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Immunobridging approach to assess clinical benefit as the basis for licensure of the monovalent Ebola vaccine

Viki Bockstal*, Ramon Roozendaal*, Thierry Van Effelterre, Nadia Verbruggen, Ben Van Baelen, Jeroen Stoop, Cynthia Robinson, An Vandebosch, Laura Solforosi, Roland Zahn, Macaya Douoguih, Jenny Hendriks, Benoit Callendret, Kerstin Luhn

Facts & Figures

EBOVAC1	EBOVAC2
Start date: 01/12/2014	Start date: 01/12/2014
End date: 30/11/2019	End date: 30/11/2019
Contributions	Contributions
IMI funding: 58 292 722€	IMI funding: 22 790 820€
EFPIA in kind: 33 745 758€	EFPIA in kind: 27 920 073 €
Total Cost: 92 038 481€	Total Cost: 50 710 893 €
www.ebovac.org	www.ebovac2.com

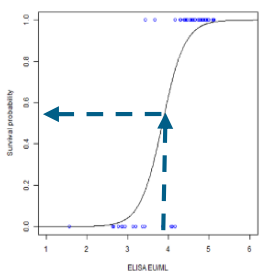
Challenge

In the absence of clinical efficacy data, the likelihood of clinical benefit needs to be inferred by bridging human immunogenicity data (Phase 2/3 trials) to the relationship between immunogenicity and survival outcome (efficacy) in the NHP EBOV challenge model

= ***Immunobridging (IBr)*** (similar approach used for Anthrax vaccine, published in Schiffer et al, 2015)

Approach & Methodology

1. Identified **correlate(s) of protection (CoP)** that best predict **survival** in **NHP** in EBOV challenge studies (EBOV Kikwit)
2. Characterized the **relationship** between the selected **immune correlate** at week 3 post-boost (Wk3 pb) and **survival** in NHP through **logistic modelling**
3. Use logistic model and **immunogenicity data in humans** at same time point (Wk3 pb) to **predict survival probability** for each individual subject per vaccine regimen
4. Obtain **mean predicted survival probability** with 95% Confidence Interval (CI)



Example of the use of the fitted logistic regression model (ELISA) to estimate the survival probability in humans (using an arbitrarily binding antibody concentration, indicated by an arrow)

Results: Statistical approach

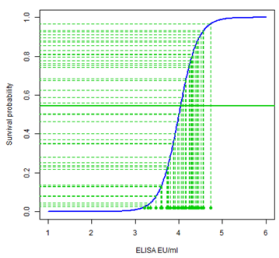
- Logistic models constructed for survival vs potential CoP:
  - **Single correlate** models with **ELISA**, **VNA** and **ELISpot**
  - **Dual correlate** model with **ELISA** and **ELISpot**

  → **Single correlate model based on ELISA selected for Ibr** (VNA responses largely reflected by ELISA responses and ELISpot had limited added value for predicting survival on top of ELISA)
- NHP model much more stringent than Ebola Virus Disease (EVD) in humans (more rapid progression, higher case fatality rate)

  → Janssen agreed with **FDA and EMA** to test the lower limit of the 95% CI of the mean predicted survival probability in humans against a **pre-specified success criterion of 20%** (= acceptable level when directly bridging 1:1 from NHP to human)

Results: Preliminary Immunobridging based on Phase 1 data

- Using the single correlate logistic regression model based on ELISA and survival in NHP, immunobridging was performed using data from 3 Phase I studies (N=44).
- Point estimates for the main vaccine regimen Ad26.ZEBOV/MVA-BN-Filo with 56-day prime-boost interval are in line with the pre-set criterion for Immunobridging agreed with the FDA.



Blue: logistic immunobridging model based on NHP ELISA data from the Ad26.ZEBOV/MVA-BN-Filo regimen with 56-day interval

Green dots with associated dashed lines: individual human ELISA data (N=44) assessed against the NHP logistic model

Clinical studies	Mean predicted survival probability in humans *Ad26.ZEBOV/MVA-BN-Filo with 56-day prime-boost interval*		
	Point estimate	Lower limit 95% CI	Upper limit 95% CI
3 Phase 1 studies (N=44)	54.5%	34.8%	71.3%

NEXT STEPS

Final immunobridging analysis pooling data from all Phase 2 and 3 clinical studies (no Phase 1) on the Ad26.ZEBOV/MVA-BN-Filo vaccine regimen with 56-day prime-boost interval (N= ±1200).

Note: One-lab strategy for ELISA analysis for final immunobridging NHP logistic model, as well as clinical Phase II and III sample analysis

Value of IMI collaboration

The Ebola vaccine projects, among which EBOVAC1 and EBOVAC2, are a series of clinical trials and associated projects aiming to evaluate the heterologous prime-boost Ad26.ZEBOV/MVA-BN-Filo vaccine regimen against EVD. The Phase II (EBL2001 and EBL2002) and Phase III (EBL3001) clinical trials performed under EBOVAC1 and EBOVAC2 contribute to the immunobridging analysis.

Impact & take home message

- In the absence of human efficacy data, clinical benefit of the Ad26.ZEBOV/MVA-BN®-Filo vaccine regimen with 56-day interval has to be inferred via a process called immunobridging
- A single correlate logistic model based on ELISA selected as immunobridging model
- FDA and EMA agreed to test the lower bound of the 95% CI of the mean predicted survival probability in humans against a pre-specified success criterion of 20%
- Survival probability estimates derived are considered to be very conservative due to the stringency of the NHP model. → 1:1 translation gives underestimation of clinical benefit and actual efficacy in humans to be determined in field study
- Preliminary immunobridging assessment based on Phase 1 clinical data (N=44) gives a mean predicted survival probability of 54.5% for the main 0,56 regimen (95% CI: 34.8%; 71.3%), in line with the defined success criterion.
- Next step: Final immunobridging analysis with ELISA data from pooled Phase 2 and 3 clinical studies

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