SCTO day: Selected Success Stories

Dr G. Wuerzner, PD
What makes a clinical study successful?

A. Grant allocation
B. Publication and impact factor
C. Buzz in the media
D. Patients’ satisfaction
On the 23rd March 2014 WHO’s African Regional Office reported an outbreak of Ebola virus disease in Guinea.

This outbreak extended to be the "largest, most severe and most complex outbreak in the nearly four-decade history of the disease"

Declared a public health emergency of international concern by WHO Director-General Margaret Chan.
Research & Product Development: the primary objective of this work is to fast-track access to treatment and vaccine options to address EVD, with major activities focused on facilitating the use of experimental medicines and vaccines through:

• guidance on safety, efficacy, quality, regulatory standards and ethical use of therapies in the R&D pipeline.
• accelerated development and clinical evaluation of promising experimental interventions.
• coordination and facilitation of the ethical deployment of existing experimental treatments and vaccines.
• convening the research community to ensure R&D is oriented towards actual, current needs.
The Food and Drug Administration Modernization Act of 1997 (FDAMA) includes Section 112, "Expediting study and approval of fast track drugs." This section mandates the Agency to facilitate the development and expedite review of drugs and biologics intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Fast track adds to existing programs, such as accelerated approval, the possibility of a "rolling review" for an application. An important feature of fast track is that it emphasizes the critical nature of close early communication between the FDA and sponsor to improve the efficiency of product development.

To be eligible for the fast track program, an applicant must submit a request with supporting documentation for fast track designation for the product and its proposed use. FDA is required by the statute to decide within 60 days of receipt of the request whether the conditions for fast track designation have been met. This report illustrates CBER’s performance in reviewing and deciding on these requests.

Details on the FDA fast track program, including Section 112 of FDAMA and the proposed and final rules in the Federal Register can be found in the Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics - 5/2014; Appendix 2; Appendix 3 - (CDER MAPP 6020.3); CBER SOPP 8405; Appendix 4.
Modification of the information sheet "Explanations regarding fast-track authorisation procedure"

• 18.09.2014 - The information sheet Expliations regarding fast-track authorisation procedure has been modified.

For the authorisation of a human medicinal product, a fast-track procedure can be carried out as long as all of the criteria as stated in Article 5 of the Ordinance on Medicinal Products (VAM, SR 812.212.21) are fulfilled.

In contrast to the normal procedure, a request for a fast-track procedure must be submitted to Swissmedic in advance, and be approved. Part 1 of the information sheet describes the requirements and criteria that must be fulfilled in order for an application to be eligible for the fast-track procedure. Following input from the stakeholders, the description of the criteria to be fulfilled for a fast-track procedure, and particularly regarding clinical relevance, has been clarified as follows:

The assessment of the clinical relevance depends on the individual clinical presentation and the clinical and scientific practice related thereto. Only in cases where clinical hard endpoints such as overall survival cannot be investigated at reasonable expense, surrogate parameters that are clinically established, scientifically validated and recognised by international guidelines may be appropriate in order to demonstrate clinical relevance. In the relevant clinical context, such surrogate parameters could be functional capacity in daily life, or the progression of a disease.
From West Africa to Lausanne
Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014 – August 22, 2014,
The vaccines

cAd3-EBOZ US Study in Lausanne

rVSV-ZEBOV Canada Study in Geneva
Design: A randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study

150 participants screened
120 eligible

Group potentially deployed
18

Arm
Low dose
2.5 \times 10^{10} \text{ vp}
9

Arm
High dose
5 \times 10^{10} \text{ vp}
9

Group non-deployed volunteers
120

Arm
Low dose
2.5 \times 10^{10} \text{ vp}
42

Arm
High dose
5 \times 10^{10} \text{ vp}
40

Arm
Placebo
20

30 were not enrolled
• 28 were ineligible
• 1 withdrew consent
• 1 because accrual goal had been met

>400 persons interested in participating

Screening
D0 D1 D7 D14
\ldots D28 \ldots D90 \ldots D180

All volunteers attended all visits, except for two deployed volunteers who did not attend one visit, one at D14, and the other at D28.
How long would it take to submit file to IRB and to Swissmedic?

A. 2 weeks
B. 1 months
C. 2 months
D. 6 months
Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014–Septembre 30, 2014, by date of WHO Situation Report, n=23694
How long would it take to complete study (last participant, last visit)?

A. 1 month
B. 2 months
C. 6 months
D. 12 months
Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014 – February 22, 2015, by date of WHO Situation Report, n=23694
Crash CTU team formed

Crash CTU team
• 100% + dedicated to study

Usually
• 100% + usual task of crash CTU team
Clinical Trial cAd3-EBOZ Lau

Presentation of site & team

SPONSOR
CHUV represented by Clinical Trial Unit of Lausanne

MONITOR
Swiss Tropical and Public Health Institute

EXTERNAL COLLABORATIONS
WHO, GSK, VRC/NIH

PRINCIPAL INVESTIGATOR
Prof. Blaise Genton
Service des maladies Infectieuses & PMU

CLINICAL SITE
CHUV
Clinical Trial Unit of Lausanne

LABORATORIES
CHUV – Lab. Chimie Clinique (LCC)
CHUV – Lab. Hématologie (LCH)
CHUV – Service d’immunologie & Allergie (IAL)

PHARMACY
CHUV – Service of Pharmacy
Prevalence, Characteristics, and Publication of Discontinued Randomized Trials

- 25% of trials discontinued (rare for RCTs involving healthy volunteers (3%))
- 38% of discontinuations reported to REC
- Slow recruitment is most frequent reason:
  - 10% of all trials
- Protects against discontinuation for poor recruitment:
  - Industry sponsorship: OR=0.25 [0.15 – 0.43]
  - Larger planned sample size: OR=0.96 [0.92 – 1.00] per increment of 100
- Discontinued trials more likely to remain unpublished
  - OR=3.19 [2.29 – 4.43]

Kasenda et al. JAMA. 2014;311(10):1045-1051
Success as a team and collaborations?
Success as a publication?

Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study


Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe
The cascade of pathological events that results in the rapid severity of Ebola virus infection.

Success as far as visibility is concerned?
The media: a double edged sword
Success for the patients?

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases (Suspected, Probable, and Confirmed)</th>
<th>Laboratory-Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea (^2)</td>
<td>3814</td>
<td>3358</td>
<td>2544</td>
</tr>
<tr>
<td>Sierra Leone (^3)</td>
<td>14124</td>
<td>8706</td>
<td>3956</td>
</tr>
<tr>
<td>Liberia (^4)</td>
<td>10678</td>
<td>3163</td>
<td>4810</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28616</strong></td>
<td><strong>15227</strong></td>
<td><strong>11310</strong></td>
</tr>
</tbody>
</table>
But the clinical development plan could go on

- **Non-affected areas**
  - GMP grade vaccine
  - Non-clinical eval in NHPs

- **Phase 1a&b**
  - Safety and dose selection

- **Phase 2a**
  - Safety and dose selection
  - Lausanne

- **Phase 2b**
  - Safety and immunogenicity

- **Phase 3**
  - Preliminary efficacy

- **3000 adults**
- **600 children**

- **First quarter 2014**
- **1st half 2015**

- **Non-affected areas and affected areas**
Conclusions

• Unique experience
• Only possible with a dedicated team (CTU)
• Only possible with intense networking/collaboration with stakeholders
• Only possible with funding
• Could we create a similar buzz for all our clinical trials?
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Camille Cochet
Daniel Estoppey
Sophie Longchampt

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L’ACCEPTATION DE L’INITIATIVE SUR L’IMMIGRATION DE MASSE ET SES CONSÉQUENCES SUR LA PARTICIPATION DE LA SUISSE AU PROGRAMME HORIZON 2020

Information du 5 décembre 2014

Le Secrétariat d’Etat à la formation, à la recherche et à l’innovation SEFRI actualise de manière continue les informations sur l’état de la situation par rapport au programme Horizon 2020:

⇒ La Suisse et l’UE ont signé le 5 décembre 2014 un accord sur une association partielle qui était déjà provisoirement appliquée depuis le 15 septembre 2014 et qui vaut pour l’instant jusqu’à la fin 2016.

⇒ Cette association partielle permet aux chercheurs suisses depuis le 15 septembre 2014 de participer en tant que partenaires associés à droits égaux à toutes les activités du «premier pilier» d’Horizon 2020, qui comprend les bourses ERC, les actions Marie-Sklodowska-Curie, les Future and Emerging Technologies (FET) et les Infrastructures de recherche. De même, les chercheurs suisses peuvent participer au programme Euratom et au volet «Spreading Excellence and Widening Participation» en tant que partenaires associés. En cette qualité, les chercheurs suisses sont financés directement par des fonds européens.
What makes a clinical trial successful?

Reasons for discontinuation

Based on interim analysis:

- **Futility**: little chance of a significant difference between groups
- Early evidence for *harm* in one study group
- Early evidence for *benefit* in one study group

**NOT** based on interim analysis:

- New external evidence (e.g. treatment is outdated)
- Retraction of sponsor (e.g. drug no longer marketed)
- Poor recruitment of participants
Les tests de vaccins contre Ebola pourraient débuter en novembre
cAd3-EBOZ Lau - Financement et Consortium EbolaVac

- Budget de l’essai clinique: env. CHF 1.7 millions

- Essai clinique intégré au **Consortium EbolaVac**:
  - **Partenaires**: GSK (coordinateur), Université d’Oxford, CHUV, BNITM
  - **Financement**: Horizon2020
  - **But**: Développement d’un vaccin cAd3-EBOZ contre Ebola

  - Plusieurs essais cliniques de Phases 1-2a en cours (dont cAd3-EBOZ Lau)
  - Essais cliniques de Phases 2b-3 vont débuter durant Q2 2015 en Afrique de l'Ouest, chez des adultes et enfants dans des zones non touchées par Ebola
  - Essais cliniques de Phase 3 dans les zones épidémiques (modèle à définir)