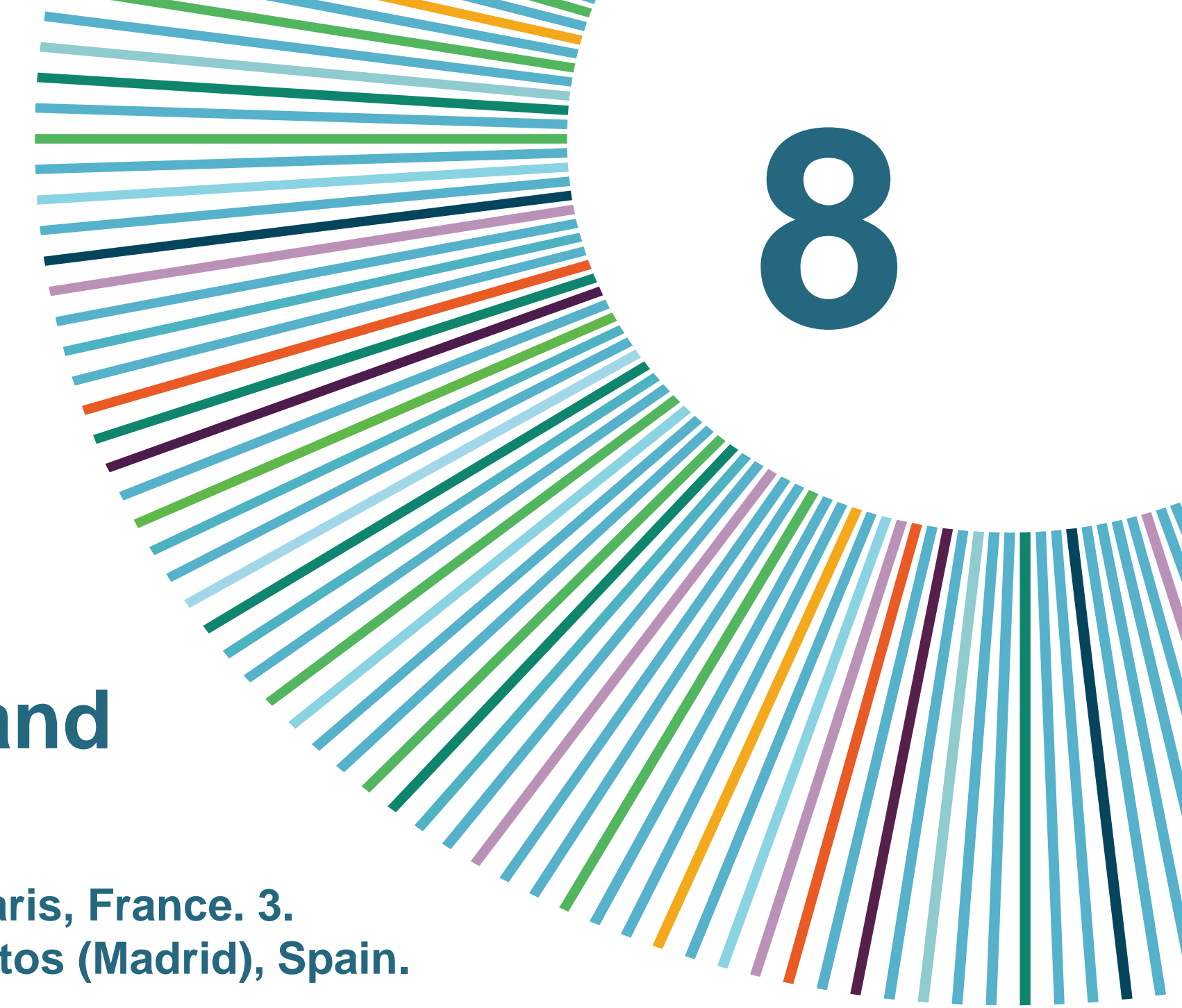
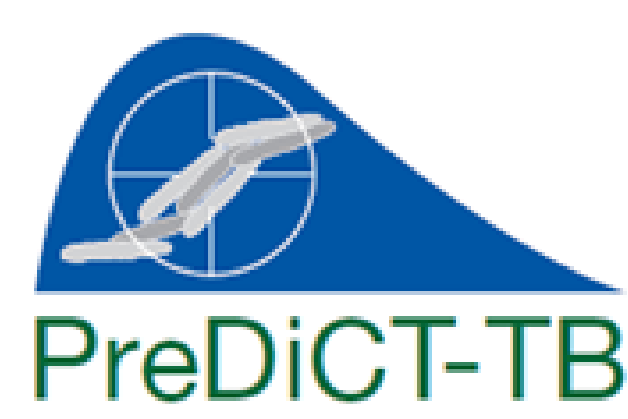


10 YEARS OF
BREAKTHROUGHS
A HEALTHIER
FUTURE



DRUG EVALUATION IN GUINEA PIG MODEL

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FACTS AND FIGURES

Start date:	01/05/2012
End date:	31/10/2017
Contributions	
IMI funding:	14 778 855 €
EFPIA in kind:	9 296 106 €
Other:	4 478 125 €
Total Cost:	28 553 086 €
Project website:	www.predict-tb.eu
Social media:	@PreDiCT_TB

Work Packages:

- **WP1:** *in vitro* models
- **WP2: in vivo models**
 - Zebrafish, mouse models that span multiple aspects of TB disease, guinea pigs, non human primates.
- **WP3:** Enabling technologies
- **WP4:** Clinical Data
 - Individual patient datasets from relevant clinical trials.
- **WP5:** *in silico* modelling
 - Translation of pre-clinical and clinical data into models
- **WP6:** Project management
- **WP7:** Data management

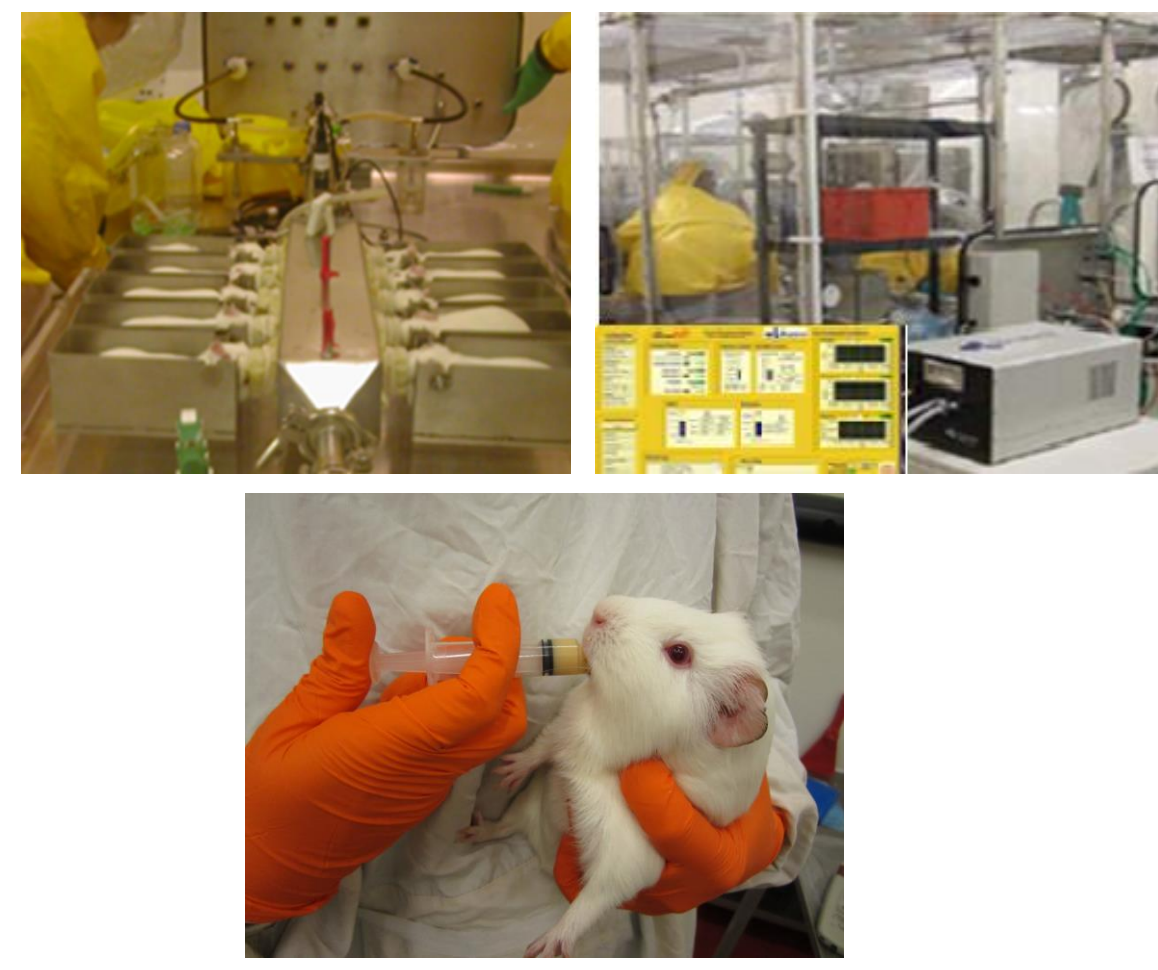
CHALLENGE

Tuberculosis is a global health problem with approximately 10.8 million people each year contracting the disease (1). The standard first line drugs used to treat tuberculosis (TB) are a combination of isoniazid, rifampicin, ethambutol and pyrazinamide. Although relatively successful, the emergence of Multi Drug Resistant (MDR) and Extensively Drug resistant (XDR) TB, due to lack of patient adherence to the drug regimen, the expense of the drugs and the ability of *Mycobacterium tuberculosis* (M.tb) to enter into a latent state, has made it essential that there new drugs are developed (2).

The overall goal of PreDiCT-TB was to develop and enhance an integrated set of pre-clinical *in vitro* and *in vivo* models that provide critical data for the purpose of identifying decision criteria for the progression of novel drugs and combinations to innovate early phase drug development and clinical trials. The specific role of PHE and IP, under work package 2 (WP2), is to perform drug evaluation studies in guinea pigs to inform the consortia on preclinical PK/PD data from new and existing drugs. This collaboration between the 2 sites will ensure that as many drug regimens as possible are evaluated in the guinea pig.

The guinea pig model is used due to the high susceptibility of these animals to aerosol infection by M.tb, as well as histologically resembling humans in the pathogenesis of TB and in the development of necrotic granulomas.

APPROACH AND METHODOLOGY



- Female dunkin hartley guinea pigs infected with *M. tuberculosis* H37Rv via aerosol route (3).
- Treatment delivered 4 weeks post challenge delivered in fruit puree or pina colada mix.
- Novel sampling scheme (Figure 1) 3 guinea pigs euthanized at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 weeks post challenge.
 - Designed by ULIV (WP5) and adopted across both sites.
 - Blood samples analysed by GSK (WP2) and data analysed by ULIV (WP5).
- Lungs and spleens taken at necropsy for bacterial load (Colony Forming Units; CFU).
 - Data modelled by ULIV (WP5) and uploaded to TransSmart (WP7).
- Samples were also stored for use with novel bacterial load assay (MBL) (WP3).

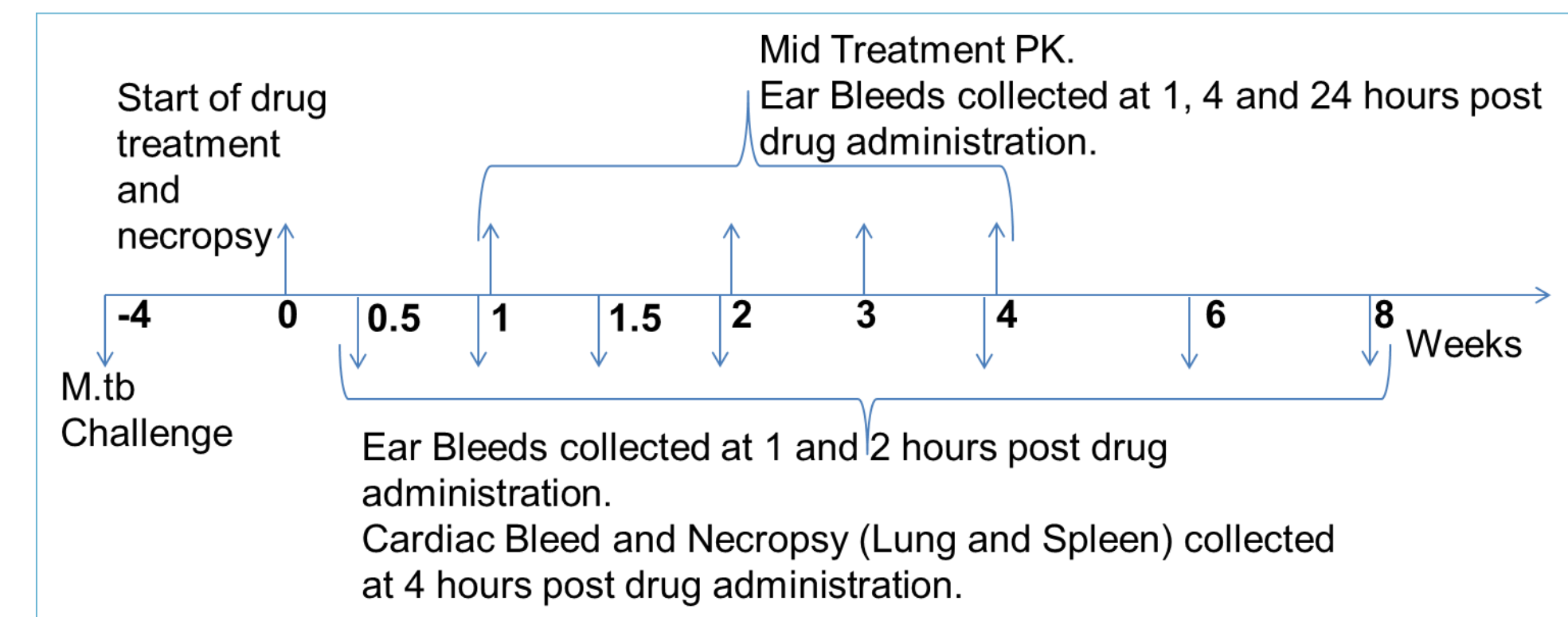


Figure 1: Novel Sampling Scheme designed by ULIV

RESULTS

Pharmacokinetics

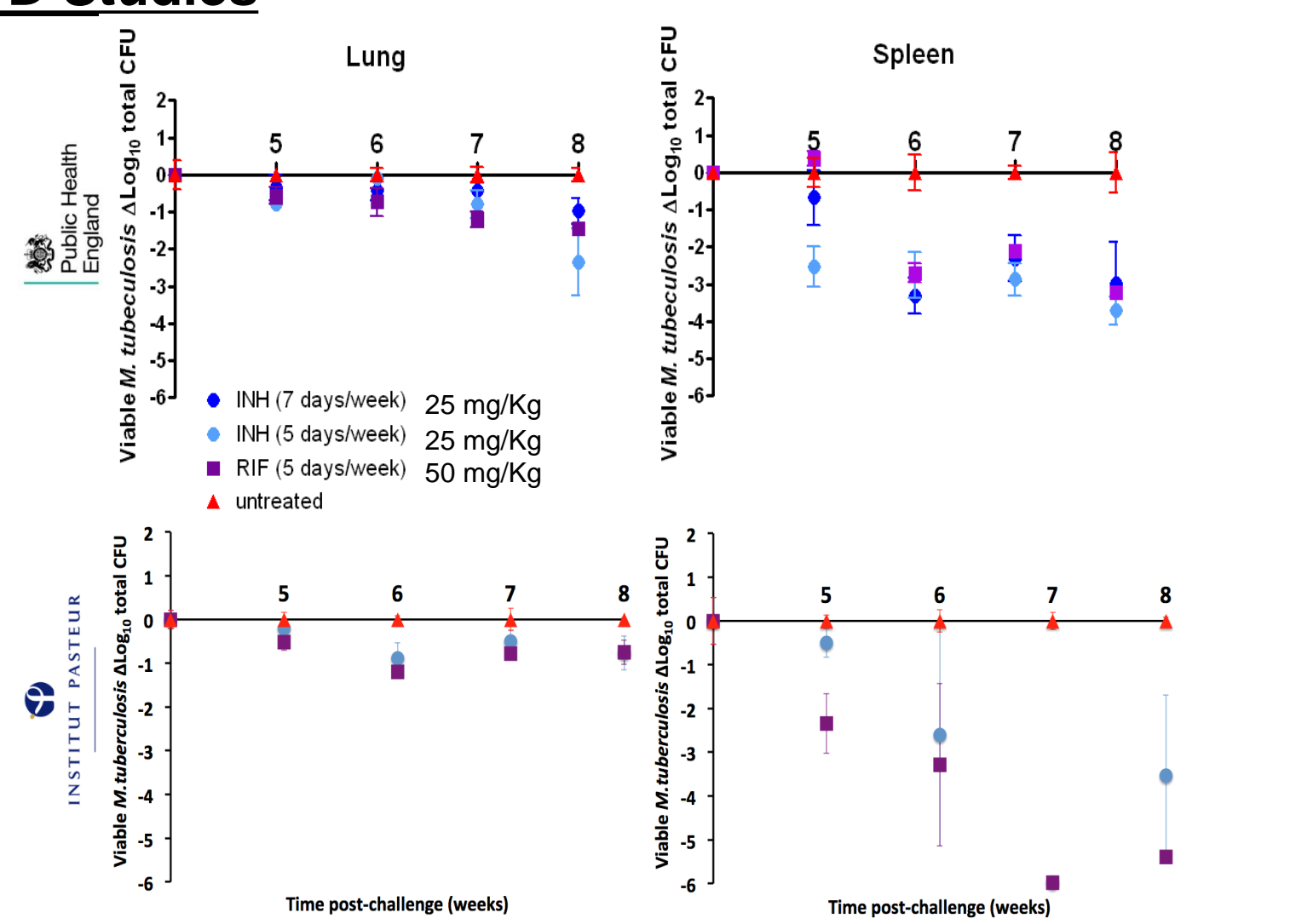
- PK sampling conducted prior to PK/PD studies with the aim of obtaining human like exposure levels from the dose given.
- PK sampling has proved problematic due to the coagulation of guinea pig blood.
- Analysis has shown unusual results! Led to refined methodology as well as novel sampling schemes.
- PK samples taken during PK/PD studies at 1, 2 and 4 hours post administration for PHE and 1 and 4 hours for IP. PHE also performed mid-treatment PK with samples taken at 1, 4 and 24 hours post drug admin.
- PK studies conducted on H, R, Z, E, M monotherapy. HR, RZ, HRZE, HRZ, MRZE, HRZM combinations.

Single Drug Evaluation PK/PD Studies

Study Specific Aims

- Evaluate PK/PD of single drugs in the guinea pig model.
- Harmonisation of data between PHE and IP.

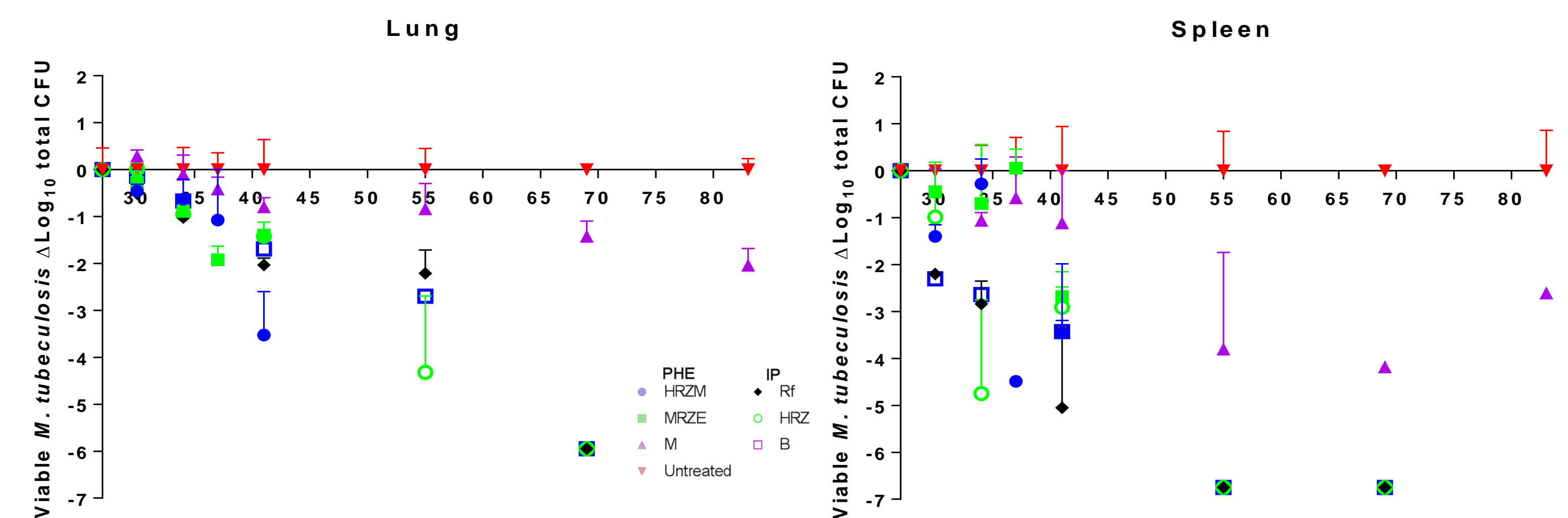
- Significant reduction in bacterial load between the drug treated groups and the untreated control group.
- No significant differences observed between any of the treatment groups including 5 vs 7 day dosing regimens.
- Greatest effect seen in lung at 4 weeks post-treatment initiation.
- Data comparable between two sites; more drug regimens trialled.



Novel Combination Drug Evaluation PK/PD Studies

Study Specific Aims

- Evaluate PK/PD of moxifloxacin monotherapy, rifapentine monotherapy and bedaquiline monotherapy in the guinea pig model.
- Evaluate PK/PD of round two drug combination regimens in the guinea pig model.

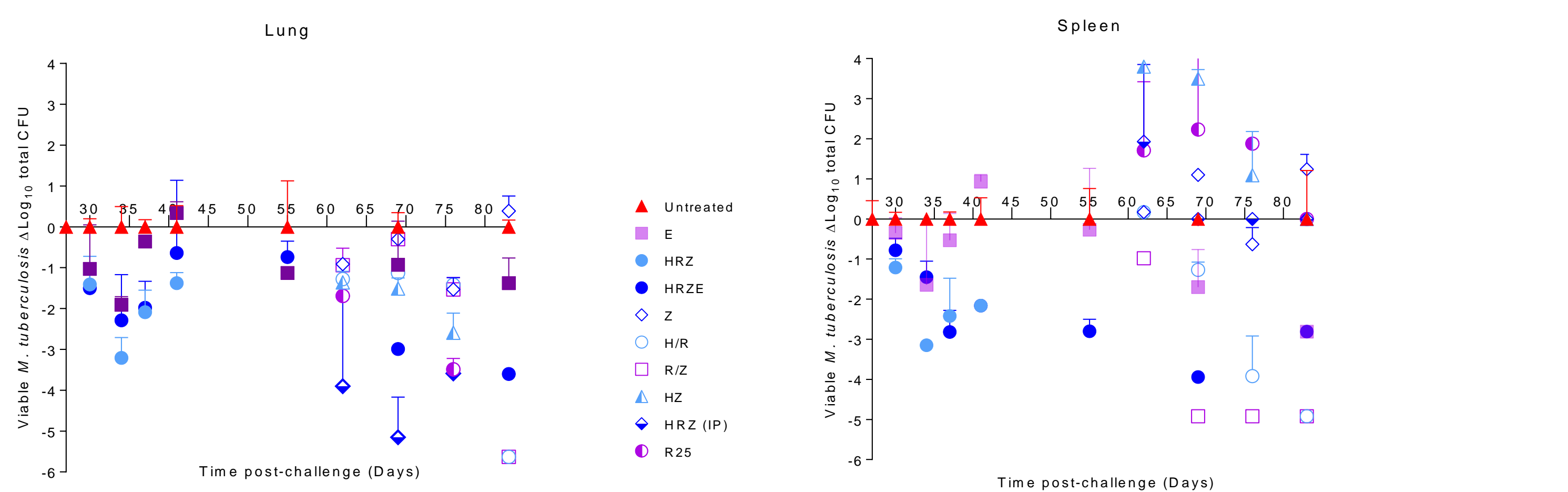


- All regimens showed early bactericidal activity when compared to untreated group.
- Multi-drug regimens more efficacious than monotherapy.
- Spread and noise of data makes it difficult to prove differences between regimens are statistically significant.
- Rp and B monotherapy superior to M and E monotherapy.
- Rp monotherapy decreases bacterial load more than HRZ at D70 in lung.

Standard Combination Drug Evaluation PK/PD Studies

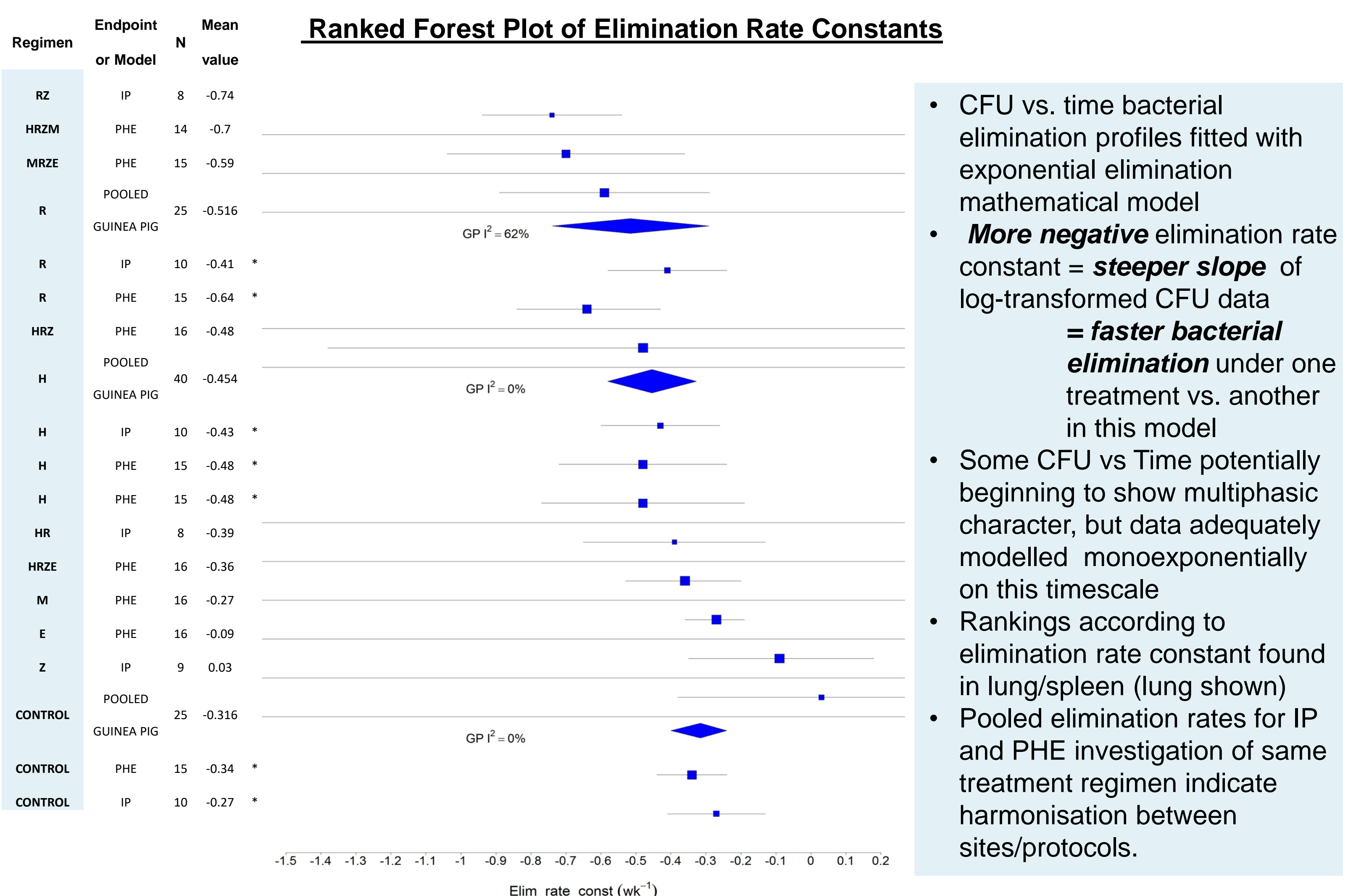
Study Specific Aims

- Evaluate PK/PD of standard drug combination regimens in the guinea pig model.
- Evaluate PK/PD of E monotherapy, R monotherapy and Z monotherapy in the guinea pig model.



- **Lung:** All regimens (excluding Z monotherapy) show bactericidal activity. Over time course, E alone becomes less potent but still effective. HRZE continues to decrease bacterial load. Z monotherapy did not decrease bacterial load. This drug alone has proven to be ineffective in guinea pigs (4). H/R and R/Z decreased bacterial load compared to untreated control. R monotherapy/R containing regimens most effective.
- **Spleen:** Most effective combinations: PHE: HRZE IP: RZ & HR. Monotherapy has no effect.

Ranked Forest Plot of Elimination Rate Constants



- CFU vs. time bacterial elimination profiles fitted with exponential elimination mathematical model
- **More negative** elimination rate constant = **steeper slope** of log-transformed CFU data = **faster bacterial elimination** under one treatment vs. another in this model
- Some CFU vs Time potentially beginning to show multiphasic character, but data adequately modelled monoexponentially on this timescale
- Rankings according to elimination rate constant found in lung/spleen (lung shown)
- Pooled elimination rates for IP and PHE investigation of same treatment regimen indicate harmonisation between sites/protocols.

• Meta regression analysis of the guinea pig data with clinical outcome indicated a relationship with 8 week culture conversion in clinical trials (a recognised surrogate endpoint) suggested that the guinea pig model has useful predictive validity.

VALUE OF IMI COLLABORATION

- Innovative study designs and data analysis in collaboration with WP5;
 - Reducing number of animals and length of experiments.
 - Minimum sample volumes required for analysis.
- EFPIA partner provided expertise and capability in bio-analysis which allowed harmonised and standardised pharmacokinetics data.
 - Improved relevance of animal data, 18 different animal models including zebrafish, mice and NHPs; access to all data and clinical trial data (WP4); may improve productivity of pre-clinical data package.
- Collaboration with partners developing novel technologies (WP3) to enhance *in vivo* models and provide validation of novel assays.

IMPACT AND TAKE HOME MESSAGE

PreDiCT TB Project

- Database of preclinical data on TB drug combinations – potentially the largest and most diverse dataset available.
- New biomarkers for drug efficacy developed and rolled out to improve pre-clinical and clinical evaluation.
- Creation of the first viable and sustainable clinical trials repository and clinical trial simulation tools.
- Comprehensive analysis of pre-clinical and clinical databases which informs on the predictive value of the preclinical tools, with the ultimate outcome of accelerating the drug development pathway to the clinic.

Guinea Pig Studies in PreDiCT TB

- Novel study designs for evaluation of TB drugs shown to generate valid data whilst having 3Rs impact.
- Analysis of clinical and guinea pig outcomes suggest that the guinea pig has useful predictive validity.

REFERENCES AND ACKNOWLEDGMENTS

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