Biostatistics

Use of historical data in Phase II dose-finding and confirmatory phase III trials

Heinz Schmidli, Cornelia Dunger-Baldauf, Björn Bornkamp
EFSPI Regulatory Statistics Workshop, Basel
September 25, 2018

NOVARTIS

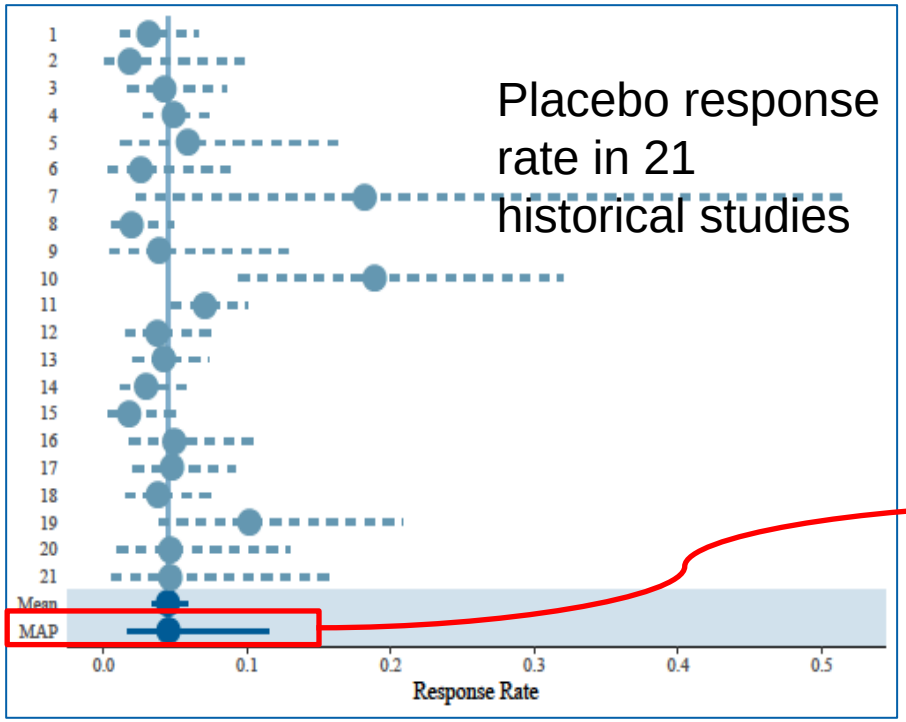
Background

- In the past decade, considerable advances on how to use historical information adequately
  - **Methodology**, e.g. how to „down-weight“ historical data in a scientifically justifiable way, how to achieve robustness, etc.
  - **Practical implementation in clinical trials**

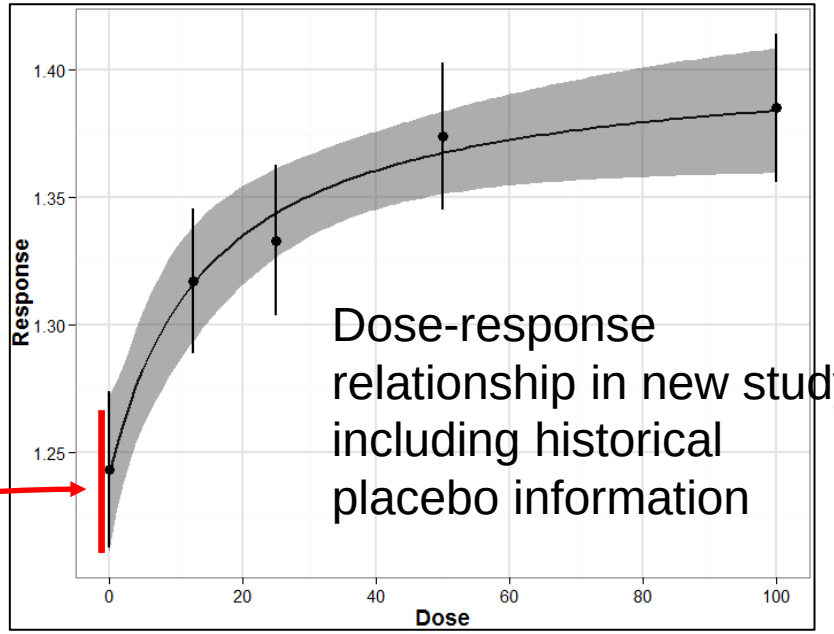
  See e.g. Viele et al. (2014), Neuenschwander and Schmidli (2018)
- Methods have been taken up in
  - Early phase trials, such as PoC studies (see e.g. Baeten et al. 2013) or
  - Specific settings (pediatrics, orphan diseases)
- ... but rarely in
  - Phase II Dose-Finding Studies
  - Phase III studies

NOVARTIS

Phase II Dose-Finding Studies



Placebo response rate in 21 historical studies



Dose-response relationship in new study, including historical placebo information

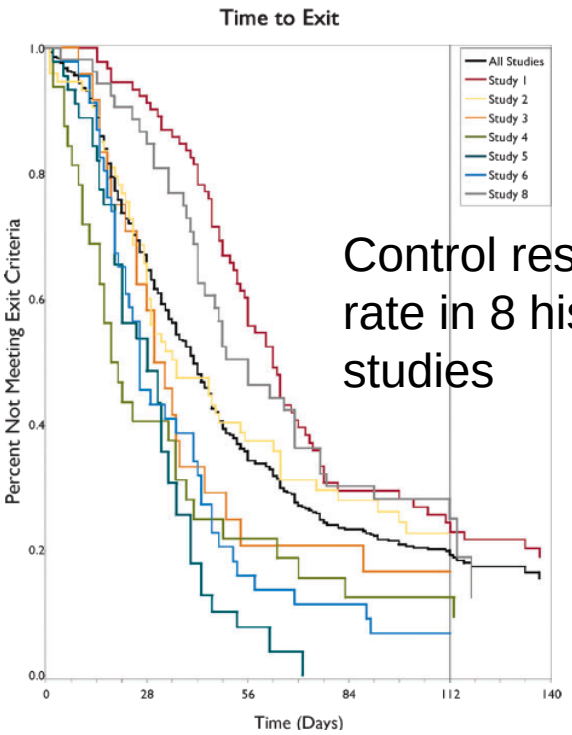
Question

- Would you agree that use of historical control information in dose-finding studies is generally acceptable?
- What considerations should play a role (from a regulatory perspective) when a company considers to use historical data in the analysis?

NOVARTIS

Phase III Studies

- FDA accepts use of historical control (single-arm design) in phase III for *monotherapy treatments in epilepsy*
- Historical control information derived from random-effects meta-analysis of eight studies, and prediction to new study



Control response rate in 8 historical studies

Question

Under which circumstances is partial (reduced control arm + historical controls) or full (single-arm design) use of historical data acceptable in phase III?

NOVARTIS

Questions

Phase II Dose-Finding Studies

- Would you agree that use of historical control information in dose-finding studies is generally acceptable?
- What considerations should play a role (from a regulatory perspective) when a company considers to use historical data in the analysis?

Phase III Studies

- Under which circumstances is partial (reduced control arm + historical controls) or full (single-arm design) use of historical data acceptable in phase III?

NOVARTIS

References

- Baeten et al (2013) Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo controlled trial. Lancet, 382(9906):1705{1713
- French et al. (2010) Historical control monotherapy design in the treatment of epilepsy. Epilepsia, 51(10):1936–1943.
- Neuenschwander B., Schmidli H. (2018): Use of historical data. In Lesaffre E., Baio G., Boulanger B. (eds) Bayesian Methods in Pharmaceutical Research, CRC Press, forthcoming.
- Viele et al. (2014) Use of historical control data for assessing treatment effects in clinical trials. Pharmaceutical Statistics, 13(1):41-54.

NOVARTIS