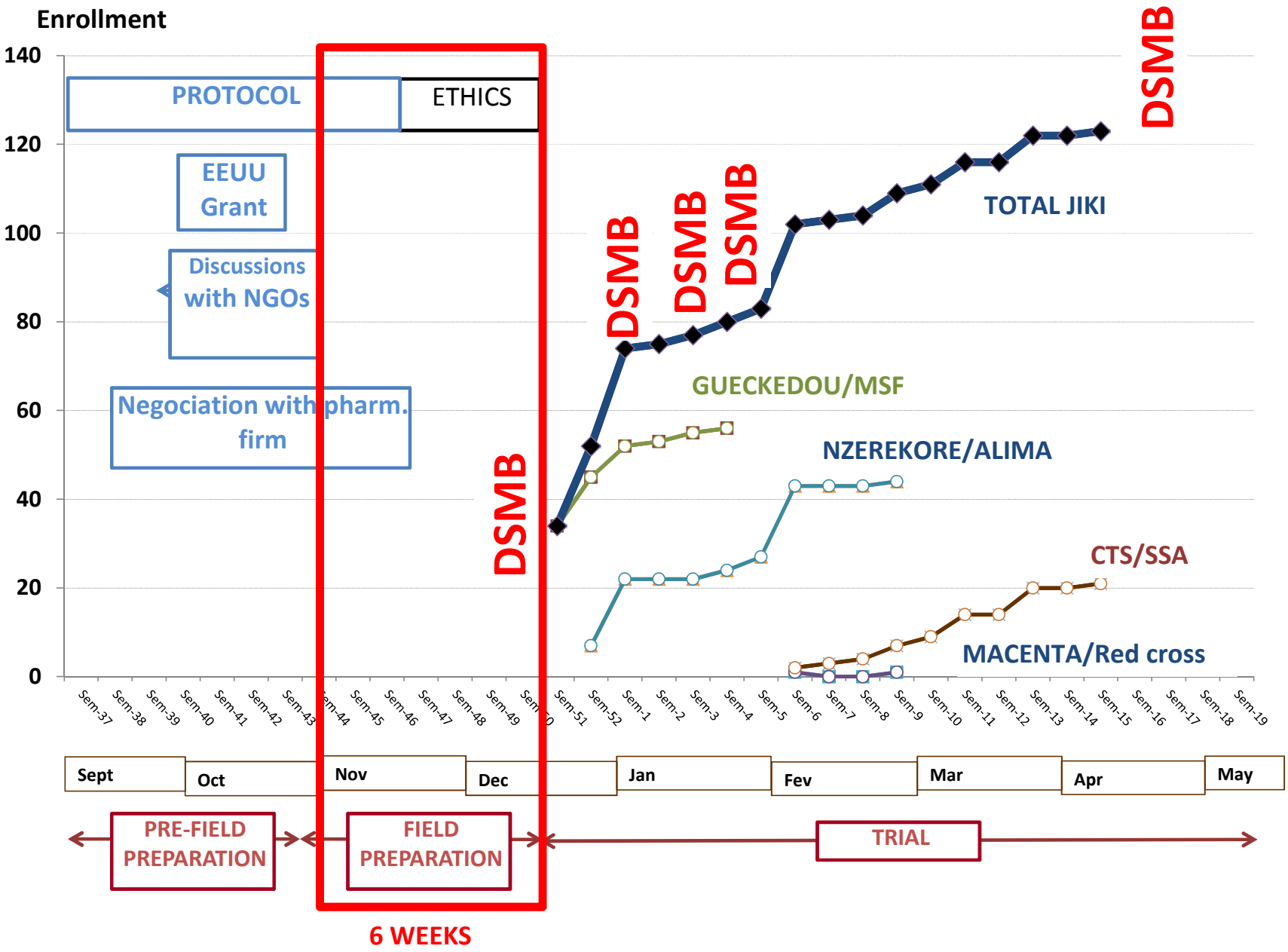
Settings and teams

- **Funding**:
  - EU/H2020
  - Inserm
- **Partners**: Inserm, MSF, EuroMobLA, ALIMA, Pasteur, French Red Cross, B-FAST, French Army Health Service



Settings: 4 Ebola Treatment Centers :

- 3 in the southern Guinean Highlands (Gueckedou, Nzerekore, Macenta),
- 1 in costal Guinea (Conakry)


Enrollment
140
120
100
80
60
40
20
0
PROTOCOL
ETHICS
EEUU Grant
Discussions with NGOs
Negociation with pharm. firm
DSMB
DSMB
DSMB
DSMB
DSMB
TOTAL JIKI
GUECKEDOU/MSF
NZEREKORE/ALIMA
CTS/SSA
MACENTA/Red cross
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Sept
Oct
Nov
Dec
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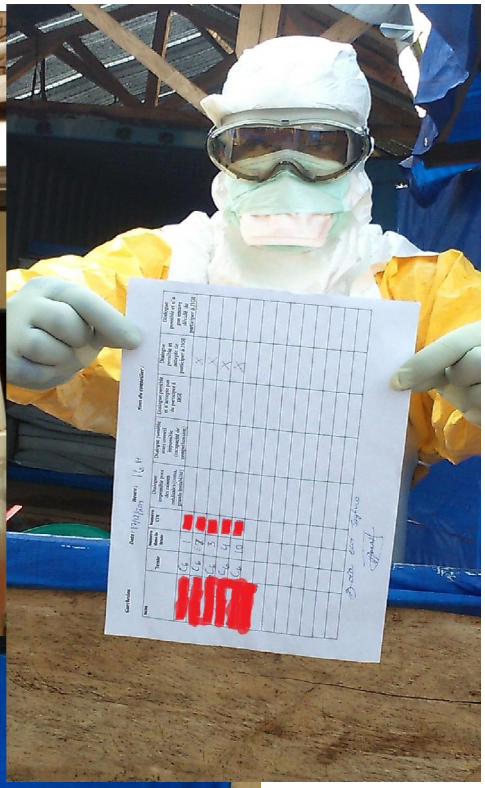
Fev
Mar
Apr
May
PRE-FIELD PREPARATION
FIELD PREPARATION
TRIAL
6 WEEKS

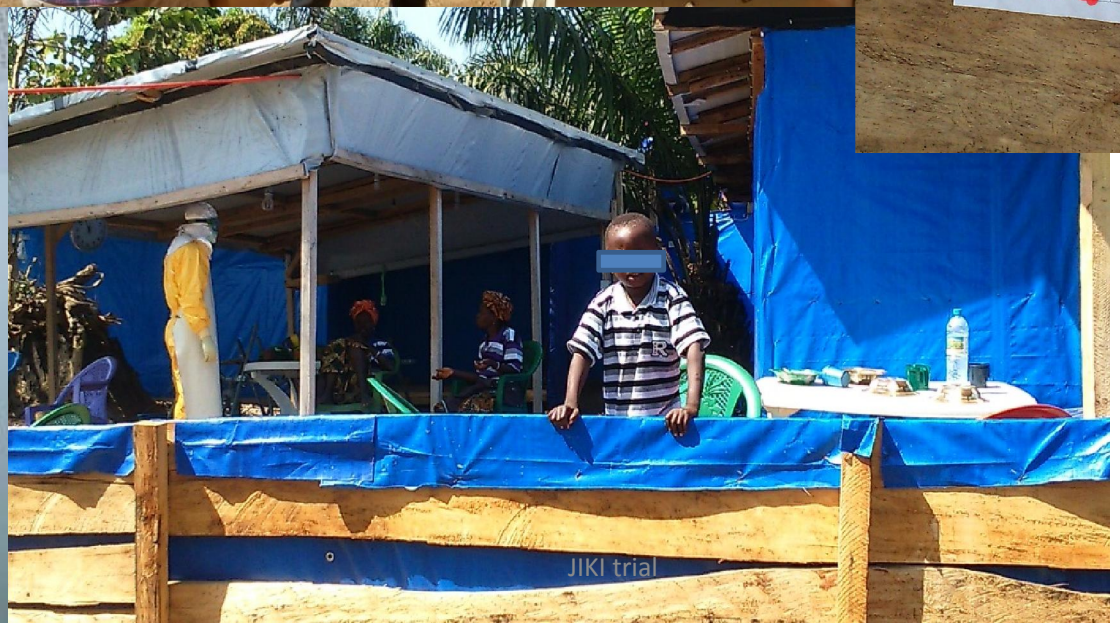
Case management center in Gueckedou

High risk zone where confirmed case-patients are hospitalized

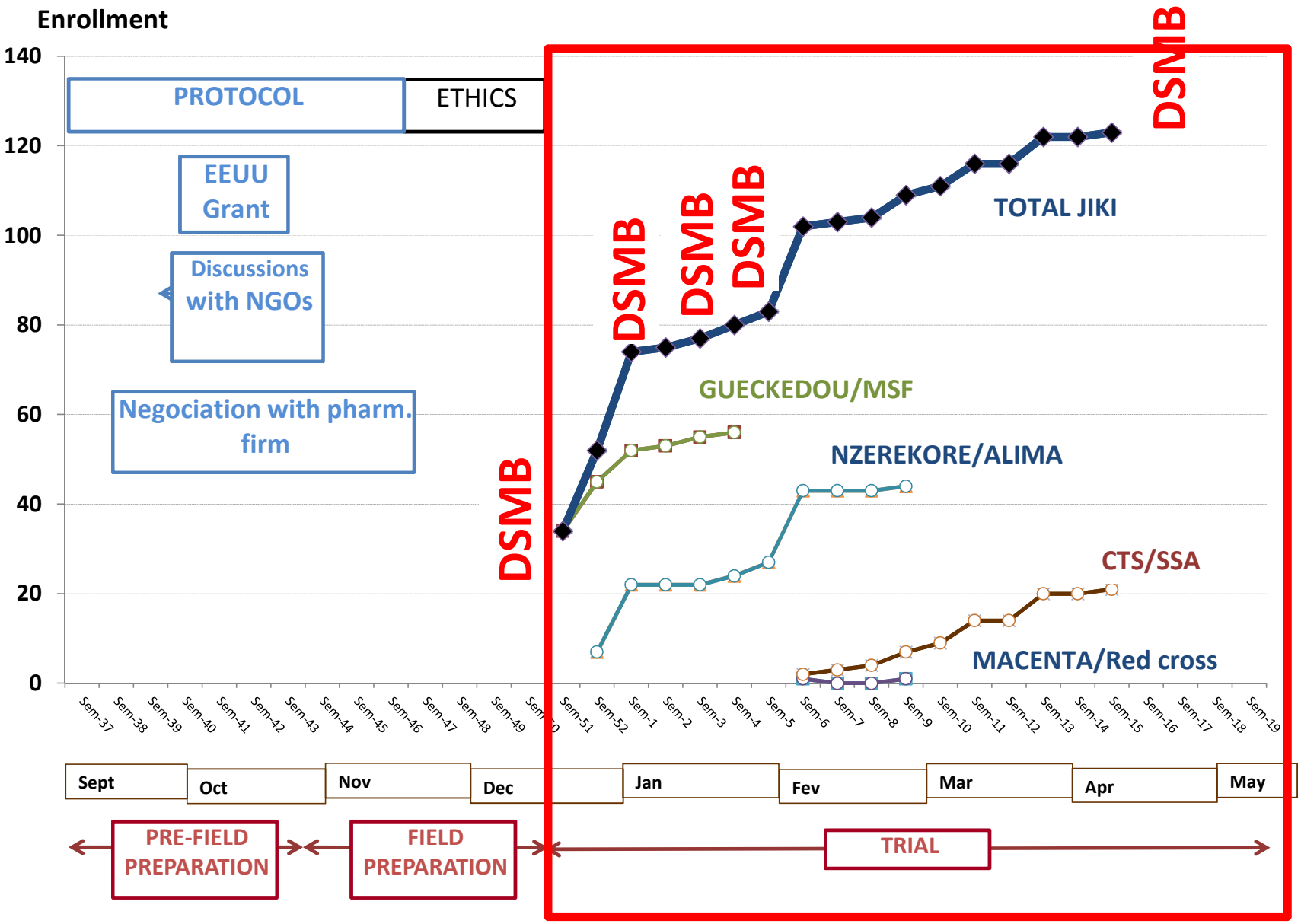
Training


WARD
Suivi Crèche
LABO





JIKI trial


Enrollment
140
120
100
80
60
40
20
0
PROTOCOL
ETHICS
EEUU Grant
Discussions with NGOs
Negociation with pharm. firm
DSMB
DSMB
DSMB
DSMB
DSMB
TOTAL JIKI
GUECKEDOU/MSF
NZEREKORE/ALIMA
CTS/SSA
MACENTA/Red cross
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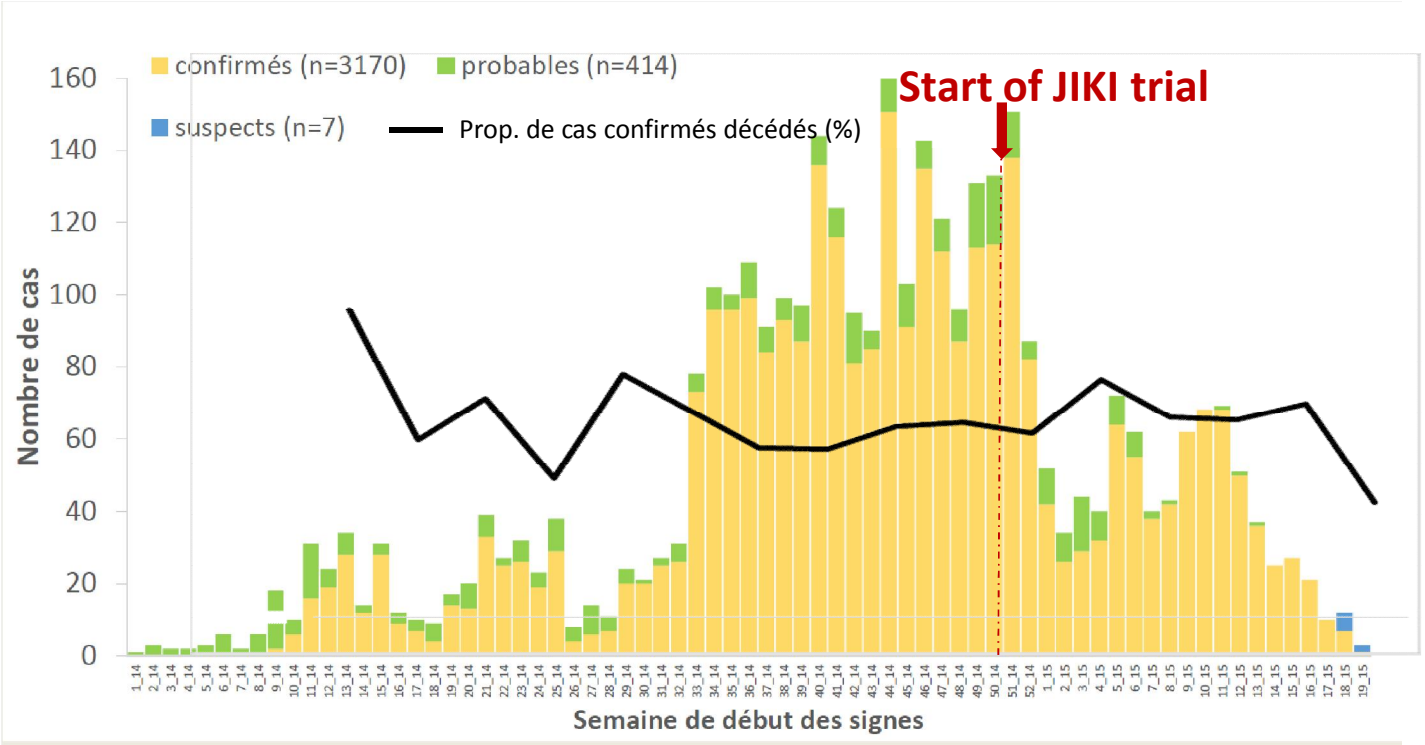
PRE-FIELD PREPARATION
FIELD PREPARATION
TRIAL

Number of cases and deaths among confirmed cases in Guinea

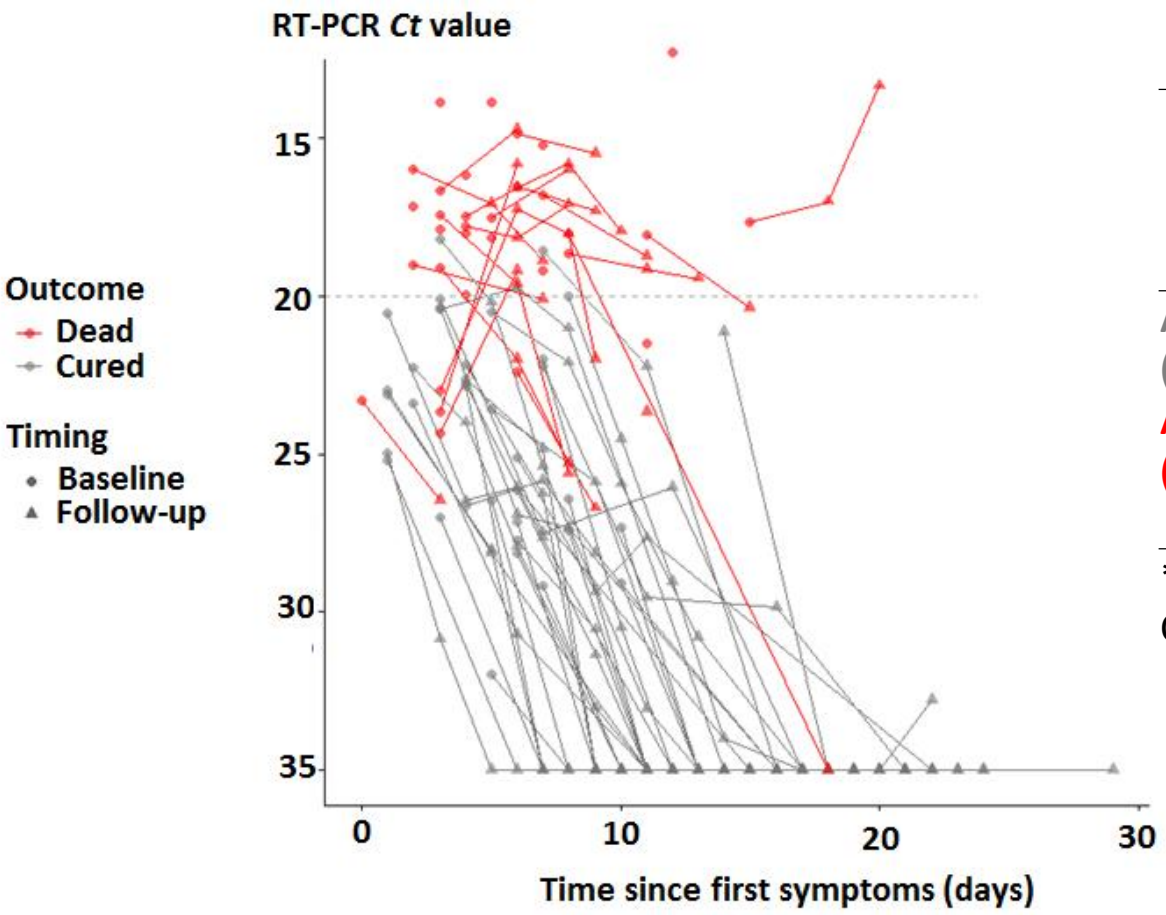


*Documentation non-exhaustive des décès communautaires non-prélevés

Source: Ebola in Guinea, Daily Sitrep. 5 may 2015 (5 may 2015). Guinean MoH and WHO

RT-PCR CT values at baseline and during follow-up

First 69 adult participants, JIKI trial, 17 DEC 2014 – 20 JAN 2015



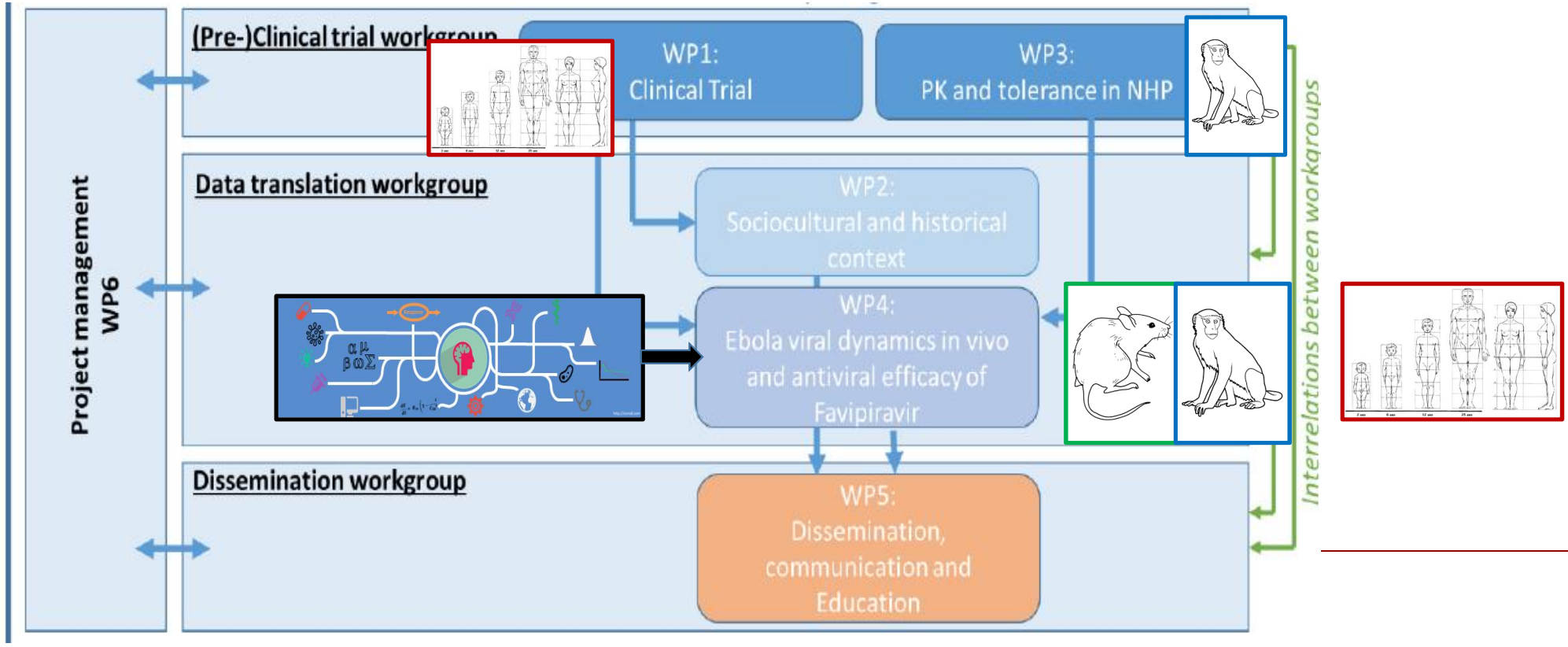
	N	Dead n	Dead %
Adults and children (> 6 yr) with CT ≥ 20	39	6	15.4
Adults and children (> 6 yr) with CT < 20	**28**	**26**	**92.9**

* 2 patients missing in JIKI for this classification because CT value at inclusion not available

REACTION!

Evaluation of efficacy and antiviral activity of favipiravir in non-human primates & humans

PI: Hervé Raoul, BSL4, INSERM,France



JIKI trial Surveillance

- SAB meetings : Nov 28, Jan 15, Jan 26
- DSMB meetings : Dec 11, Jan 5, Jan 14, Jan 26, April 14

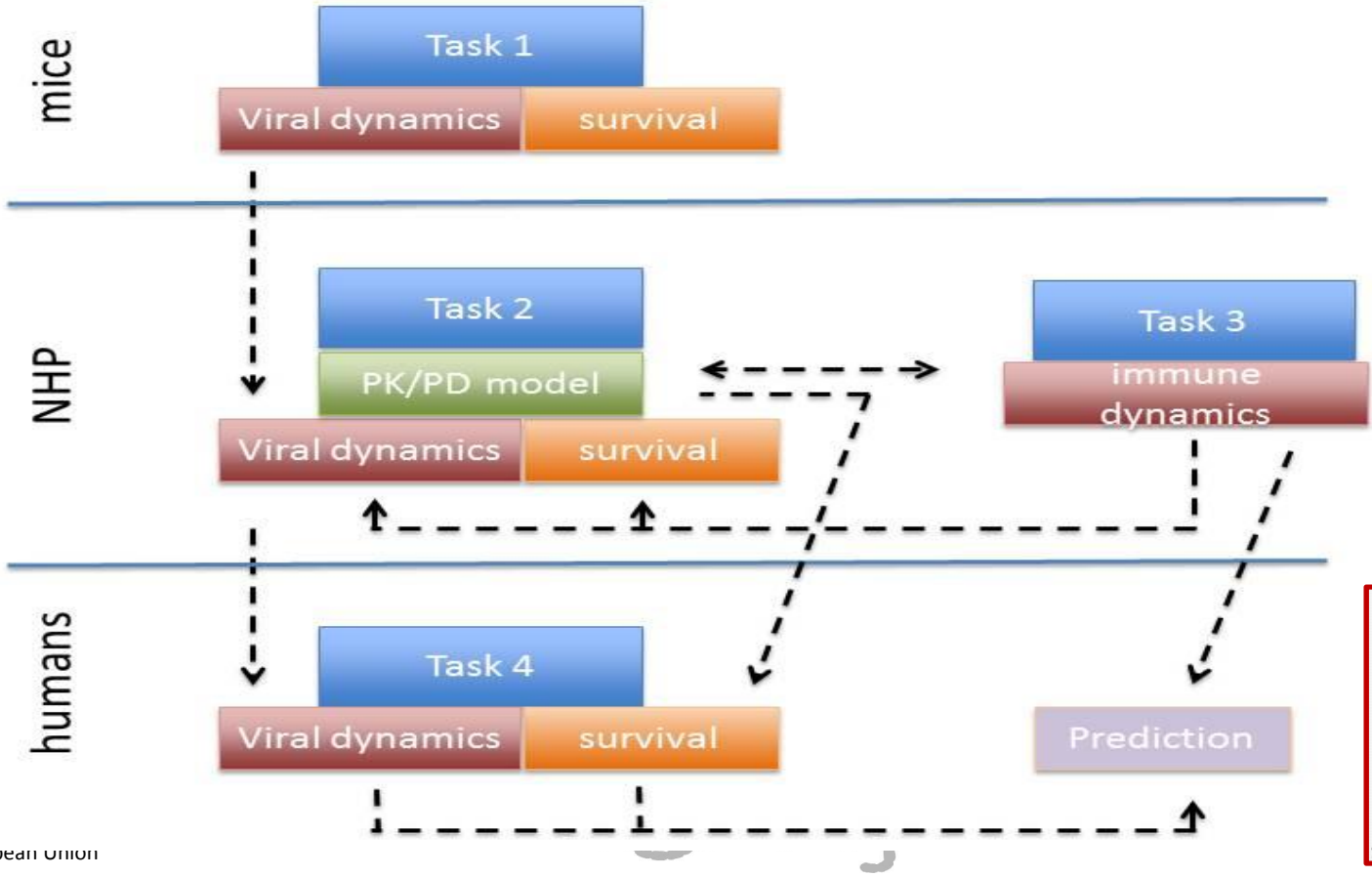
→ On Jan 26, the DSMB approved the investigators' proposal to make public data from the first 80 participants:

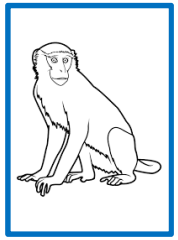
- **No conclusion regarding favipiravir effect on mortality reduction**
- **New understanding of EVD pronostic factors that may prove useful to clinicians and researchers developing Ebola treatment protocols**

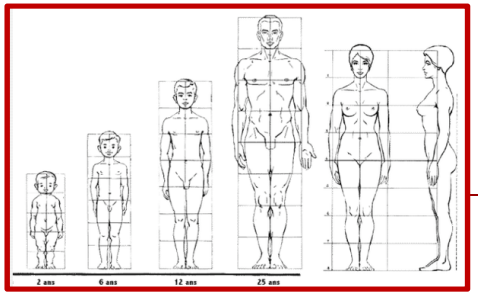
Results presented at CROI, Feb 23-26, 2015, Seattle, Washington

Sissoko et al. Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea, abs. 103-ALB

Modelling PKVK (WP4)







of the European Union

Objectives of Modelling

- To estimate important parameters of the viral lifecycle: infected cell half-life, basic reproductive number
- To estimate the effect of favipiravir in blocking viral production in animal and patients
- To quantify the effect of the immune response
- To investigate the relationship between viremia and survival

- To better understand clinical results and design next studies

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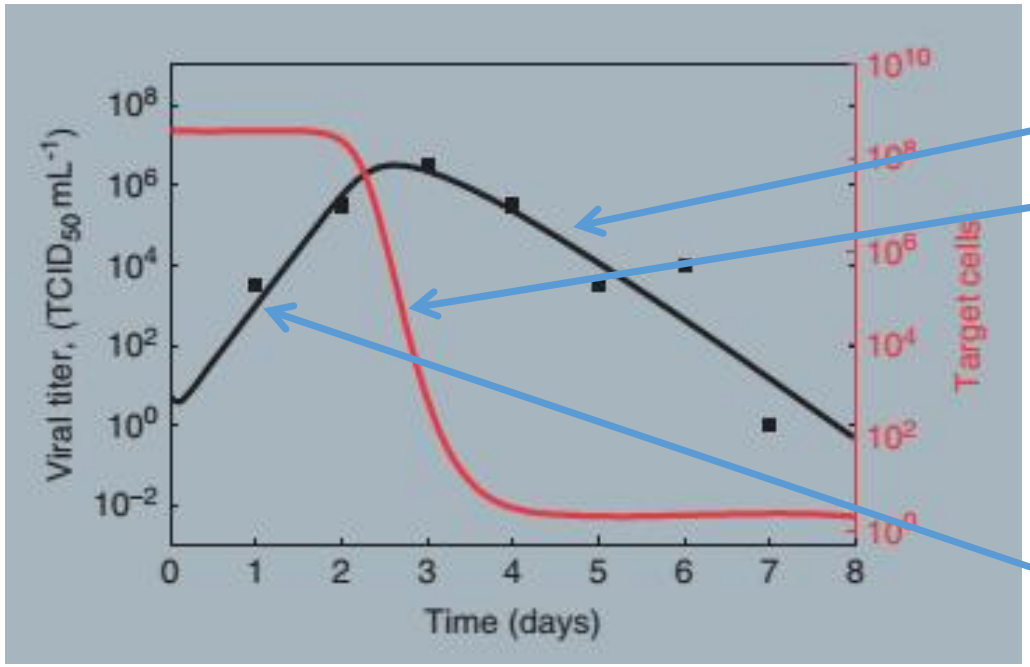
framework programme
of the European Union

Viral dynamics during acute infection

Complex interaction between the pathogen, the drug and the IR



Clearance of infected cell due to:
- immune system
- cytolytic virus
- target cell exhaustion

Viral increase:
- target cell abundance
- large viral burst (R_0)

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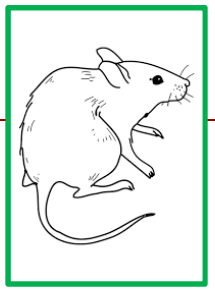
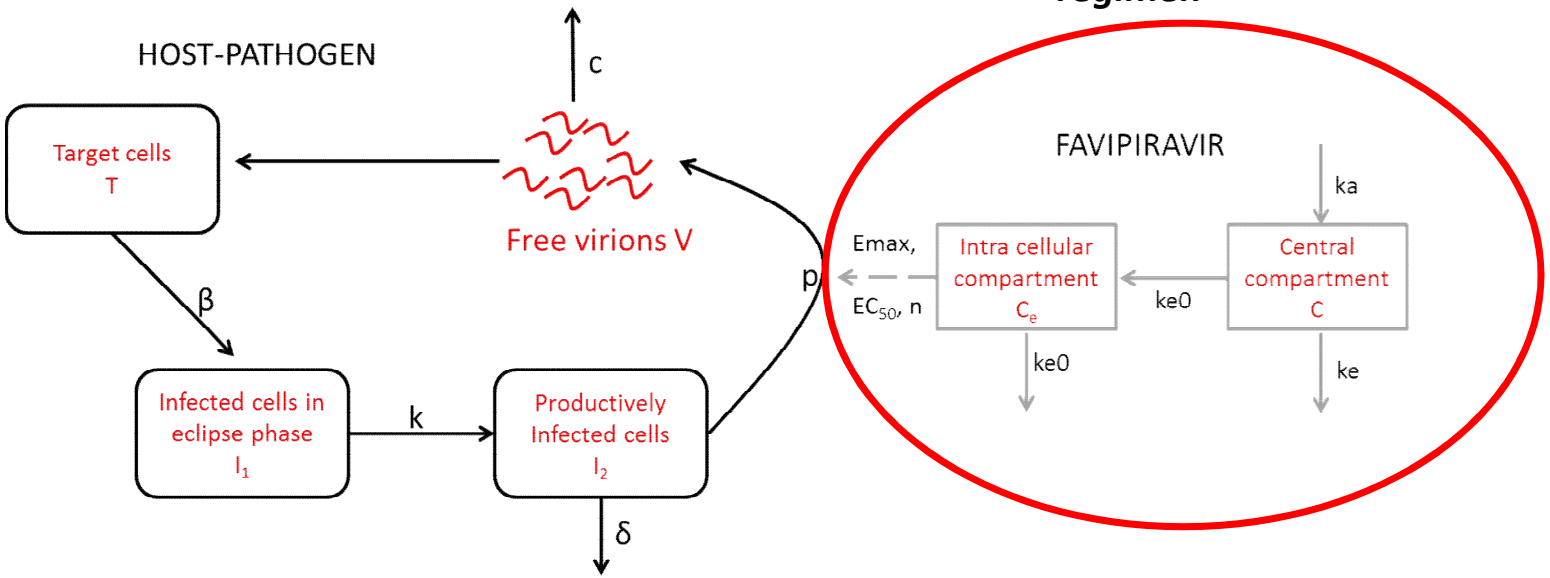
PKVK Model for favipiravir



Model for EBOV replication



Pharmacokinetic model based on data in uninfected mice receiving the same dosage regimen

$$\frac{dT}{dt} = -\beta VT$$

$$\frac{dI_1}{dt} = \beta VT - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

$$\frac{dA_c}{dt} = k_a \times A_{dep} - k_e \times A_c$$

$$C = \frac{A_c}{V}$$

$$\frac{dC_e}{dt} = k_{e0} \times (C - C_e)$$

$$\frac{dV}{dt} = \left(1 - \frac{E_{max} C_e(t)^n}{EC_{50}^n + C_e(t)^n}\right) pI_2 - c_1 V$$

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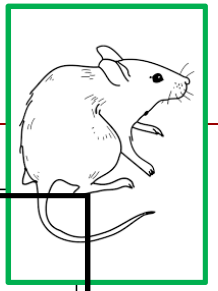
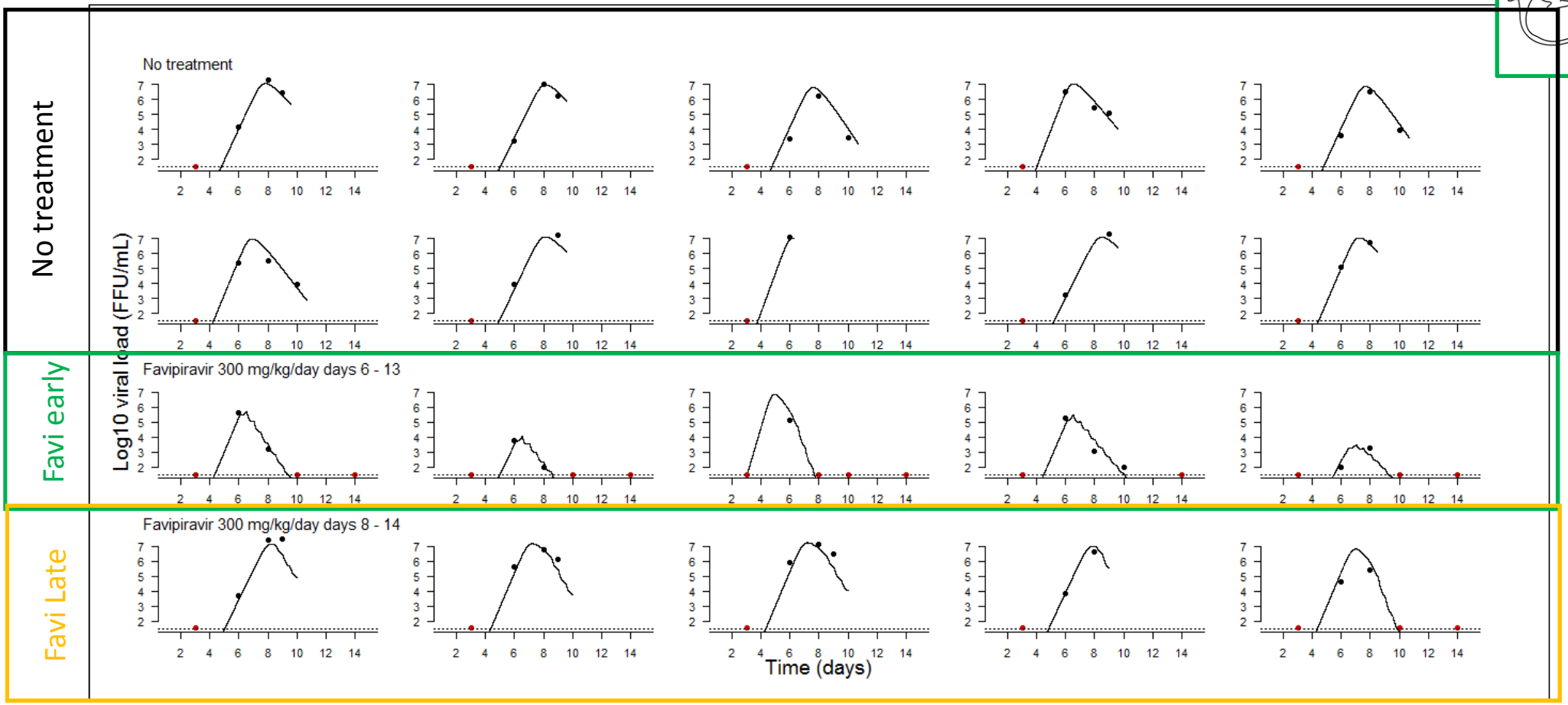
Results: data fitting





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REACTION!

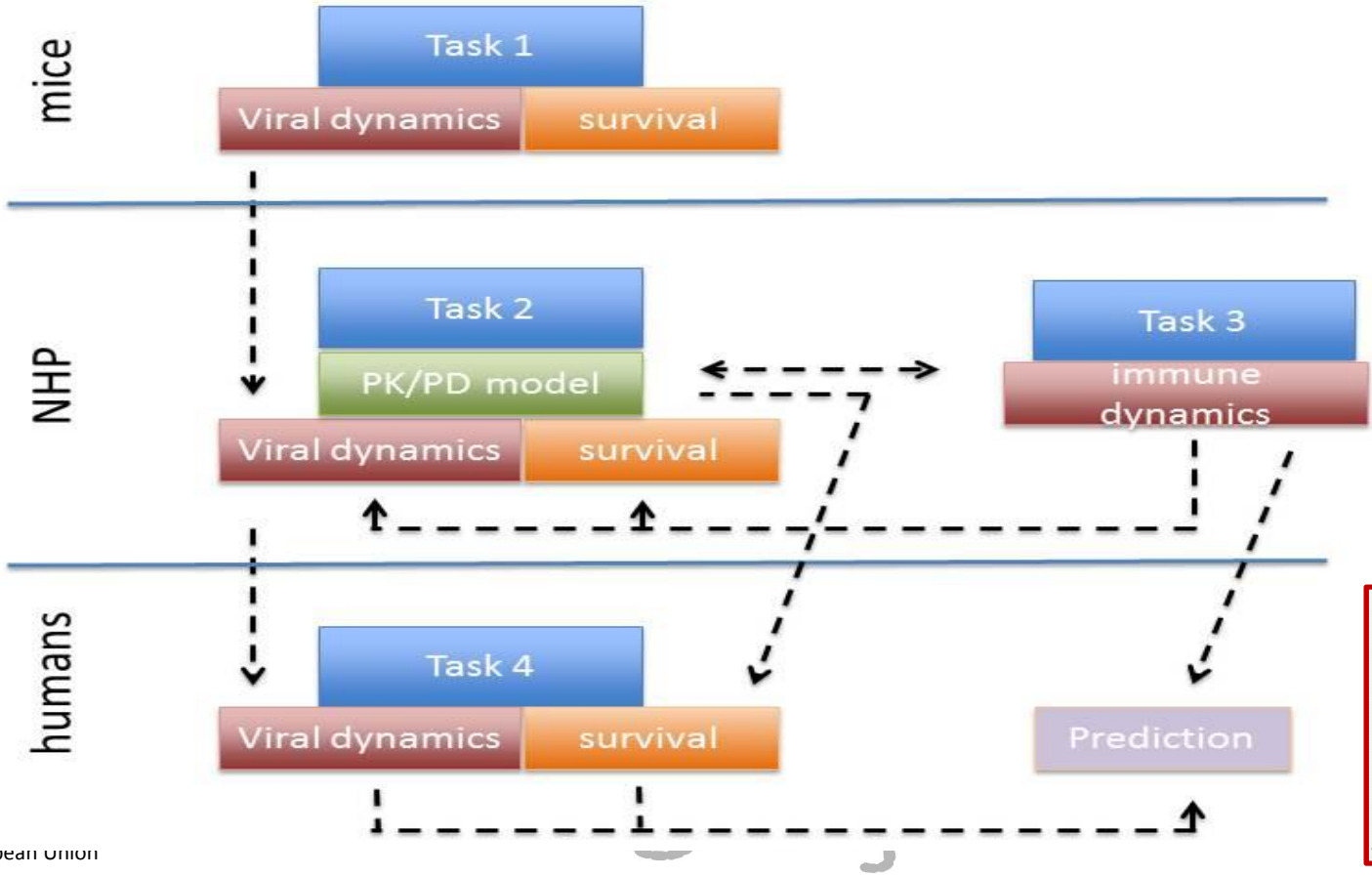
Results: insights on pathogenesis

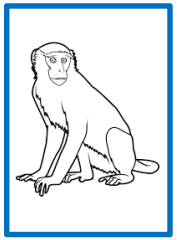
- $t_{1/2}$ productively infected cells of 6.4 hours (>10 hours for influenza)
- High steady-state effectiveness of favipiravir in blocking viral production (99.6%)
- A single infected cell could produce ~9 new productive infections (>20 in H1N1 or PR8-PB1-F2(1918))

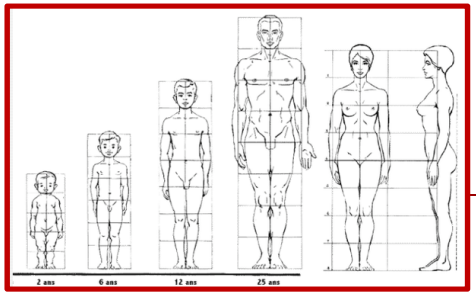
Madelain, Oestereich, Graw, Nguyen, de Lamballerie, Mentré, Günther, Guedj. Ebola viral dynamics in mice treated with favipiravir. *Targeting Ebola Word Conference*, Paris, May 28-29, 2015

Funded by the Horizon 2020 framework programme of the European Union

Modeling strategy







Lessons learnt for future outbreaks

Science	**Infrastructures**
Humans	**Money**

Lessons learnt for future outbreaks

Science	Infrastructures
• Available treatments • Dosage • Study design	• Medical centers • Treatment dispensation • Virological and biological labs
Humans	**Money**
• Local physicians involved • Link with NGO • Acceptance by population • Approval by Ethics Committee • Clinical research staff	• Seed money • Rapid grants • Easy transfer