



# Evaluating hepatotoxicity of bedaquiline treatment in multi-drug resistant tuberculosis patients

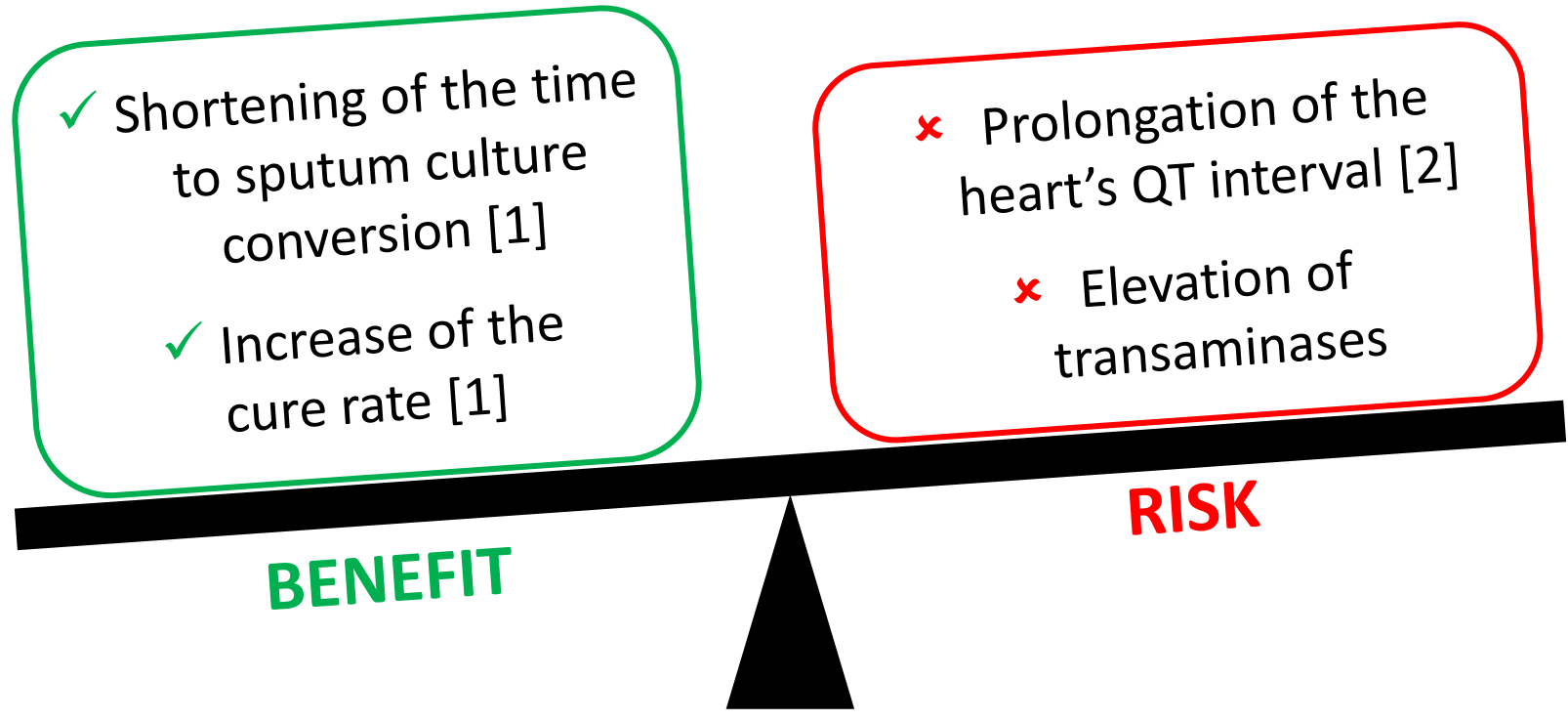
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## Introduction

BEDAQUILINE



Our **objective** was to investigate potential relationships between:

bedaquiline (BDQ) /  
main metabolite (M2)  
exposure

&

Elevation of transaminases  
(alanine aminotransferase (ALT) /  
aspartate aminotransferase (AST))

in multi-drug resistant (MDR) tuberculosis (TB) patients

## Data & Methods

### 2 phase IIb studies: C208 [1] & C209 [3]

- Enrolling **440 patients** (335 receiving BDQ, 105 receiving placebo (PLC))
- 24 weeks** of BDQ or PLC on top of a **background regimen** of 5-7 anti-TB drugs

#### ALT/AST measurements:

- C208** : at day -1 and every 2 weeks
- C209**: at day -1 and at week 2, 8 and 24

#### Modeling approach:

- Covariates** : BDQ and M2 weekly average concentrations (linear, Emax), BDQ treatment (on/off), time after start of treatment, presence of background TB drugs
- Randomization test**: Likelihood ratio test with calibration of type 1 error (C208 only)

#### Statistical approach:

- considering the highest on-treatment ALT/AST value per patient on C208 data only
- Continuous data** : Wilcoxon rank sum test to compare BDQ/PLC medians
- Categorical data**: Proportional odds model with BDQ/M2 exposures as predictors

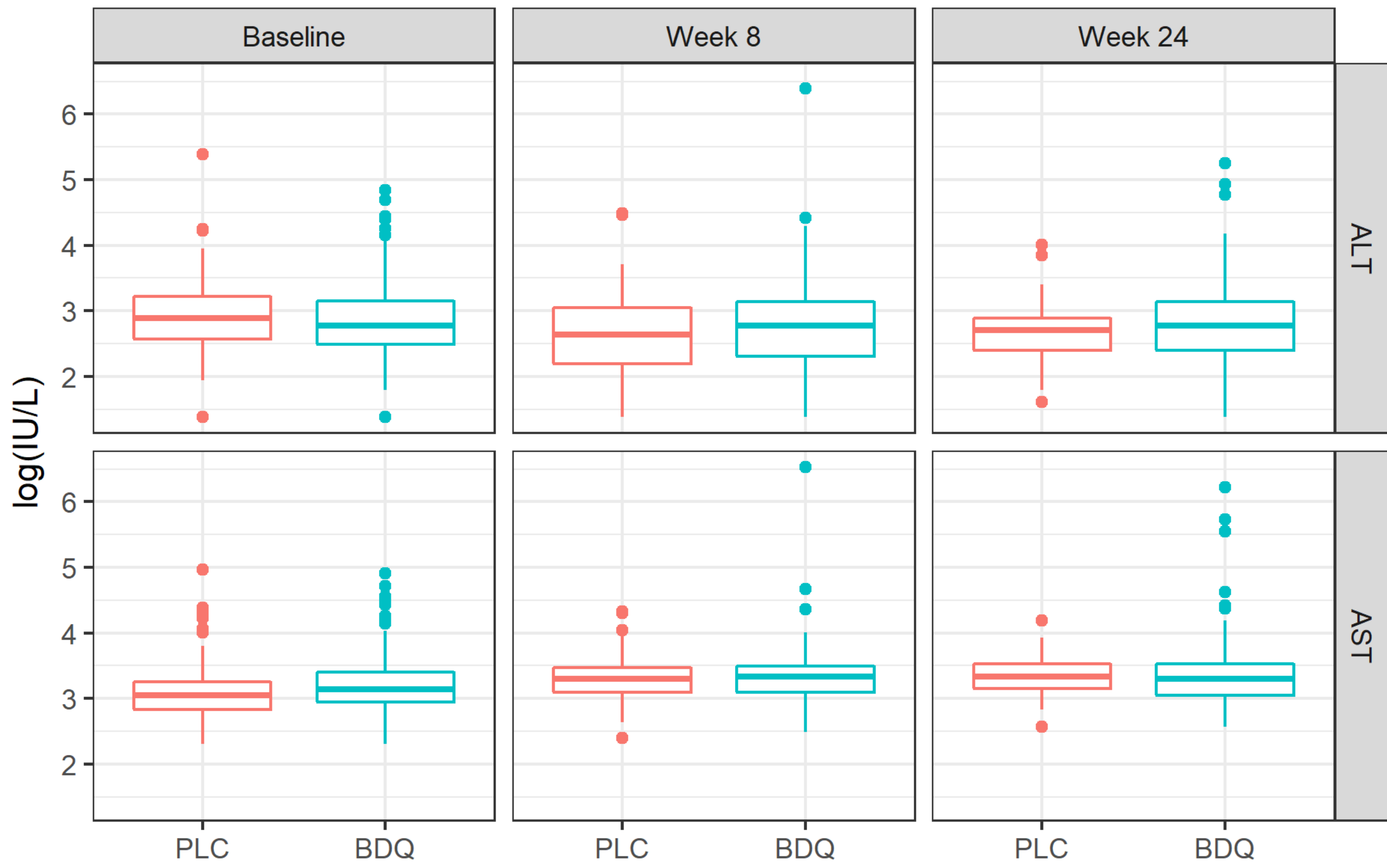


Figure 1. Boxplots of observed hepatic levels (ALT & AST) in the placebo (PLC) arm of C208 study (105 patients) and bedaquiline arm of both C208 & C209 studies (335 patients), at baseline (day -1), week 8 & 24 of treatment.

## Results

### Modeling approach

$$HEP_k = HEP_{0,k} + BG_{treat,k} + \frac{T_{max,k} * Time}{T_{50,k} + Time}$$

with  $k = ALT$  or  $AST$

Background TB  
treatment effect

Time dependency  
effect

No significant  
treatment or  
exposure effect

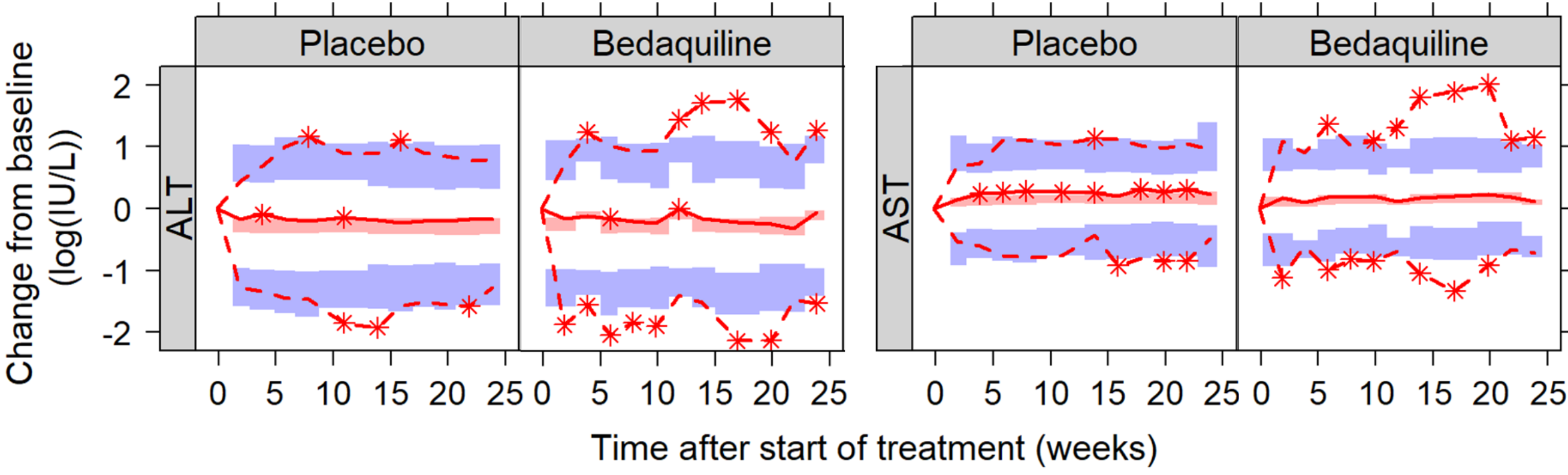


Figure 2. Visual predictive checks. Median (solid line), 2.5th, and 97.5th percentiles (dashed lines) of the observed data are compared to the 95% CI (shaded areas) for the median, 2.5th, and 97.5th percentiles of the simulated data (500 simulations)

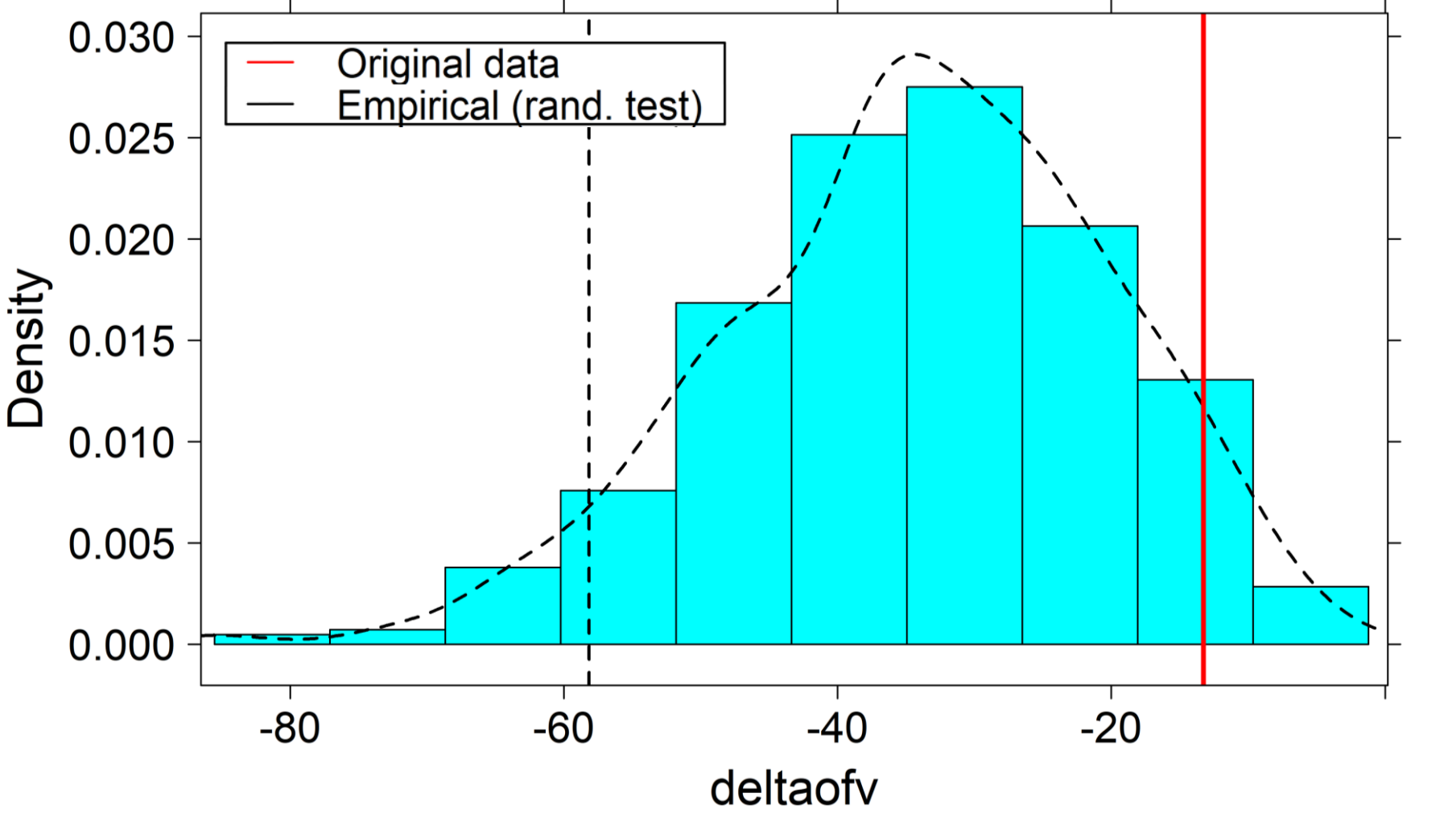


Figure 3. Plot of the randomization test results. Histogram of  $\Delta OFV$  between the models with & without randomized treatment effect. The vertical red line represents the  $\Delta OFV$  of the extended model on the original data, the black dashed line represents the empirical  $\Delta OFV$  cut-off.

No significant  
treatment effect  
( $p=0.94$ )

### Statistical approach

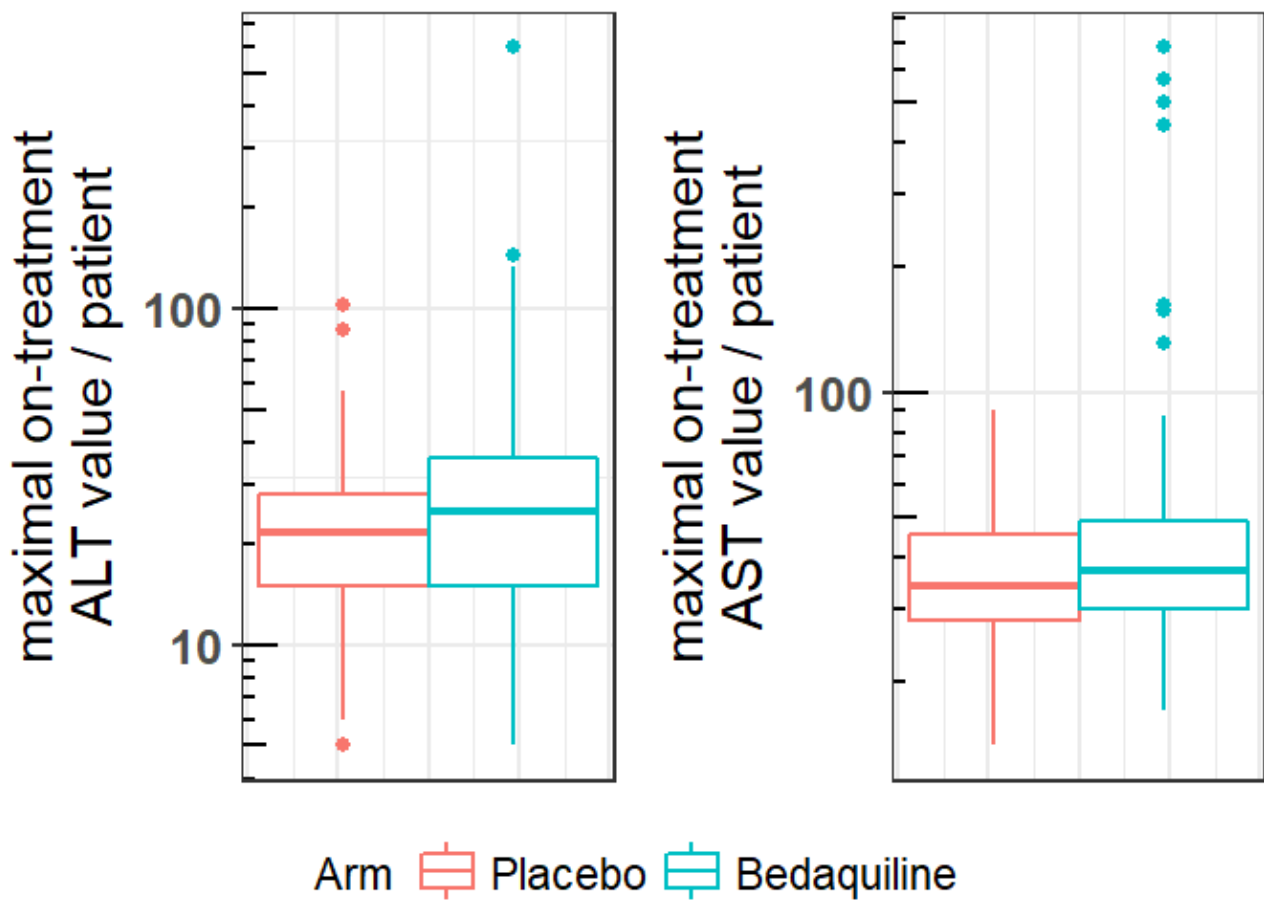


Figure 4. Boxplots of the observed maximal hepatic value (ALT & AST) per patient in the placebo arm (105 patients) and bedaquiline arm (102 patients) of C208 study.

Data treated as continuous

#### Wilcoxon rank sum test

|            | ALT   | AST   |
|------------|-------|-------|
| Median PLC | 21.5  | 34    |
| Median BDQ | 25    | 37    |
| p-value    | 0.084 | 0.115 |

No statistical  
difference  
between the  
medians of  
the PLC &  
BDQ arms in  
C208

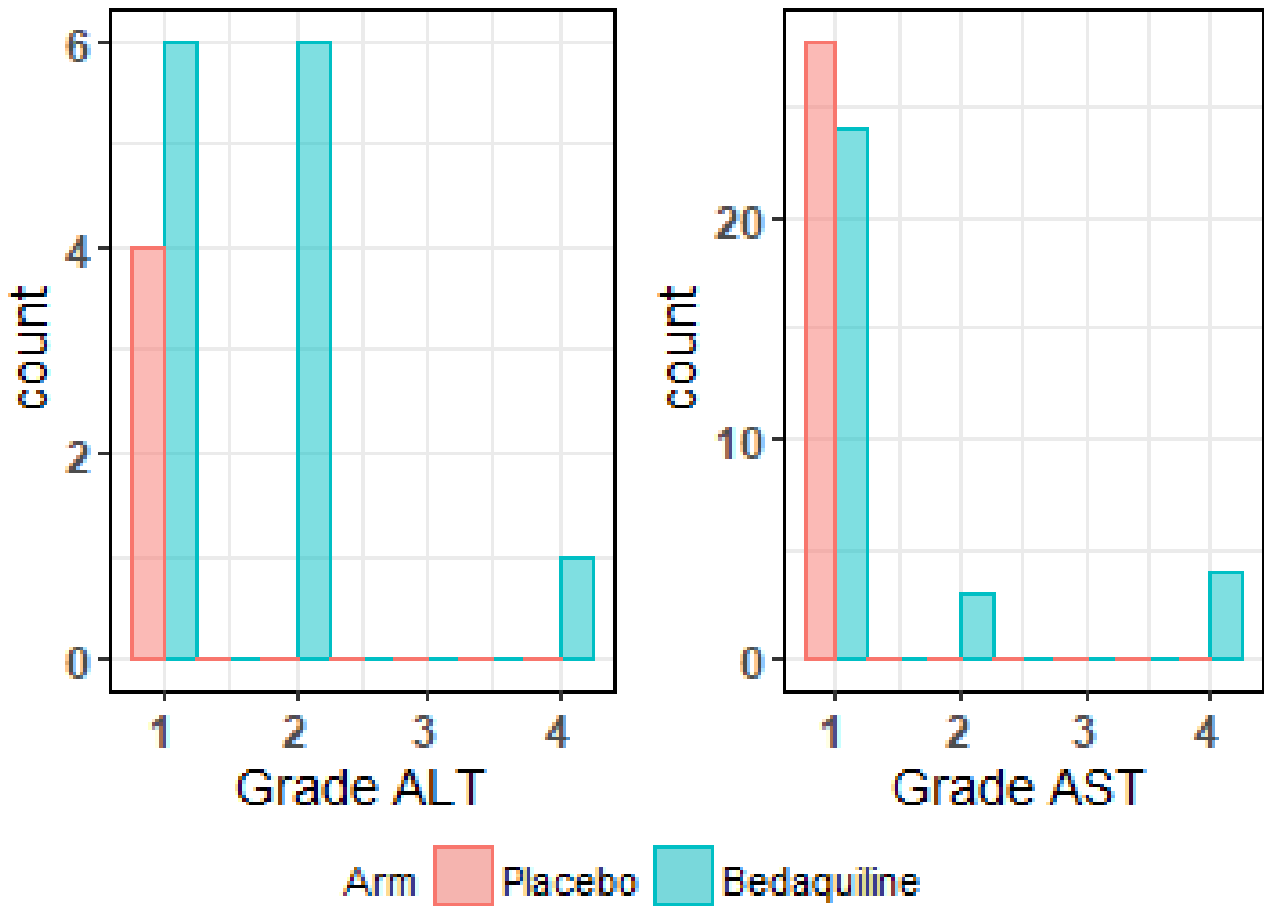


Figure 5. Histograms of the observed maximal severity GRADE for ALT & AST achieved per patient in the placebo arm (105 patients) and bedaquiline arm (102 patients) of C208 study.

Data treated as categorical

#### Proportional odds model

|         | ALT    |     | AST  |     |
|---------|--------|-----|------|-----|
| Grade   | PLC    | BDQ | PLC  | BDQ |
| I       | 4      | 6   | 28   | 24  |
| II      | 0      | 6   | 0    | 3   |
| III     | 0      | 0   | 0    | 0   |
| IV      | 0      | 1   | 0    | 4   |
| p-value | 0.014* |     | 0.38 |     |

\* $p < 0.05$

Statistical  
difference  
between PLC  
& BDQ arms  
for ALT  
**but**  
no  
significant  
relationship  
with BDQ  
and M2  
exposures

## Conclusion

Our analyses could not identify BDQ or M2 as being significantly correlated with ALT or AST increase, although higher grades of ALT were observed in the bedaquiline group compared to the placebo group

### References

[1] Diacon AH et al., N. Engl. J. Med., vol. 371, no. 8, pp. 723–732, Aug. 2014.

[2] Tanneau L et al., Abstr 8634, PAGE 27, 2018.

[3] Pym AS et al., ERJ, vol.47, no.2, pp. 564–574, Feb. 2016.