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# Model-Based Meta-Analysis (MBMA):

## Optimizing Drug Development with Public Data and Predictive Models

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# Your Speakers

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Chief Innovation Officer

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Vice President, Integrated Drug Development





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# Questions We Will Answer Today

- What is the value proposition for meta-analysis and MBMA?
- How is MBMA different from other forms of meta-analysis?
- How has MBMA been used to answer real-world drug development questions?





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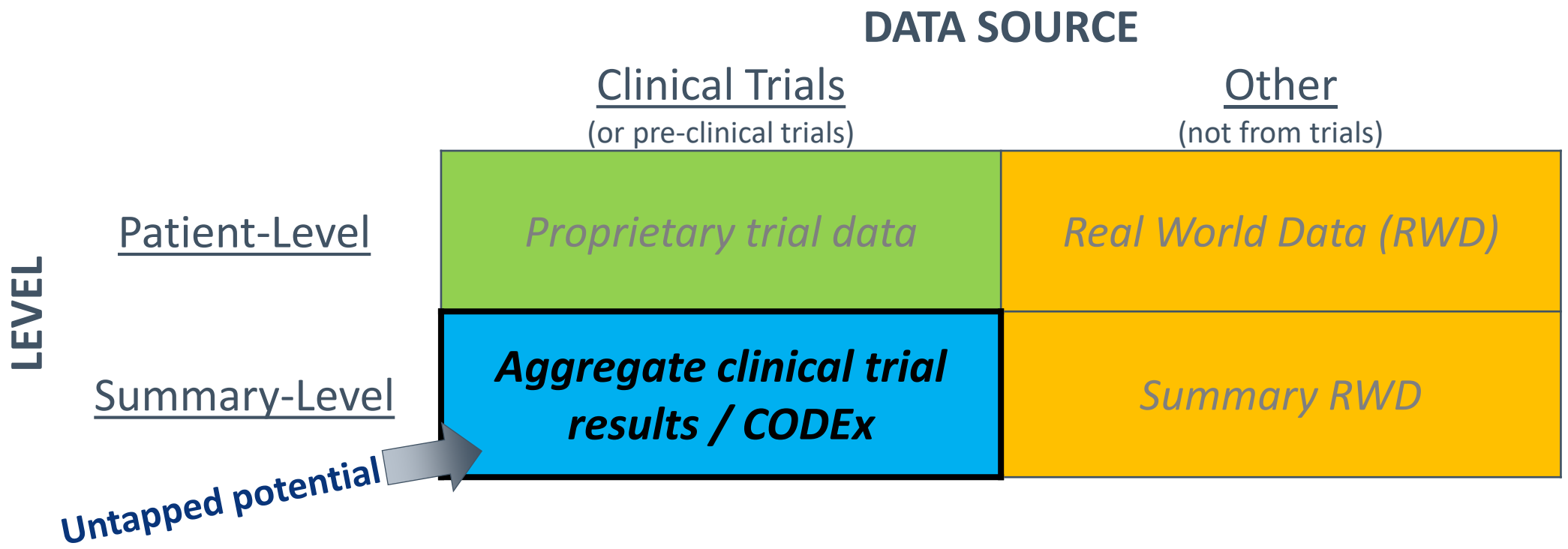
# Where does meta-analysis and MBMA fit into drug development?

## Utilizing all available data can lead to better decisions:

- Drug development decisions (R&D)
- Commercial/Marketing or other critical decisions





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# Meta-Analysis Incorporates Valuable External Information Into Drug Development Decisions

- Comparative safety and efficacy
  - There is a need to evaluate new treatment options against other existing or emerging treatment options (indirectly) for go/no-go decisions, dose selection, trial strategy
- Endpoint-to-Endpoint relationships
  - Biomarker to clinical endpoint predictions
  - Bridging across indications
- Create synthetic control arms
  - Adjusted for known and accounting for unknown factors that impact heterogeneity
- Leveraging existing information
  - Similar shape of dose response relationships of drugs within class
  - Similar impact of disease severity on treatment effect
- Optimize Trial design
  - Impact of trial design features on placebo, treatment effect, and variability



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# *How can meta-analysis and MBMA improve drug development?*

- Rigorously establish safety/efficacy targets needed for differentiation
  - Understand what is truly needed to compete in market and achieve technical success
- Design cost-effective trials that improve probability of early correct development decisions
  - Link early endpoints/biomarkers to registration endpoints
  - Simulate future trials to optimize design and understand probability of trial success
- Iteratively quantify probability of technical success (PTS) as new data are available for each compound in portfolio
  - Quantify risk and get a data-based estimate of PTRS and eNPV
  - Maximize ROI on a trial-by-trial or program-by-program basis
- Additional benefits across the organization
  - E.g., simplify knowledge transfer from detailed trial networks



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# Key Steps in the Data Curation Process

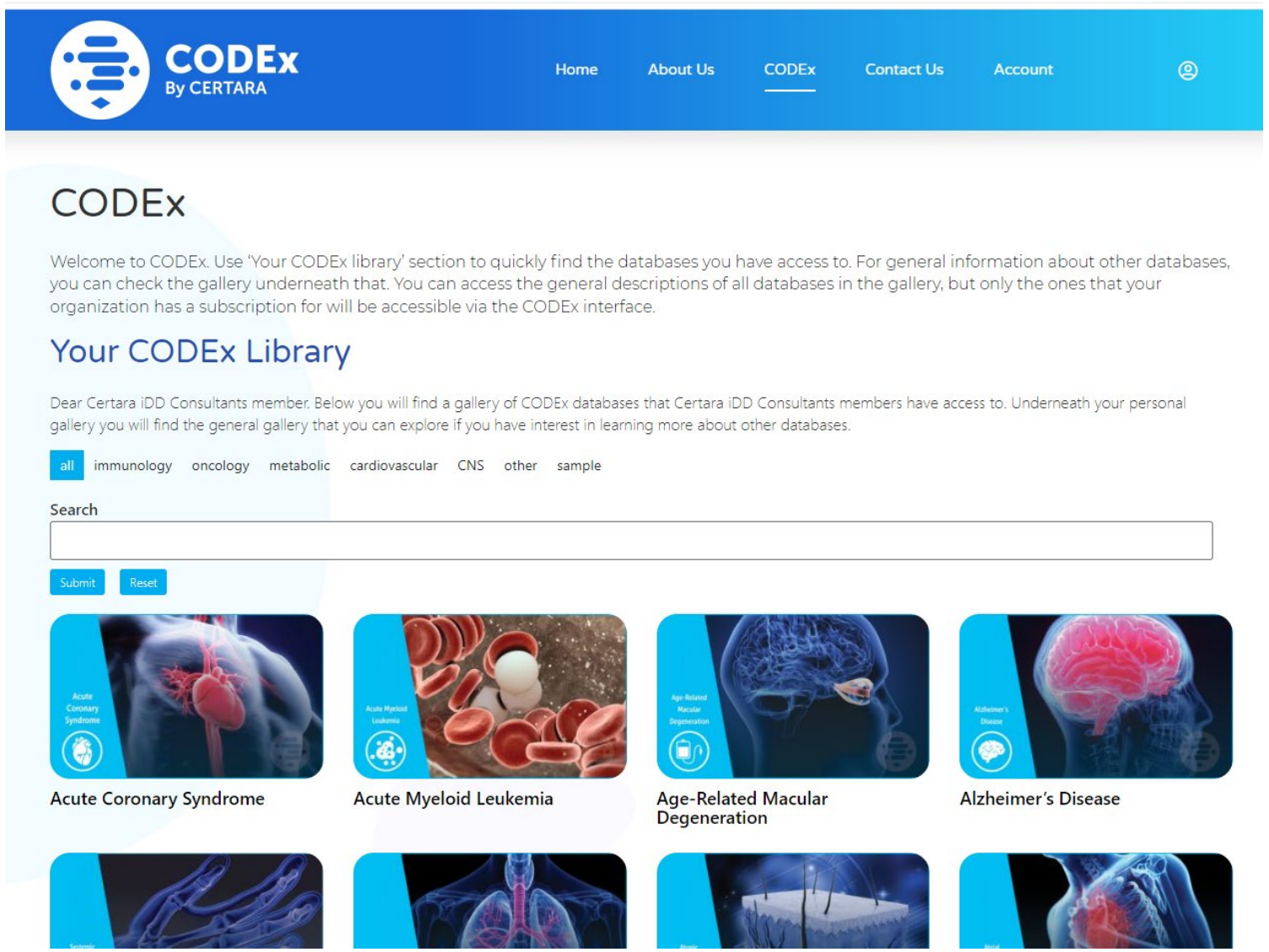
- Formulation of study objectives and protocol
- Literature search
  - Pubmed, clintrials/eudract, company websites/CSRs, conference abstracts/posters/talks
- Review and quality assessment of data sources
- Selection of data sources for inclusion
- Data extraction into CODEx outcomes database
  - CODEx: Clinical Outcomes Database Explorer

- Standard procedures for this process are well defined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).

# Clinical Outcomes Database Explorer (CODEx)

CODEx is a web-based software platform that stores curated clinical outcomes databases and provides an interactive platform to quickly investigate indication-specific databases and perform initial exploratory analytics

[codex.certara.com/codex](codex.certara.com/codex)



# Results from over 400 RA studies are available
# Filtering to relevant data enables impactful exploratory analyses

CODEx | Overview | Database | Studies | Exploration | Pairwise MA | Network MA | Settings | Contact the team

Rheumatoid Arthritis
Clinical Outcomes Database

**Data filters**

Apply filter | Reset filter

Filter variable: randomized.treatment

Filter values: tofacitinib 10 mg

☐ Filter on study-level

Reset all filters

▶ **Active filters**

▼ **Measure settings**

Default measure: value

Default binary comparison: risk difference

Default continuous comparison: mean difference

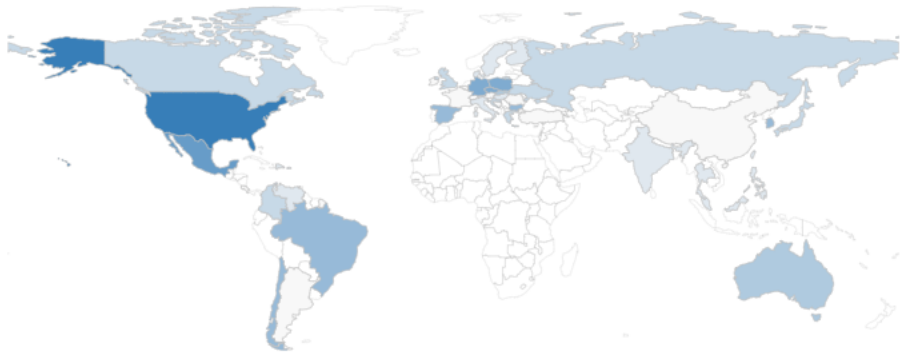
**Data settings**

Summary

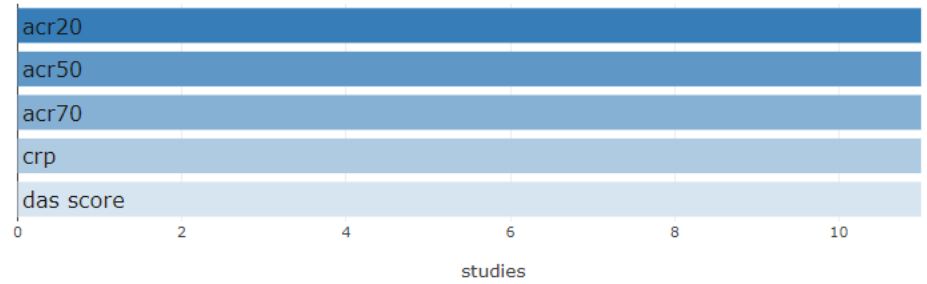
The full CODEx Rheumatoid Arthritis (RA) database contains summary-level endpoint data from 408 studies reported in 901 references. The most commonly reported efficacy and biomarker endpoints are acr20 (350 studies), das score (341 studies), acr50 (336 studies), haq (331 studies), and acr70 (319 studies).

| Key | Complete | Selected* |
|---|---|---|
| References | 901 | 40 |
| Studies | 408 | 11 |
| Study arms | 1273 | 11 |
| Patients | 137061 | 1546 |
| Data Rows | 179094 | 1648 |

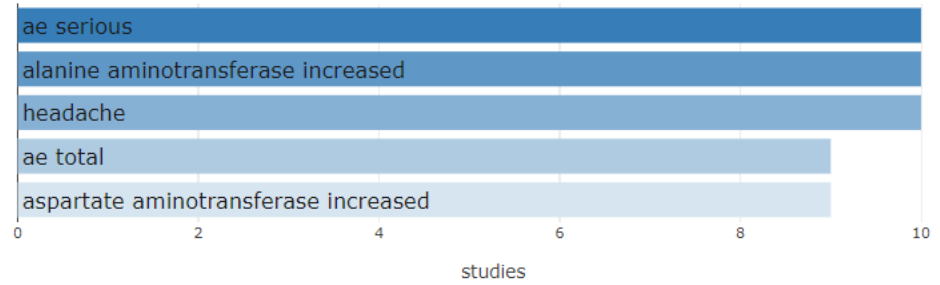
Study sites



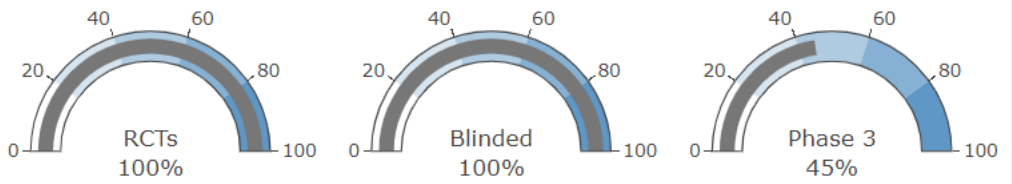
Most common efficacy endpoints




Most common safety endpoints




Evidence characteristics



# Significant between-trial heterogeneity in tofacitinib treatment effect
# Asian majority trials may help explain some of this heterogeneity

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▼ **Measure settings**

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Default binary comparison: risk difference

Default continuous comparison: mean difference

**Data settings**

Settings

Endpoint: acr20

Type: comparative

Model: random

Subgroup: none

Left column(s): asian.majority × | study × | randomized.treatment × | control.drug ×

Right column(s): measure[CI] × | weight(%) ×

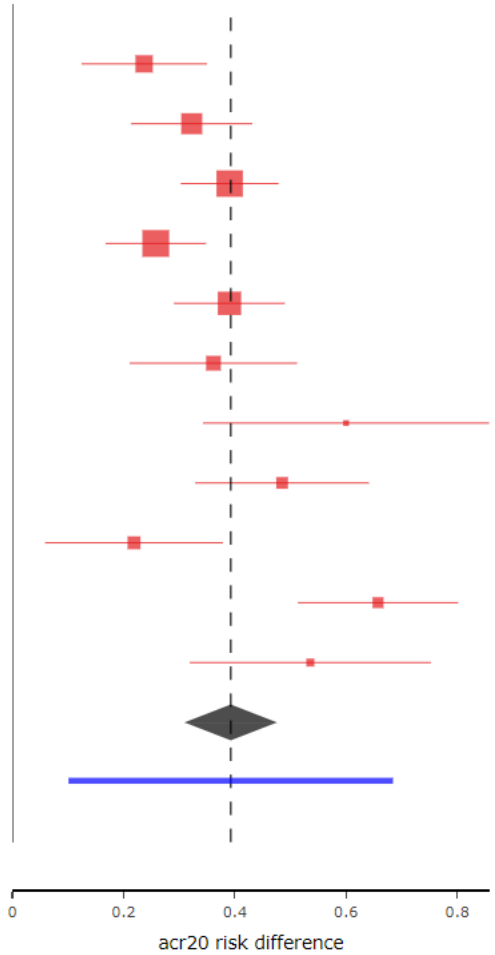
Perform Analysis

Page: 1

Pairwise analysis | Summary | Analysis set | Pairwise settings

| Asian Majority | Study | Full Treatment | Control | Risk Difference [95% CI] | Weight (%) |
|---|---|---|---|---|---|
| non Asian | ORAL-Step | tofacitinib 10 | placebo | 0.24 [0.12; 0.35] | 10.1 |
| non Asian | ORAL-Standard | tofacitinib 10 | placebo | 0.32 [0.21; 0.43] | 10.2 |
| non Asian | ORAL-Scan | tofacitinib 10 | placebo | 0.39 [0.30; 0.48] | 10.9 |
| non Asian | ORAL Sync | tofacitinib 10 | placebo | 0.26 [0.17; 0.35] | 10.8 |
| non Asian | ORAL Solo | tofacitinib 10 | placebo | 0.39 [0.29; 0.49] | 10.5 |
| non Asian | A3921152 | tofacitinib 10 | placebo | 0.36 [0.21; 0.51] | 8.8 |
| non Asian | A3921073 | tofacitinib 10 | placebo | 0.60 [0.34; 0.86] | 5.7 |
| non Asian | A3921035 | tofacitinib 10 | placebo | 0.48 [0.33; 0.64] | 8.7 |
| non Asian | A3921025 | tofacitinib 10 | placebo | 0.22 [0.06; 0.38] | 8.5 |
| Asian | A3921040 | tofacitinib 10 | placebo | 0.66 [0.51; 0.80] | 9.0 |
| Asian | A3921039 | tofacitinib 10 | placebo | 0.54 [0.32; 0.75] | 6.7 |
| **Summary (random effects model)** | | | | **0.39 [0.31; 0.48]** | **100.0%** |
| **Prediction interval** | | | | **[0.1; 0.68]** | **100.0%** |

Heterogeneity: $I^2 = 0.75$, $\tau^2 = 0.01$, $p = 0$



# Adalimumab, baricitinib, and tofacitinib are more effective than placebo
# Baricitinib has apparent dose-response

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Rheumatoid Arthritis
Clinical Outcomes Database

**Data filters**

Apply filter | Reset filter

Filter variable: randomized.treatment

Filter values: tofacitinib 10 mg, adalimumab 40 mg, baricitinib 2 mg, baricitinib 4 mg, baricitinib 8 mg, placebo

☐ Filter on study-level

Reset all filters

▶ **Active filters**

▼ **Measure settings**

Default measure: value

Default binary comparison: risk difference

Default continuous comparison:

Settings

Endpoint: acr20

Intervention: randomized.treatment

Type: comparative

Reference treatment: control

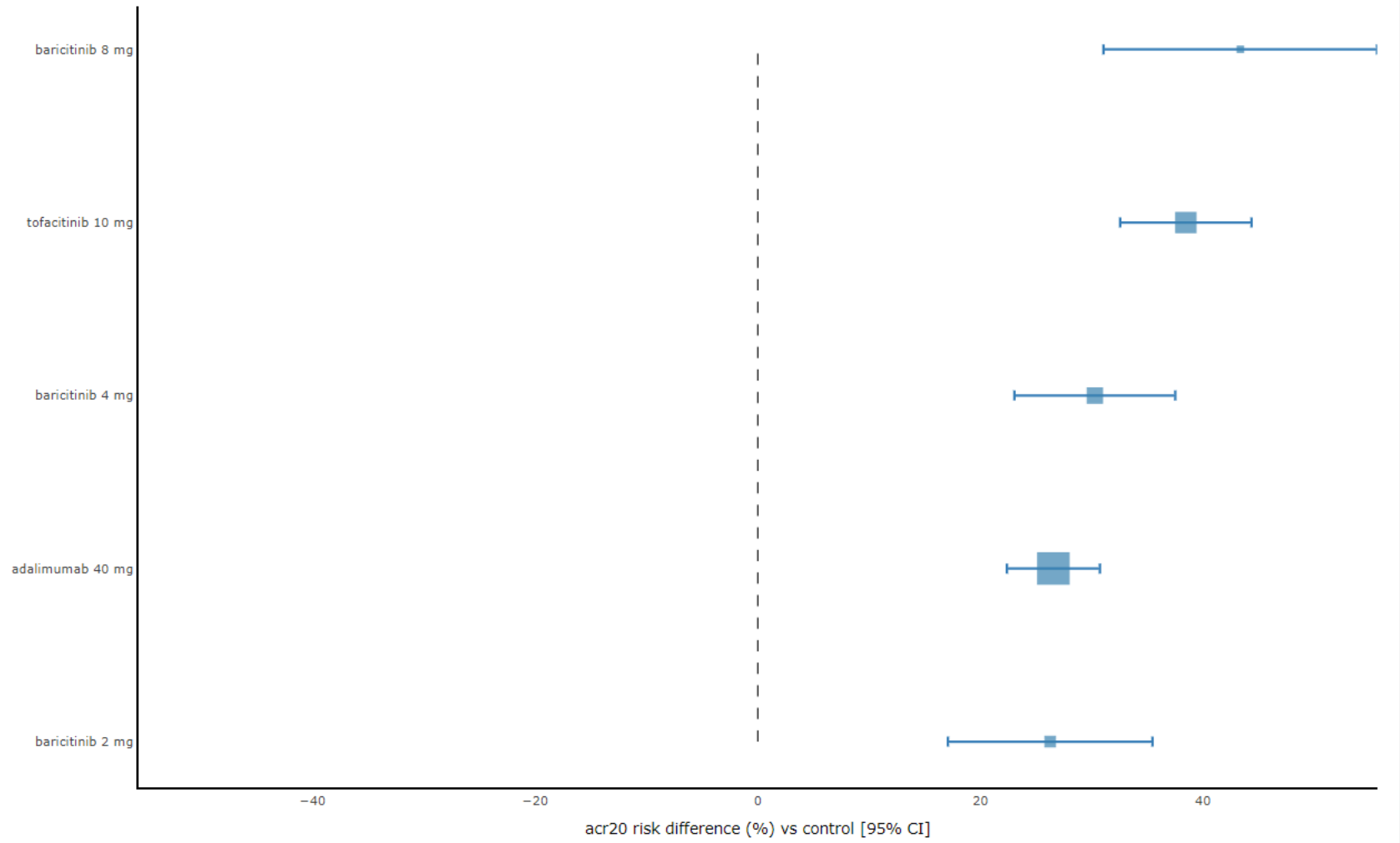
Covariate: none

Covariate effect: global

Perform Analysis

Page: 1 1

Treatment plot | Treatment table | Study plot | Network plot | Funnel plot residual | Summary | Analysis set | Network settings



# Baricitinib dose-response more apparent versus adalimumab
# Baricitinib 8mg and tofacitinib 10mg appear more effective than adalimumab

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Clinical Outcomes Database

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☐ Filter on study-level

Reset all filters

▶ **Active filters**

▼ **Measure settings**

Default measure: value

Default binary comparison: risk difference

Default continuous comparison:

Settings

Endpoint: acr20

Intervention: randomized.treatment

Type: comparative

Reference treatment: adalimumab 40 mg

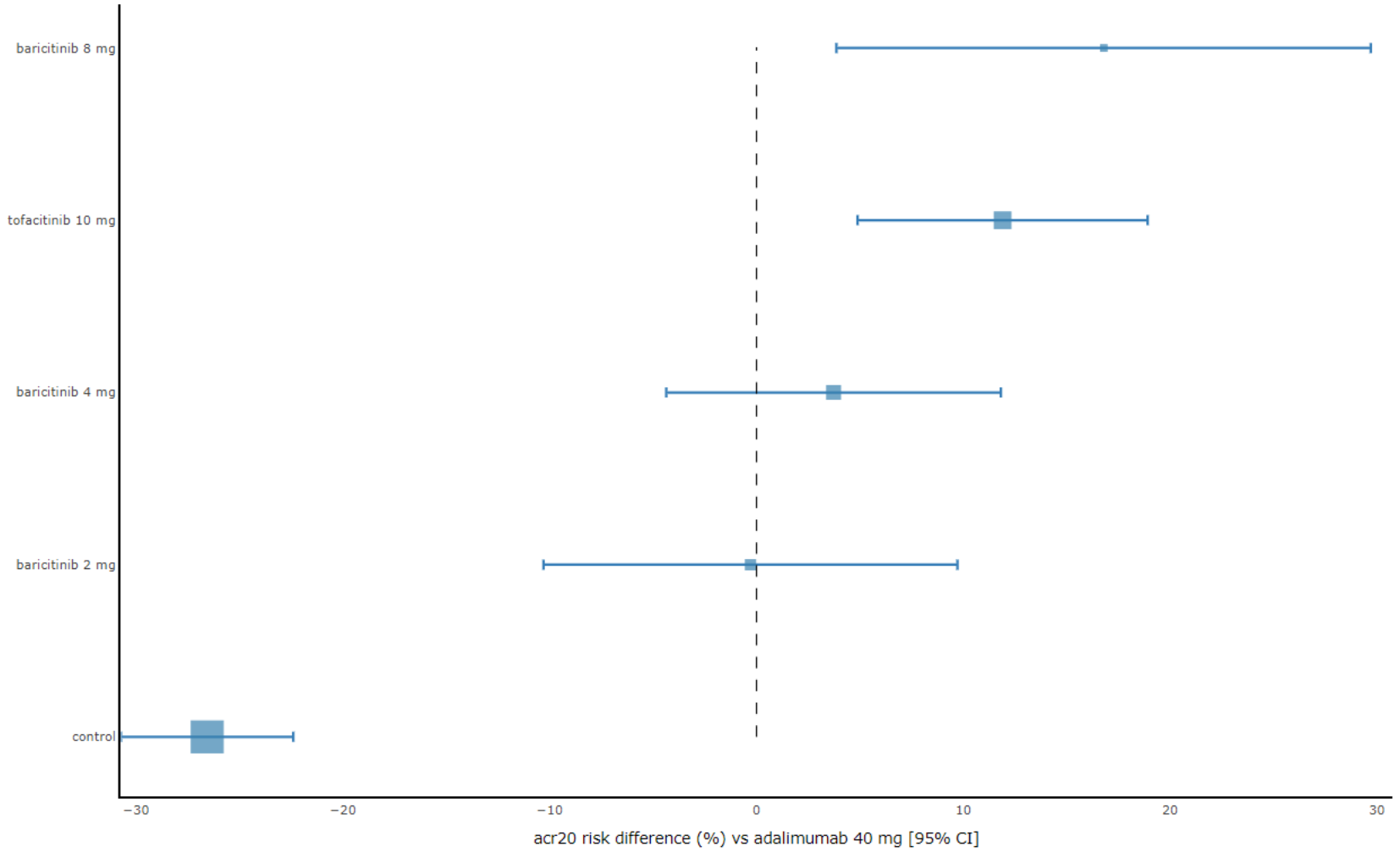
Covariate: none

Covariate effect: global

Perform Analysis

Page: 1 / 1

Treatment plot | Treatment table | Study plot | Network plot | Funnel plot residual | Summary | Analysis set | Network settings



# Majority Asian trials have an impact on anti-TNF treatment effect

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Rheumatoid Arthritis
Clinical Outcomes Database

**Data filters**

Apply filter | Reset filter

Filter variable: randomized.treatment

Filter values: tofacitinib 10 mg, adalimumab 40 mg, baricitinib 2 mg, baricitinib 4 mg, baricitinib 8 mg, placebo

☐ Filter on study-level

Reset all filters

▶ **Active filters**

▼ **Measure settings**

Default measure: value

Default binary comparison: risk difference

Default continuous comparison:

Settings

Endpoint: acr20

Intervention: randomized.treatment

Type: comparative

Reference treatment: adalimumab 40 mg

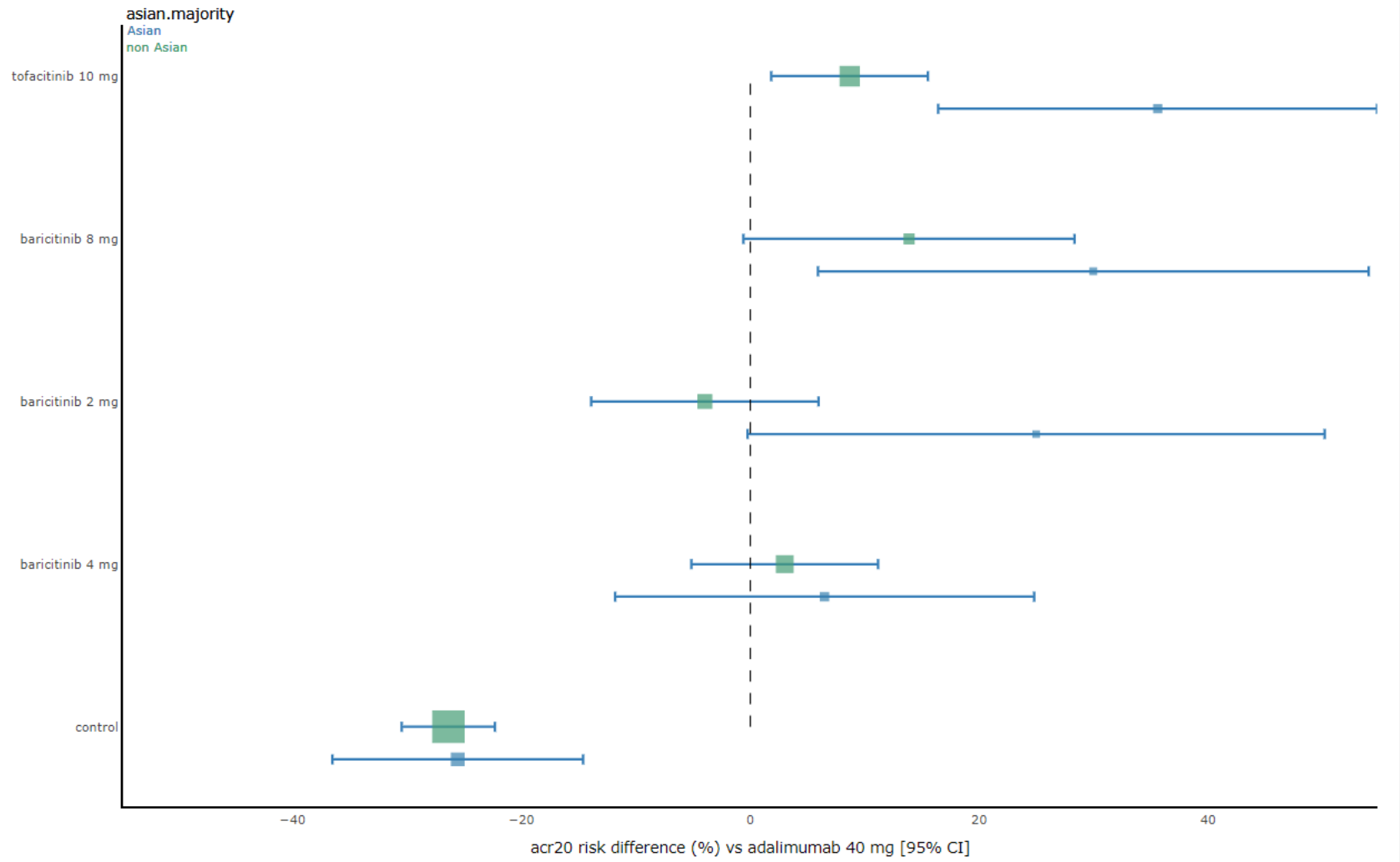
Covariate: asian.majority

Covariate effect: by intervention

Perform Analysis

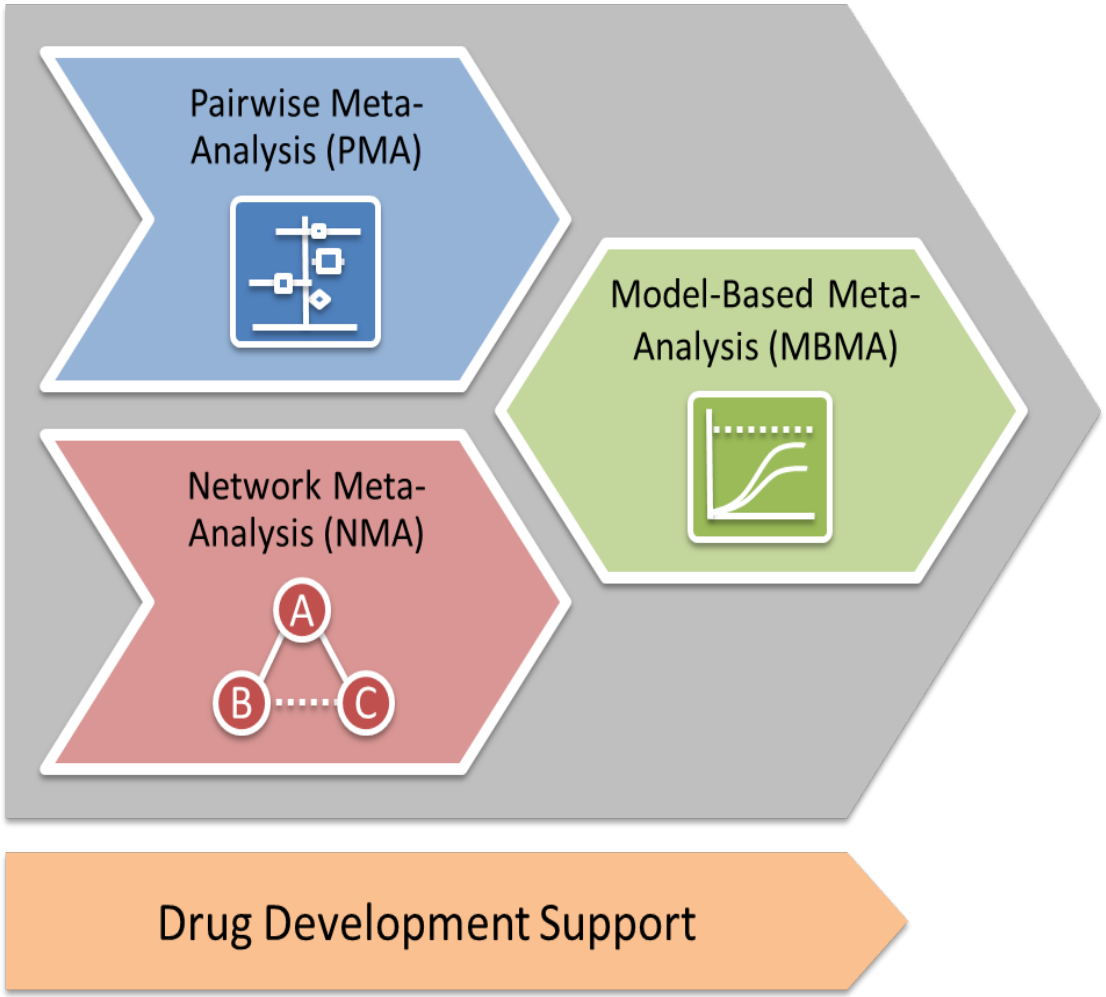
Page: 1 / 1

Treatment plot | Treatment table | Study plot | Network plot | Funnel plot residual | Summary | Analysis set | Network settings



# MBMA takes advantage of pharmacological/physiological insights

- Model-based meta-analysis (MBMA) is a type of meta-analysis that incorporates parametric models for the effect of treatment, time, and patient population characteristics on the outcomes
  - Explicitly incorporates the effect of dose and duration using standard pharmacology models and assumptions
  - Can include trial-level covariate relationships on the dose-response models to account for between trial differences in patient populations
- Allows simultaneous modeling of multiple endpoints and can therefore link biomarkers to clinical endpoints or early to late endpoints
- Like network meta-analysis, MBMA can provide indirect comparisons and simulations of head-to-head trials, but may use (longitudinal) dose-response models for individual drugs or drug classes
- Can be used for simulations of trials and predictions of trial success





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# MBMA Case study

## PHASE II to III decision point for baricitinib in RA





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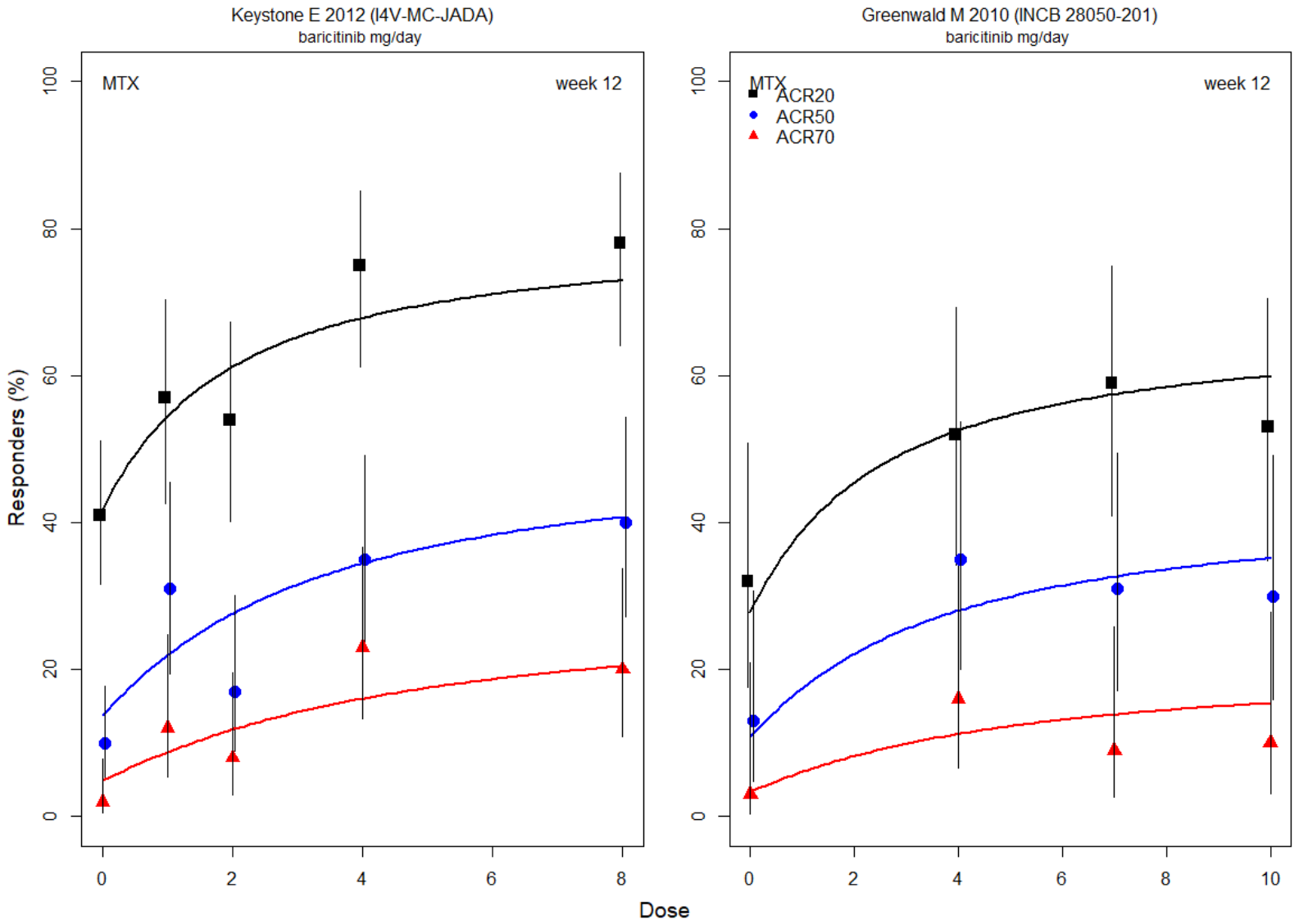
# Typical MBMA application is to compare phase II efficacy/safety results for novel treatment options against other treatment options; marketed or in development

Phase II results in RA for baricitinib, a JAK inhibitor




- What is the probability to have a better efficacy/safety profile vs. other treatments?
- What is the best endpoint to differentiate our compound?
- Can we increase precision of dose response by assuming similar Emax as other JAKs?
- Should we run a phase III trial vs. competitor? Which one? Superiority strategy? or NI? at what margin?
- Is there a difference in DR (Emax or ED50) between TNF experienced and naïve patients? MTX experienced vs. naïve?
- Would 1 phase II have been sufficient?
- Could we have reduced the time frame (4 week vs. 12-week study)?
- Could we have use a synthetic control?
- Can we quickly expand to other indications: psoriatic RA, psoriasis, Crohn's, UC?



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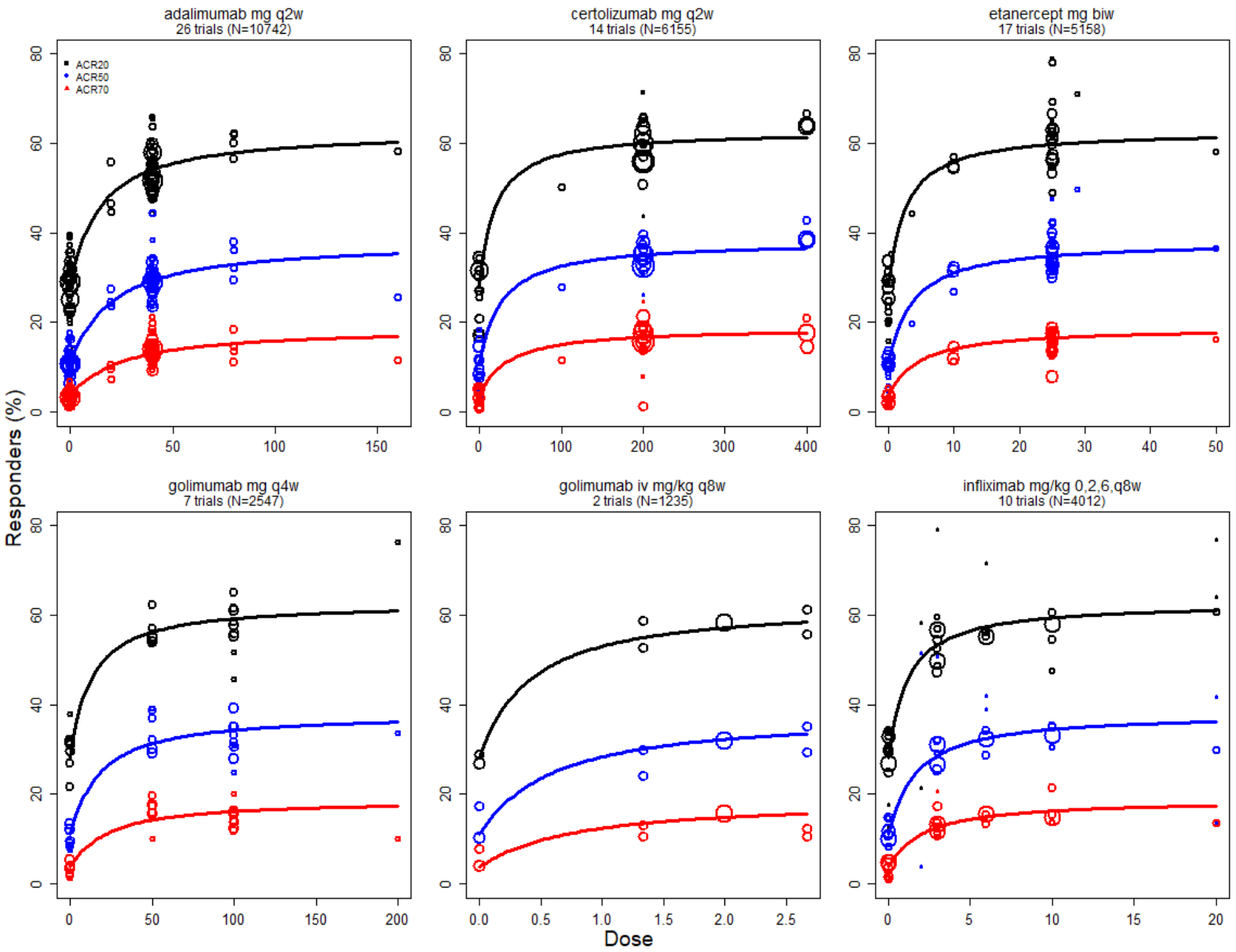
# MBMA of time course of ACR20/50/70 shows that ACR dose response relationship is consistent and well characterized for all TNF inhibitor across trials (symbol size~precision)




$$P(ACR)_{ijkt} = logit^{-1}\left(Eo_{itk} + f\left(Drug_{ij}, Dose_{ij}, t, X_{ij}, \theta_{(i)}\right) * e^{eta_i}\right)$$

- $Eo_{itk}$ represent the placebo response (intercept) accounting for the trial-to-trial variability in overall response. $Eo_{itk}$ represents a fixed-effect estimate for every time point in a study and a fixed-effect for every endpoint in a study (i.e. shift between ACR20, ACR50, and ACR70).
- $f\left(Drug_{ij}, Dose_{ij}, t, X_{ij}, \theta_{(i)}\right)$ was the model for the treatment effect for each drug, based on dose, time and relevant covariates.
- Trial-to-trial variability in treatment effect for each drug was described by study specific random effects $eta_i$ with mean 0 and variance $\omega^{2.}$



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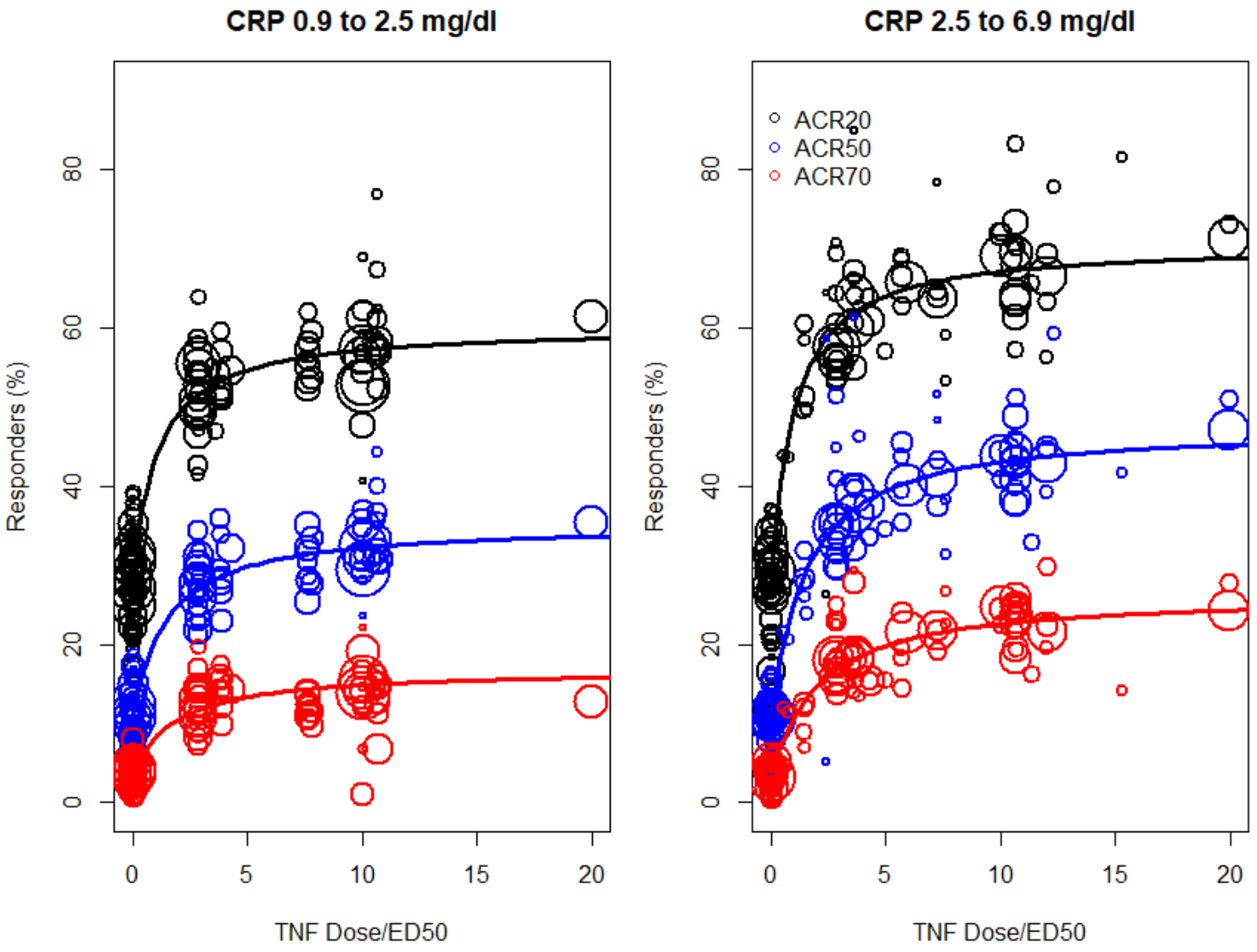
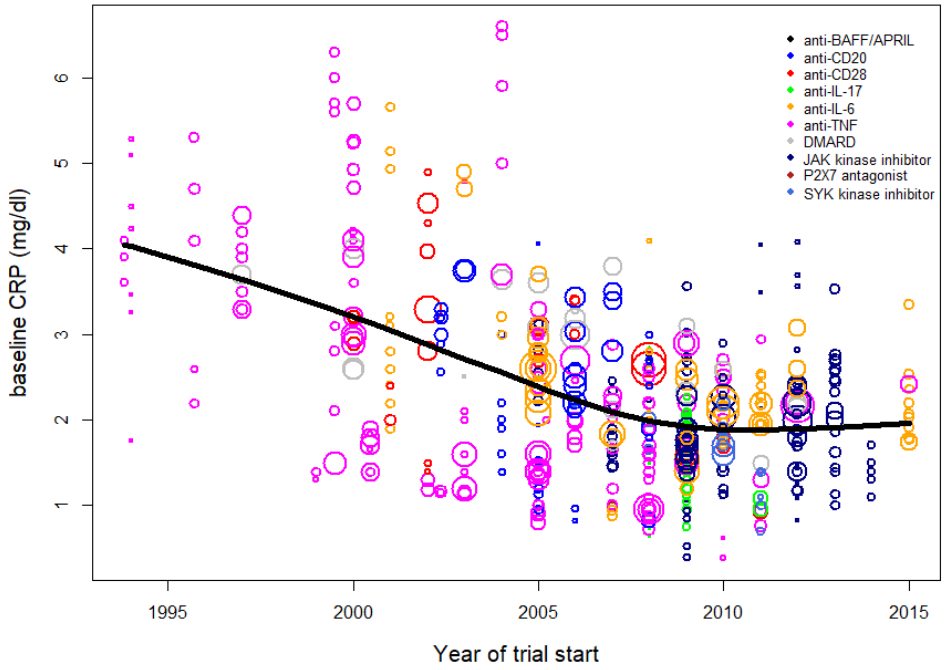
# Treatment response for ACR is significantly dependent on baseline CRP

## The decline of baseline CRP over the past 20 years explains the drift in treatment effect for anti-TNFs

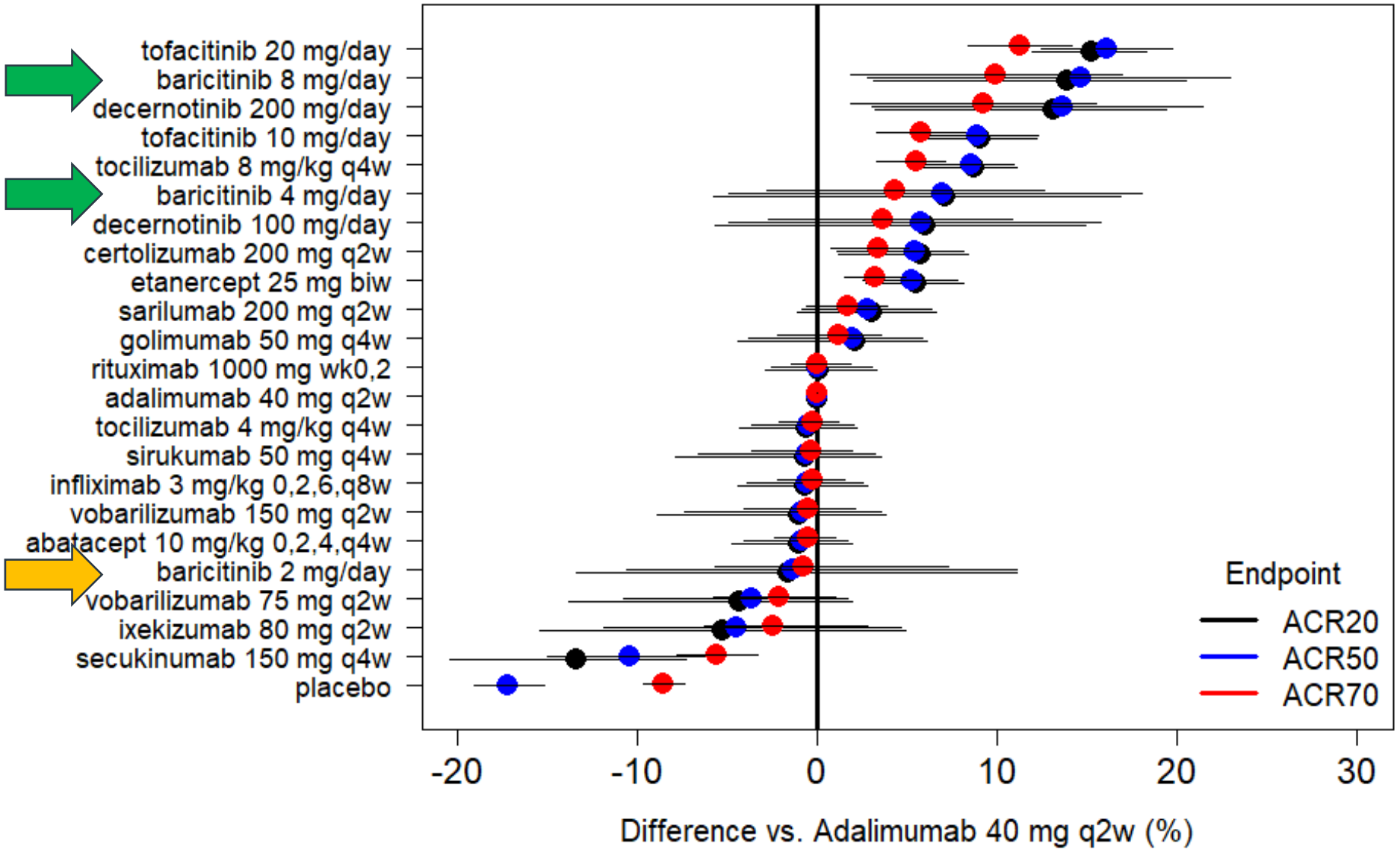



- Treatment effect was dependent on: baseline CRP, % of patients on background MTX, and Asian/non-Asian (especially for JAKs).
- 8.5% more ACR20; 7.9% more ACR50 responders for 1 mg/dl increase in mean baseline CRP

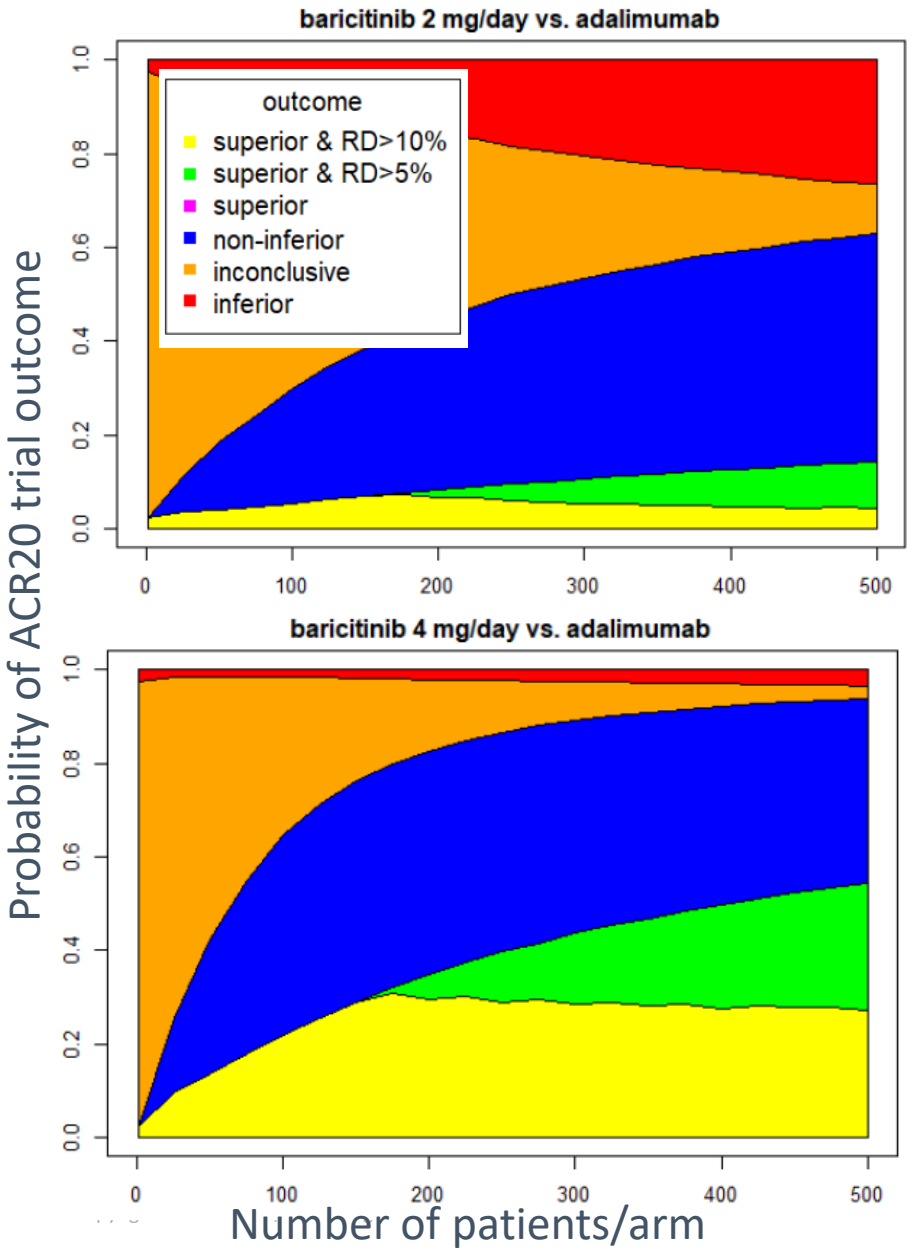


# Comparative efficacy for baricitinib relative to other treatment options in RA [95% CI]

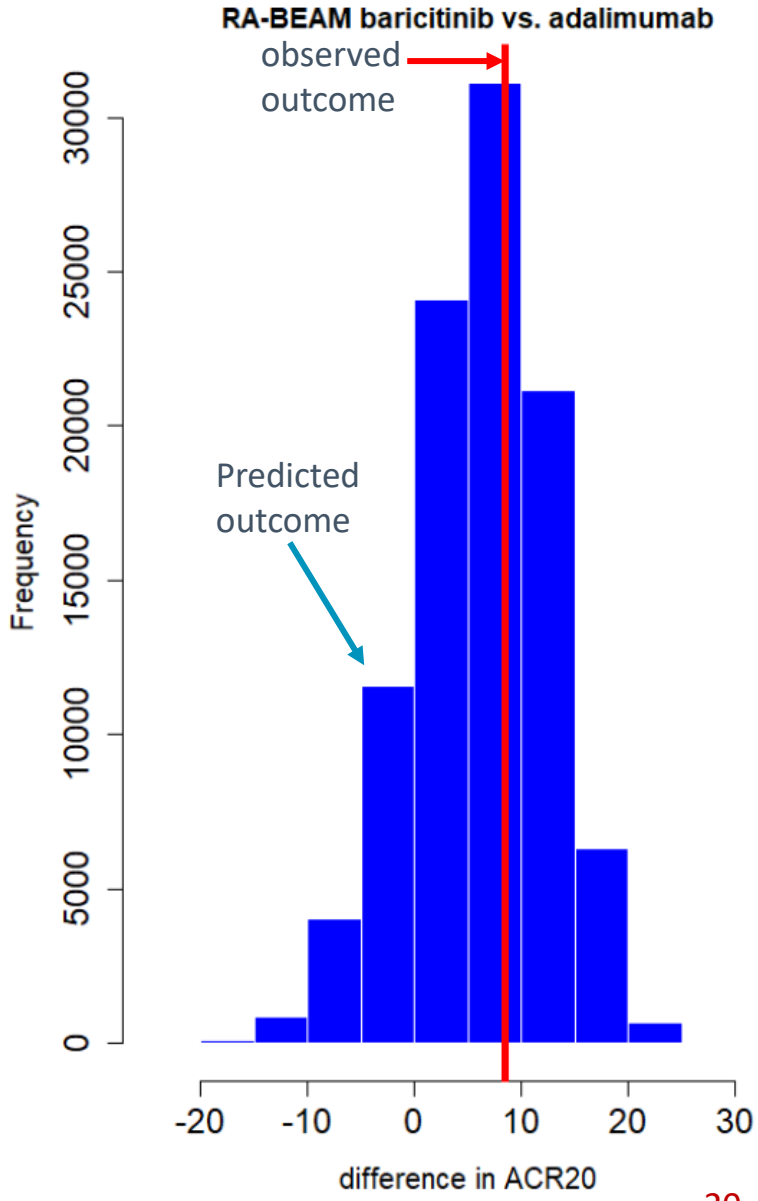
baseline CRP=2 mg/dl; MTX background; placebo=11% for ACR50



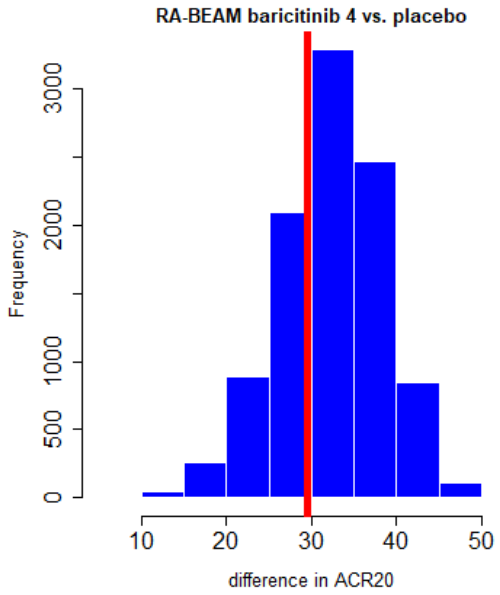
# Probability of phase III trial outcome for ACR20 comparing baricitinib to 40 mg q2w adalimumab compared to observed outcome of RA-BEAM trial

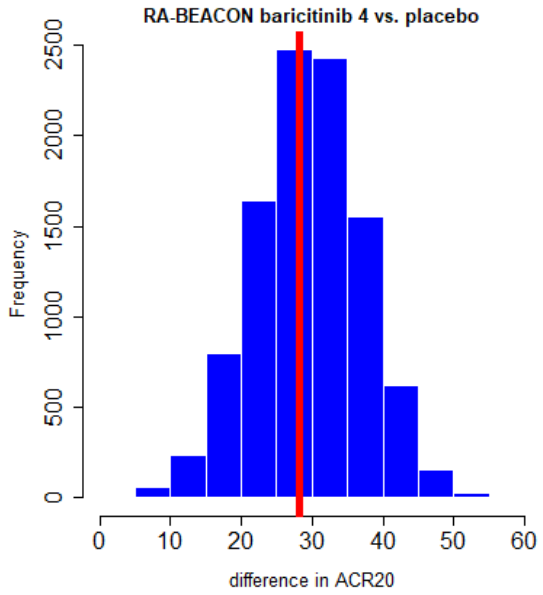


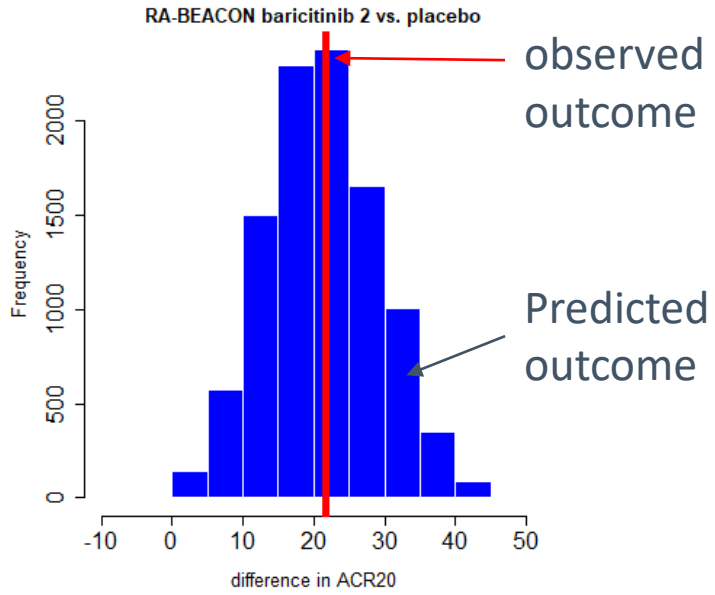

- Baricitinib 4 mg/day vs. adalimumab 40 mg q2w
- Trial simulation predicts a high, 92%, probability of non-inferiority at 400/arm and 10% margin;
- and a high probability of 50% for superiority
- Predicted trial outcome for
  - ACR20 6.7% [-5.0 to 16.0; 90% PI];
  - ACR50 7.9% [-5.0 to 19.5],
  - ACR70 5.8% [-3.8 to 16.0];
- Actual trial results showed superiority with a treatment difference of
  - ACR20 8.4% [1.7 to 15.1; 95% CI];
  - ACR50 10.1% [3.3 to 16.9]
  - ACR70 6.2% [1.2 to 11.2]

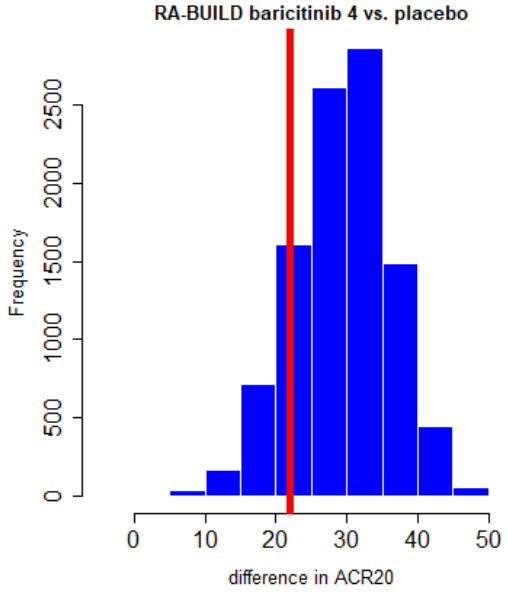


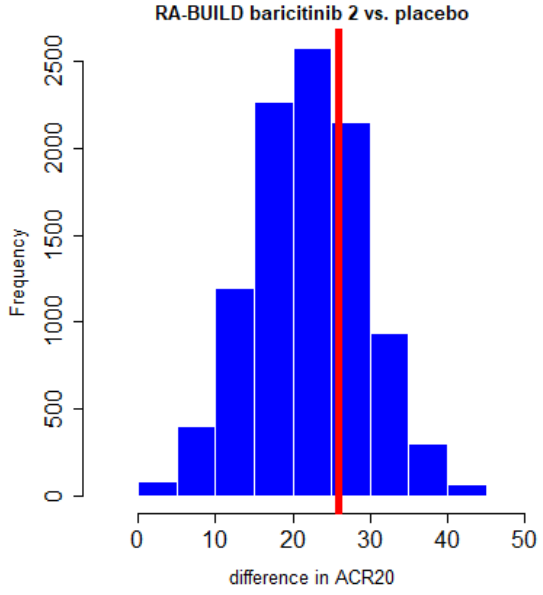
# Close agreement between simulated and observed trial outcomes of phase III program confirms that we can evaluate design options based on probability models (all simulations based on phase II data only)



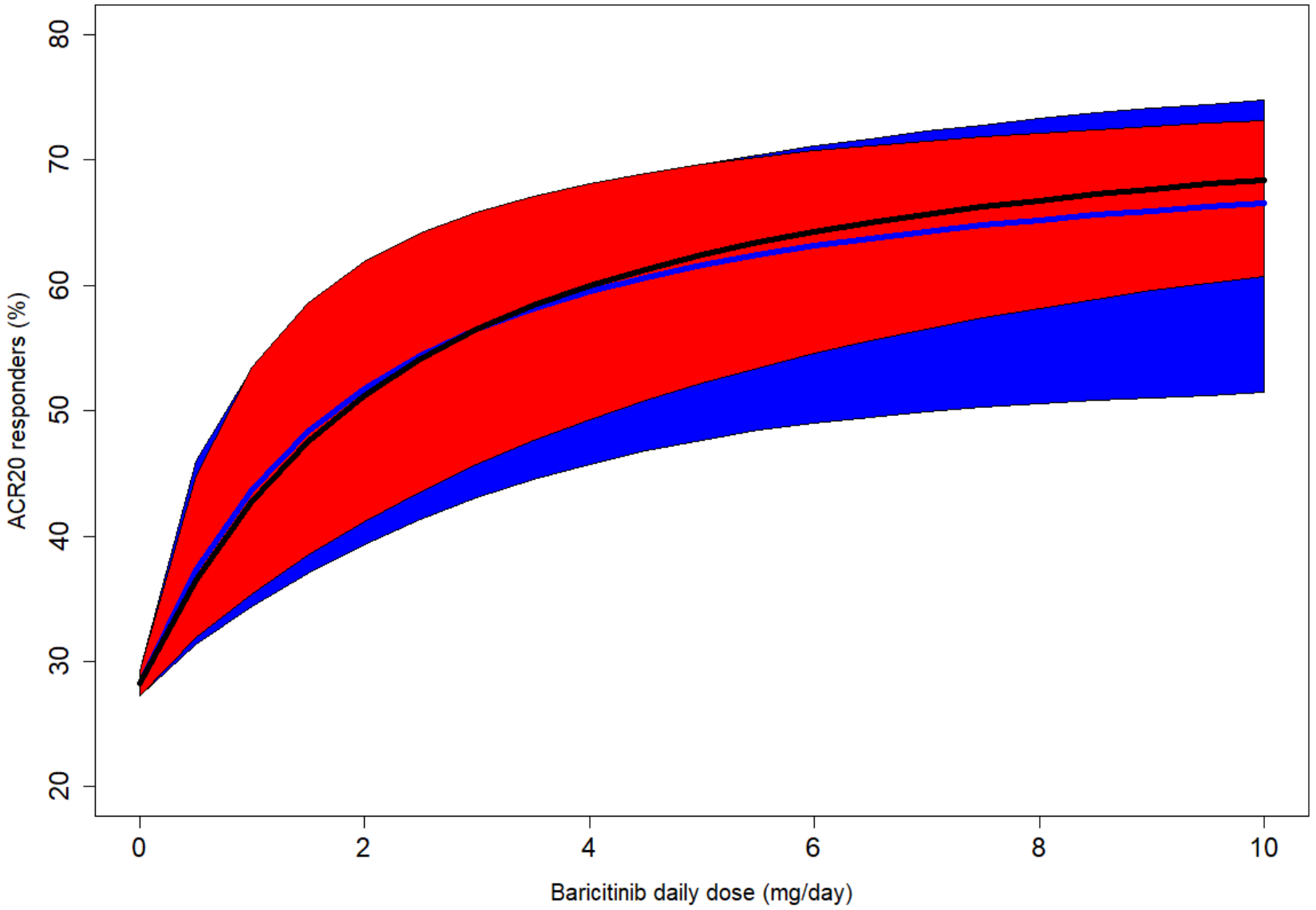




Phase III differed from phase II in trial duration; failed prior treatments; background treatments; patient characteristics

| trial | Phase | dose | control | background treatment | failed treatment | duration | N |
|---|---|---|---|---|---|---|---|
| I4V-MC-JADA | 2 | 1,2,4,8 mg | placebo | MTX | MTX | 12 | 301 |
| INCB 28050-201 | 2 | 4,7,10 mg | placebo | MTX | MTX | 12 | 124 |
| RA-BEACON | 3 | 2,4 mg | placebo | MTX | biologic | 24 | 527 |
| RA-BEAM | 3 | 4 mg | adalimumab | MTX | MTX | 52 | 1305 |
| RA-BEGIN | 3 | 4 mg | MTX | none | none | 52 | 584 |
| RA-BUILD | 3 | 2,4 mg | placebo | MTX | MTX | 24 | 684 |

# Pharmacological assumption of similar maximal effect among JAK inhibitors could have increased confidence in phase III decisions




**BLUE:** estimated dose response at end of phase II based on baricitinib data alone

**RED:** estimated dose response at end of phase II assuming a similar Emax among JAK inhibitors



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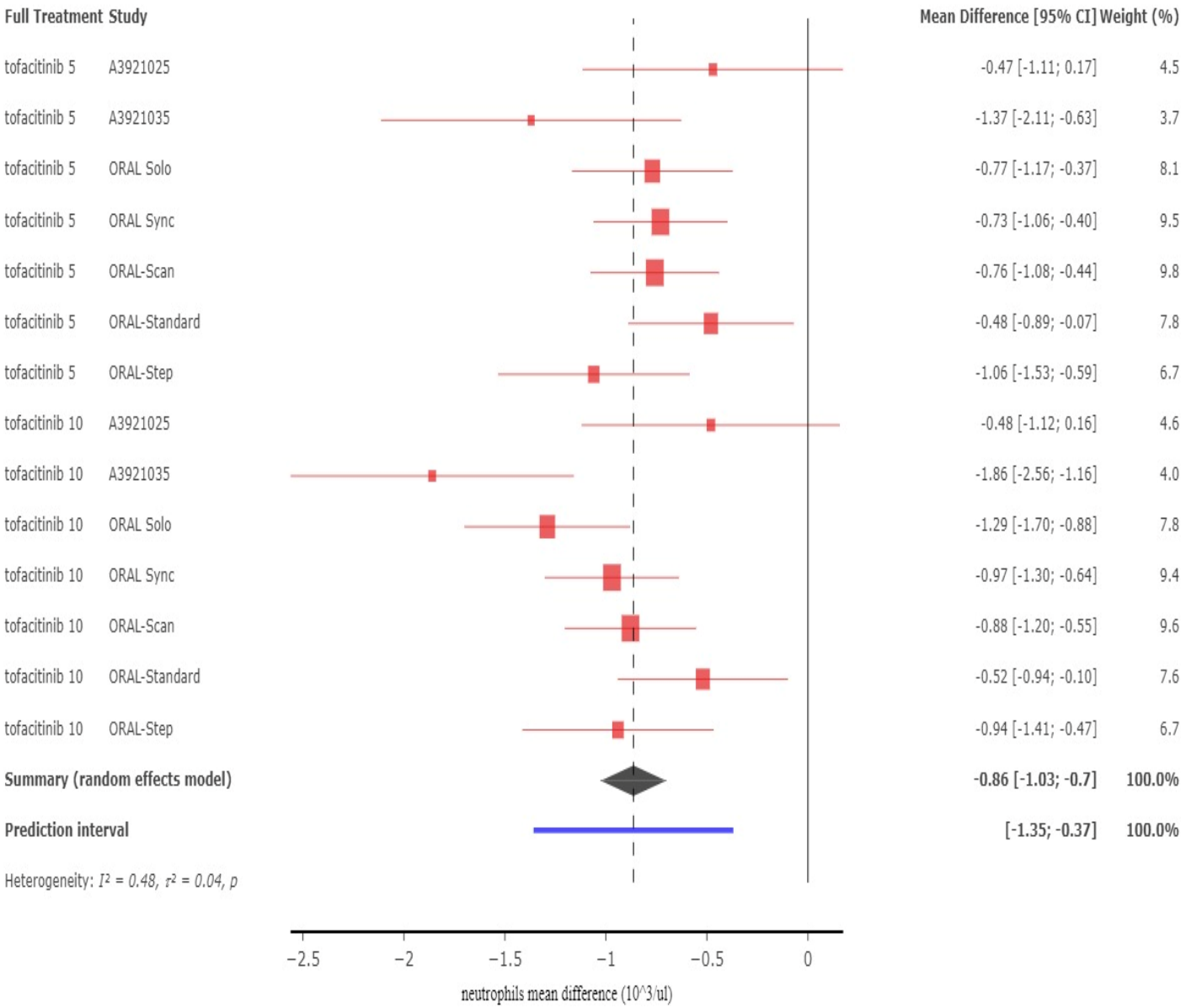
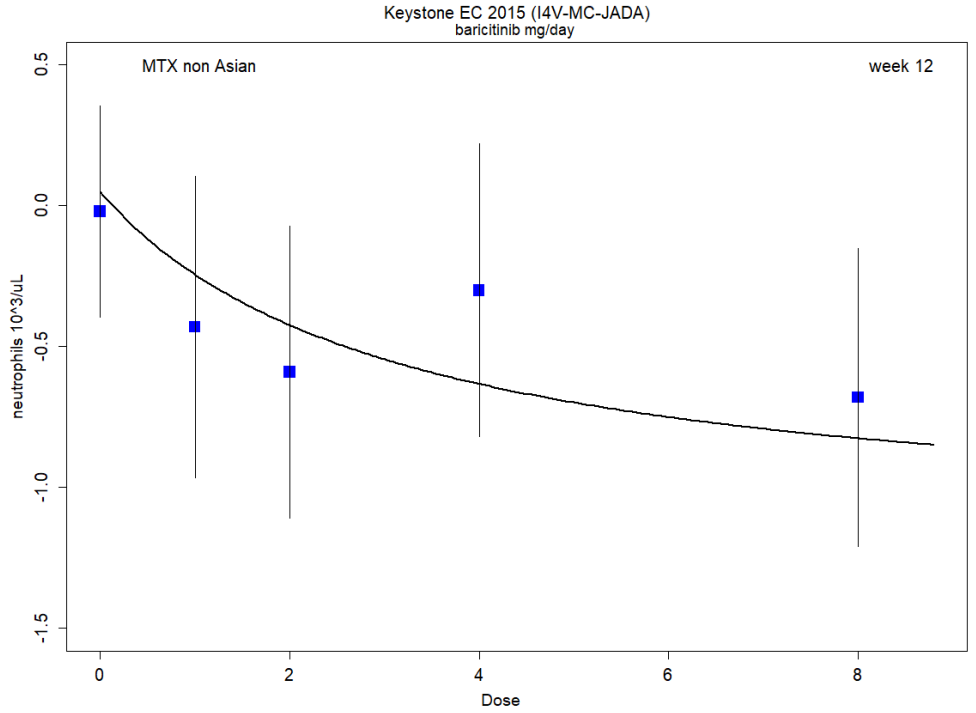
# Comparison of neutrophils vs. ACR Dose Response shows a difference in Therapeutic Index among the JAK inhibitors




| Drug | ED50 neutrophils (mg/day) | ED50 ACR (mg/day) |
|---|---|---|
| Baricitinib (JAK 1/2) | 3.2 [1.5 -6.8] | 1.8 [1.3 - 2.6] |
| Tofacitinib (JAK 1/3) | 8.4 [5.0 - 14.3] | 4.3 [3.1 - 6.1] |
| Filgotinib (JAK 1) | 109 [43 - 272] | 115 [64 - 205] |



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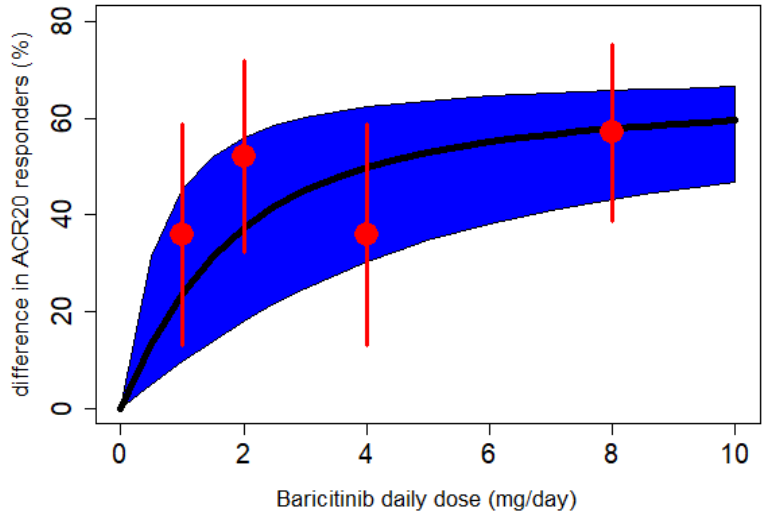
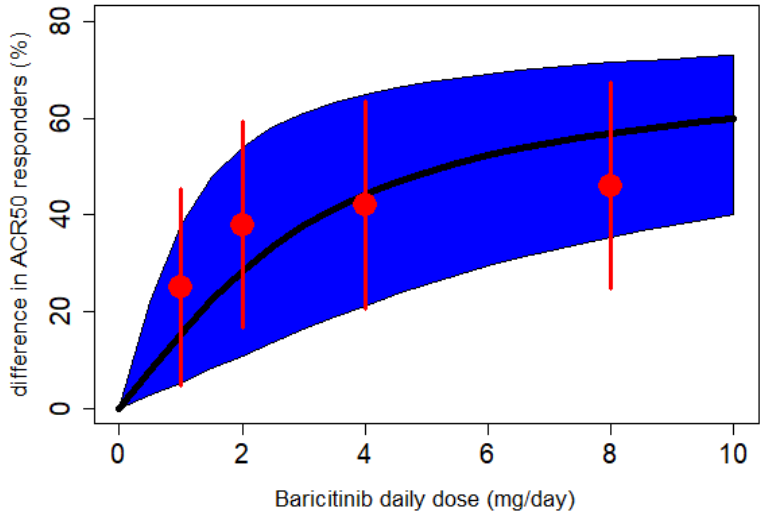
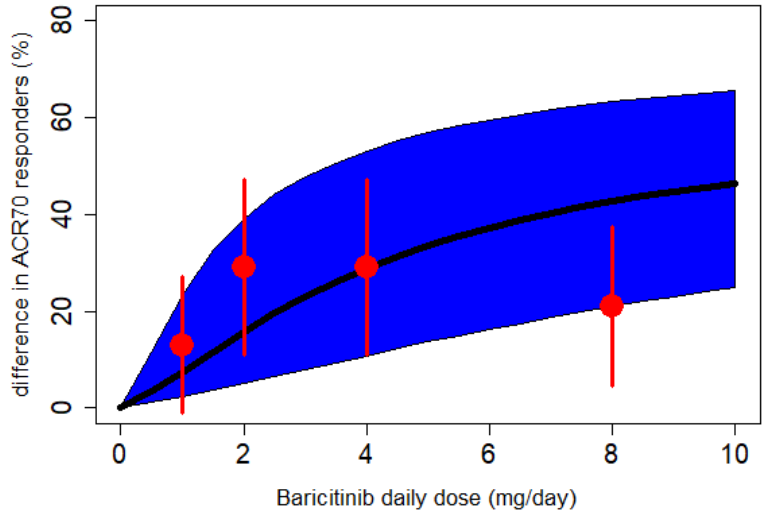
# The difference from placebo in ACR response in the Japanese phase II study I4V-JE-JADN is well predicted based on tofacitinib data




The predicted effect is 46% [28 to 64%; 95% CI] greater in Japanese studies vs. ROW; this difference was estimated from tofacitinib and applied to baricitinib





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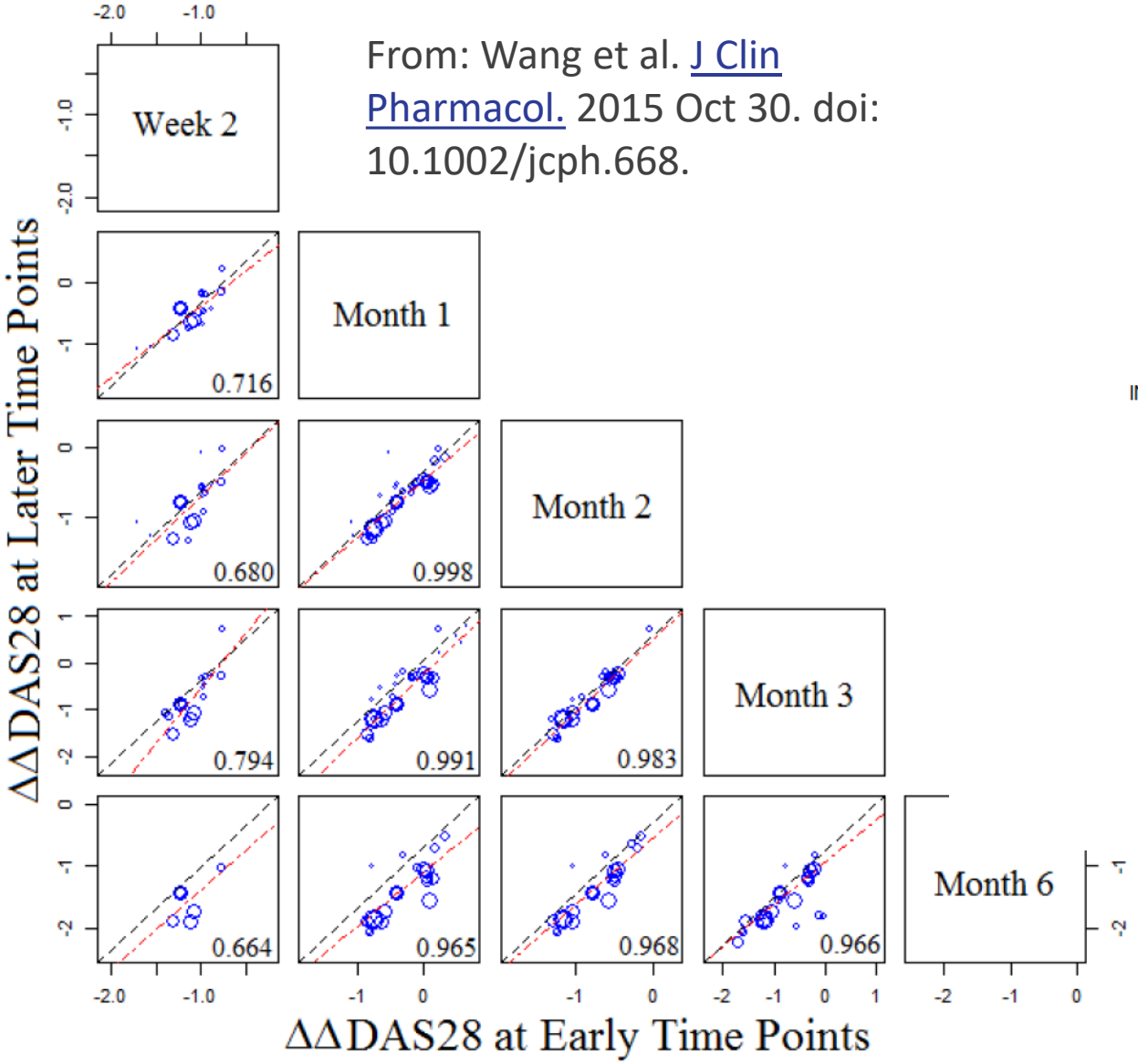
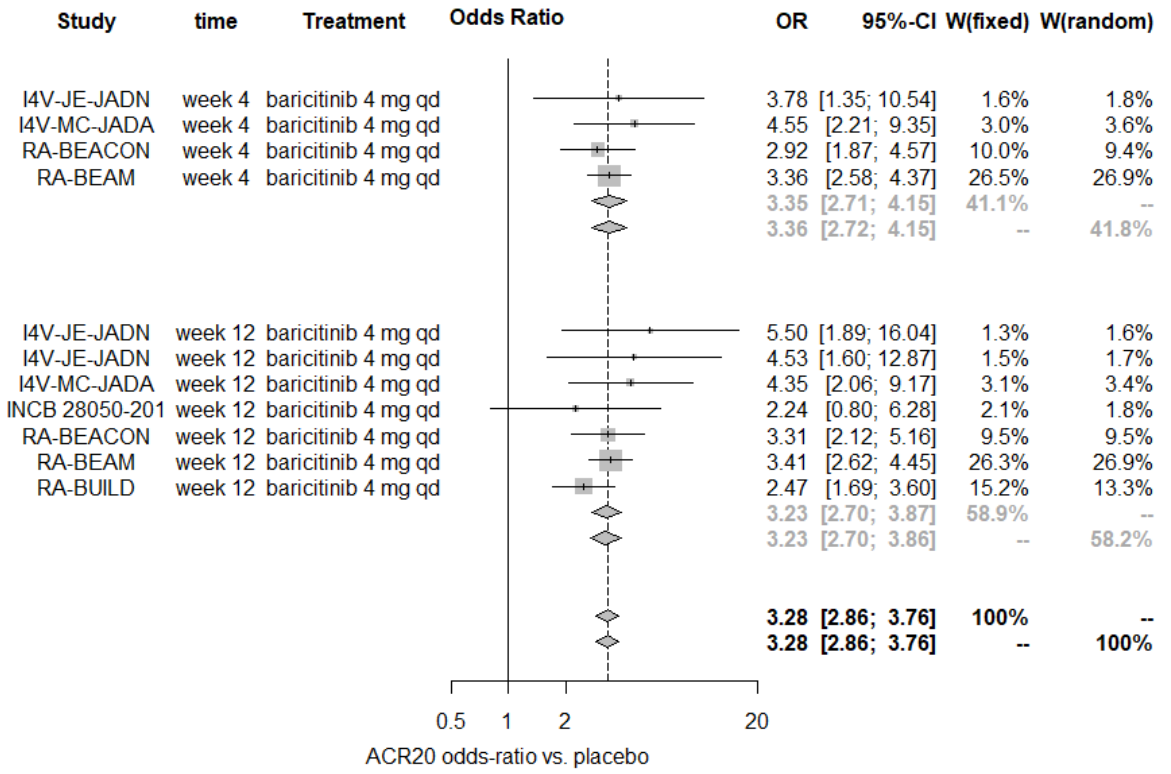
# Week 4 treatment effect is predictive for later time-points

From: Wang et al. J Clin Pharmacol. 2015 Oct 30. doi: 10.1002/jcph.668.



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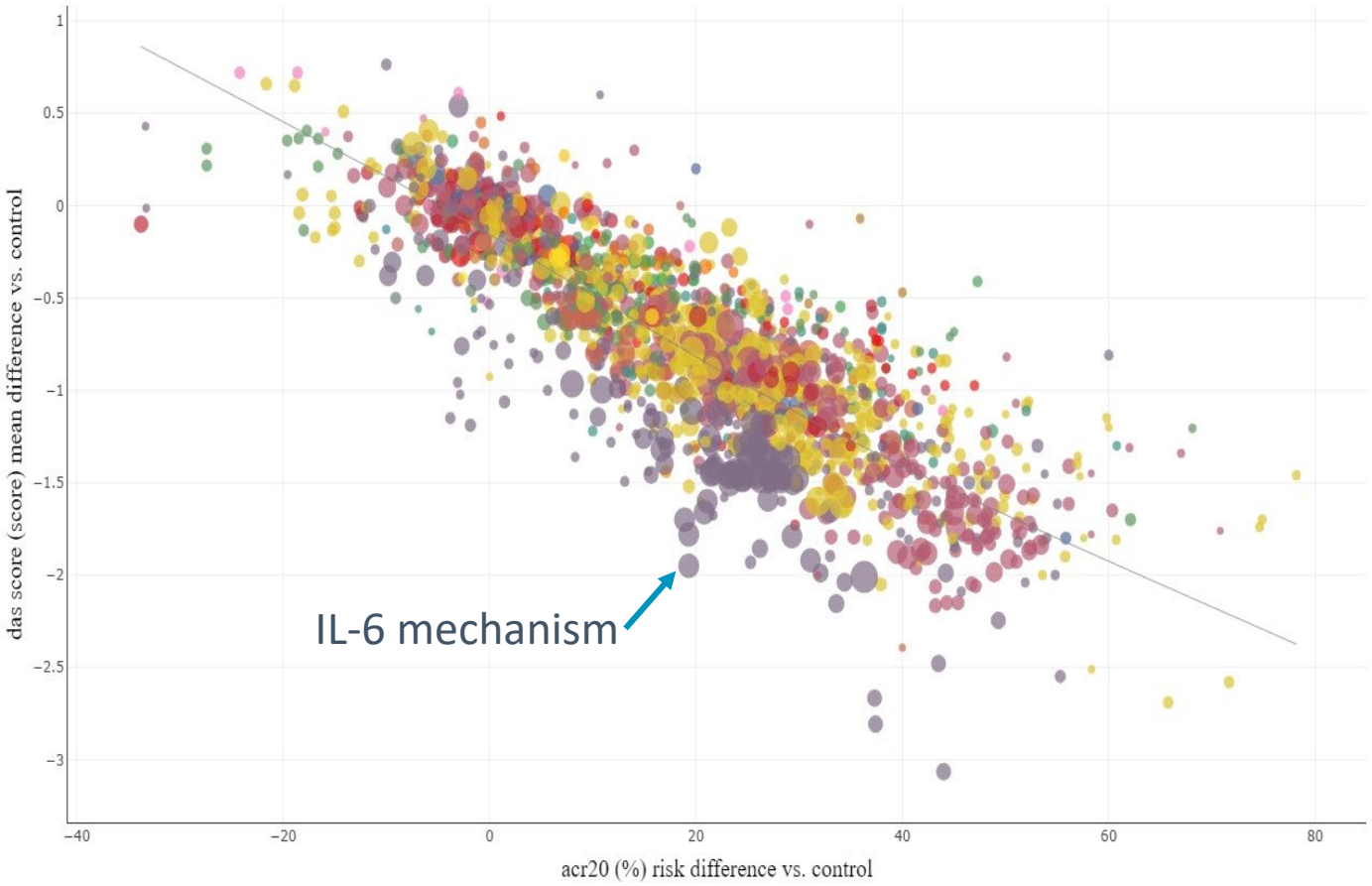
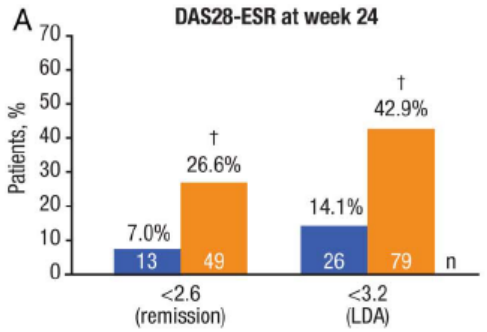
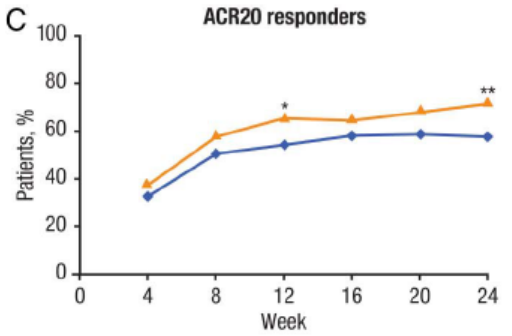
# There is strong correlation between DAS score and ACR response that is different for IL-6 vs. other mechanisms




Resulting in greater treatment differentiation based on DAS vs. ACR endpoints for IL-6 mechanism (purple dots)

Burmester GR, *et al*. *Ann Rheum Dis* 2017;**76**:840–847. doi:10.1136/annrheumdis-2016-210310




**Risk difference sarilumab (orange) vs. adalimumab (blue):**

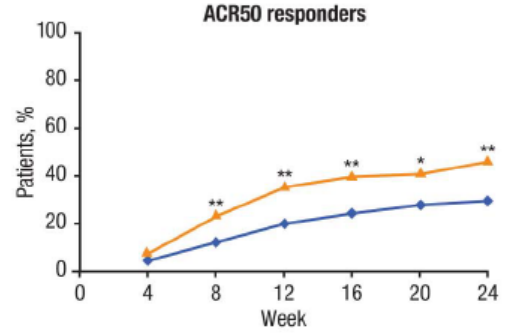
ACR20: 13.4 [3.8 - 23]

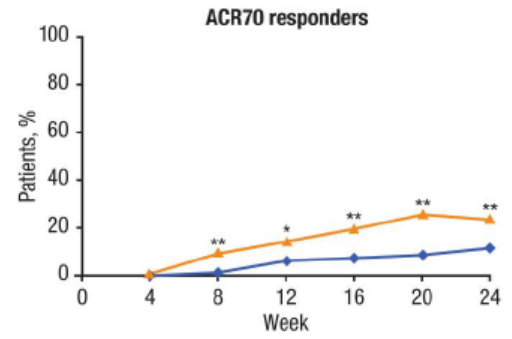
ACR50: 15.9 [6.2 - 26]

ACR70: 11.5 [3.8 - 19]

DAS LDA: 28.8 [20 - 38]

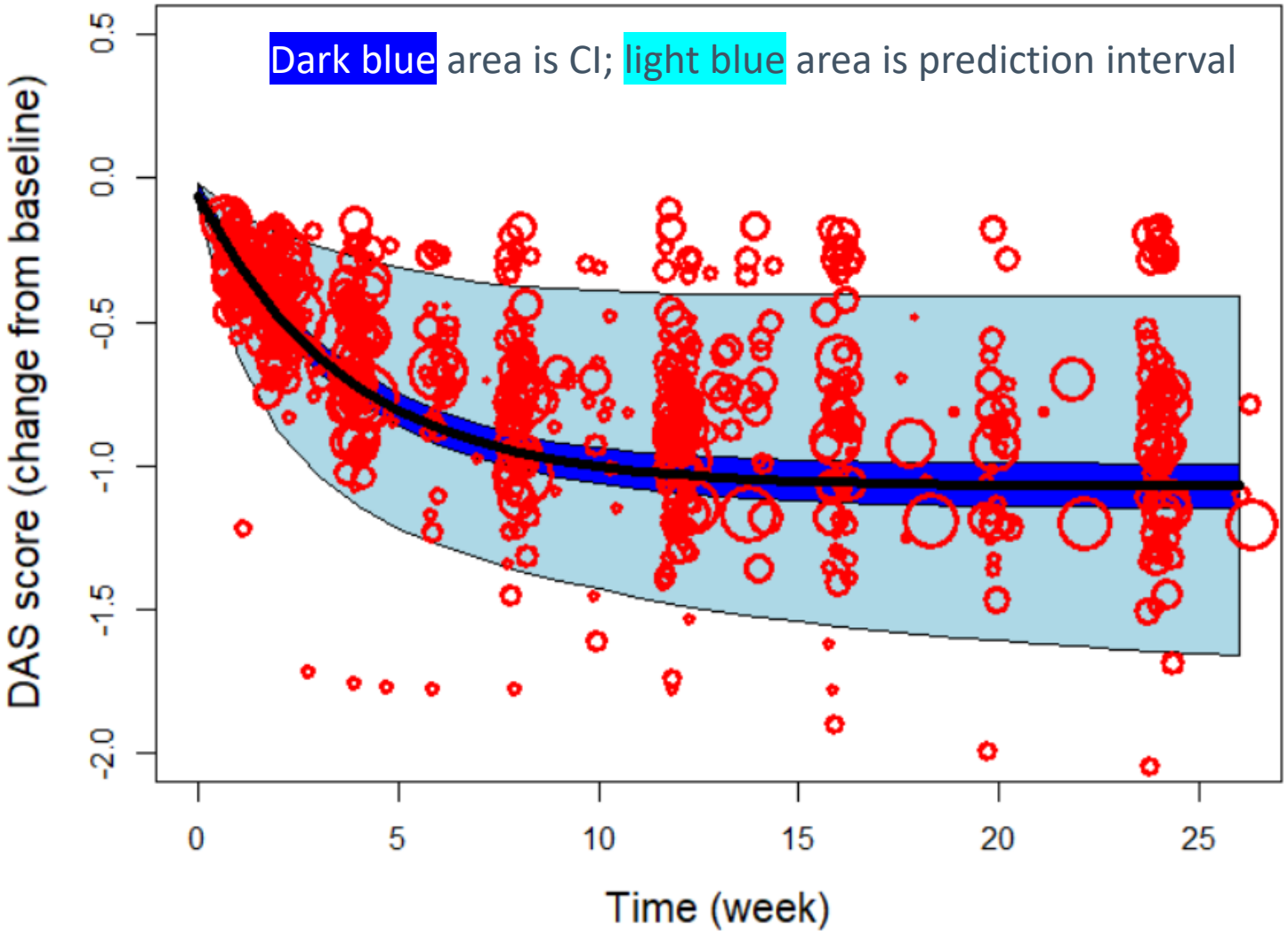
DAS rem: 19.6 [12 - 27]




Adalimumab 40 mg q2w  Sarilumab 200 mg q2w

# Synthetic Control Arm for Placebo in RA (DAS score)?




- Observed (red dots) vs. estimated (black line) time course of placebo DAS score change from baseline for RA patients.
- Whereas there is a very large amount of prior data for the placebo response from 179 studies (153 in RA; 26 in PsA)
- Whereas covariates such as baseline DAS score, DAS definition (ESR/CRP), Asian/non-Asian, and RA vs. psoriatic RA explain a significant amount of between trial heterogeneity in placebo response
- There is a large amount of unexplained heterogeneity indicated by PI
- Such that the historic placebo control is worth ~19 patients in a future study



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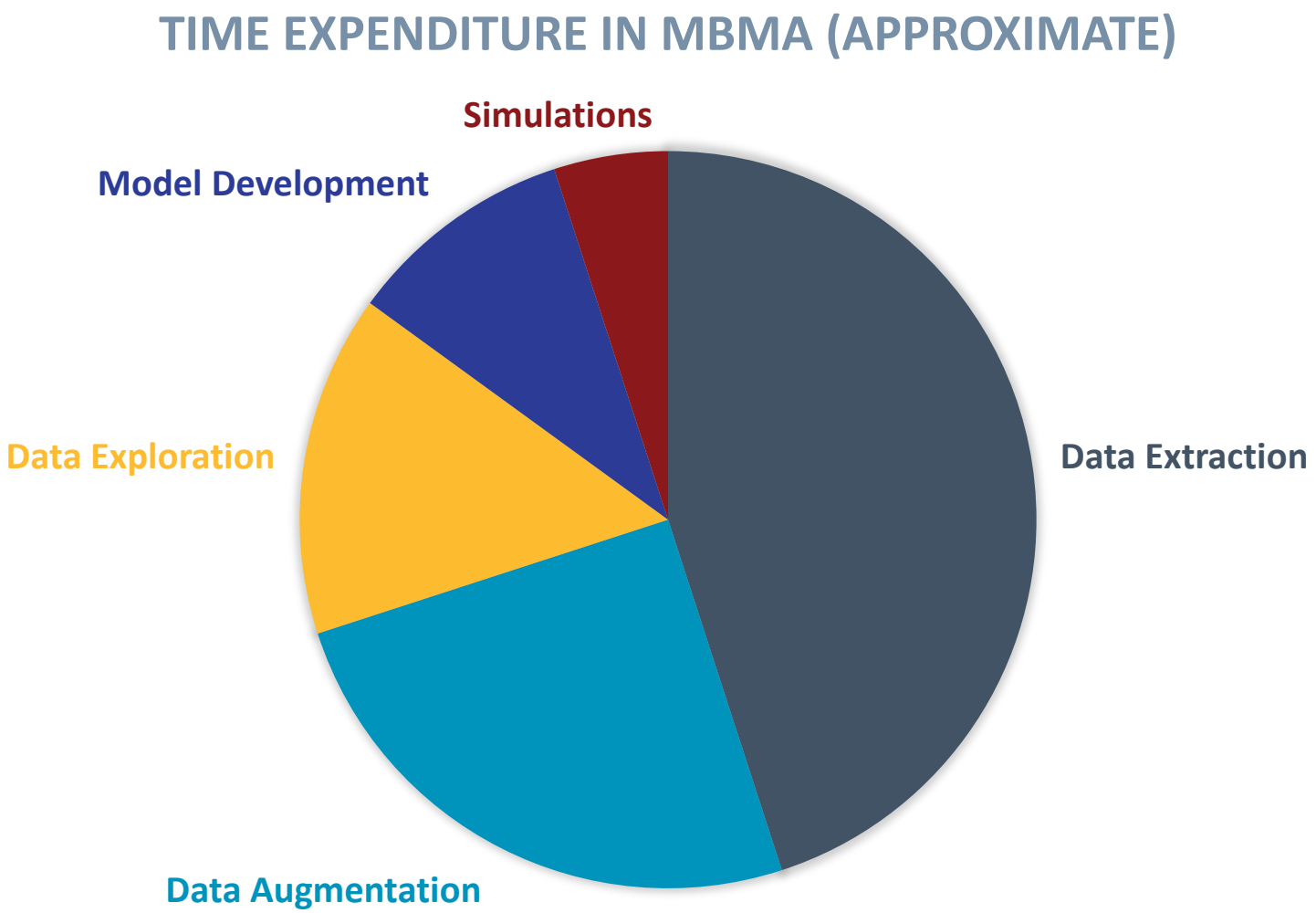
# To maximize the utility of MBMA, develop and maintain comparator models in advance of key decision points





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# MBMA provides a quantitative framework to leverage valuable external data into development and regulatory decisions

- Comparative safety and efficacy
  - There is a need to evaluate new treatment options against other existing or emerging treatment options (indirectly) for go/no-go decisions, dose selection, trial strategy
- Endpoint-to-Endpoint relationships
  - Biomarker to clinical endpoint predictions
  - Bridging across indications
- Create synthetic control arms
  - Adjusted for known and accounting for unknown factors that impact heterogeneity
- Leveraging existing information
  - Similar shape of dose response relationships of drugs within class
  - Similar impact of disease severity on treatment effect
- Optimize Trial design
  - Impact of trial design features on placebo, treatment effect, and variability



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# All questions are welcome!

## Model-Based Meta-Analysis (MBMA):

Optimizing Drug Development with Public Data and Predictive Models

codex.certara.com

# Reading Materials


- Lalonde et al. Model-based drug development. Clin. Pharmacol. Ther. 82: 21-32 (2007).
- Milligan et al. Model-Based Drug Development: a rational approach to efficiently accelerate drug development. Clin Pharmacol Ther. 93(6): 502-14 (2013).
- Visser et al. Implementation of Quantitative and Systems Pharmacology in Large Pharma. CPT Pharmacometrics Syst. Pharmacol. 3, e142 (2014)
- Mandema et al. Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond. Clin Pharmacol Ther. 90(6): 766-9 (2011).
- Mandema et al. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain – results of a model-based meta-analysis that accounts for encapsulation. Cephalalgia 25: 715-25 (2005).
- Mandema et al. A dose-response meta-analysis for quantifying relative efficacy of biologics in rheumatoid arthritis. Clin Pharmacol Ther. 90: 828-35 (2011).
- Mandema et al. Therapeutic index of anticoagulants for prevention of venous thromboembolism following orthopedic surgery: a dose-response meta-analysis. Clin Pharmacol Ther. **90**: 820-7 (2011).
- Mandema et al. Time Course of Bone Mineral Density Changes with Denosumab Compared with Other Drugs in Postmenopausal Osteoporosis: A Dose-response Based Meta-analysis. J Clin Endocrinol Metab. 99: 3746-55 (2014).
- Checchio T et al. Quantitative Evaluations of Time-Course and Treatment Effects of Systemic Agents for Psoriasis: A Model Based Meta Analysis. Clin Pharmacol Ther (2017).






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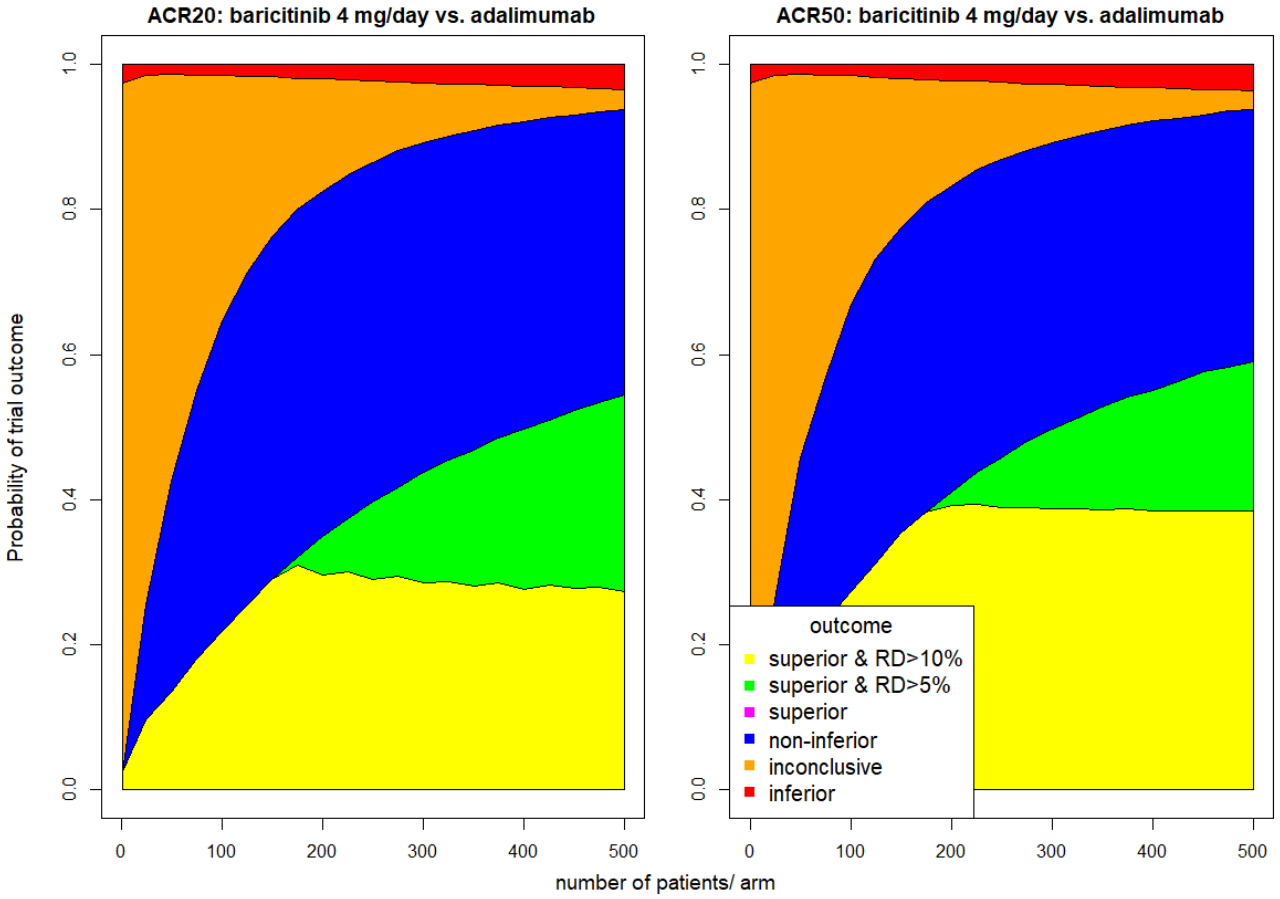
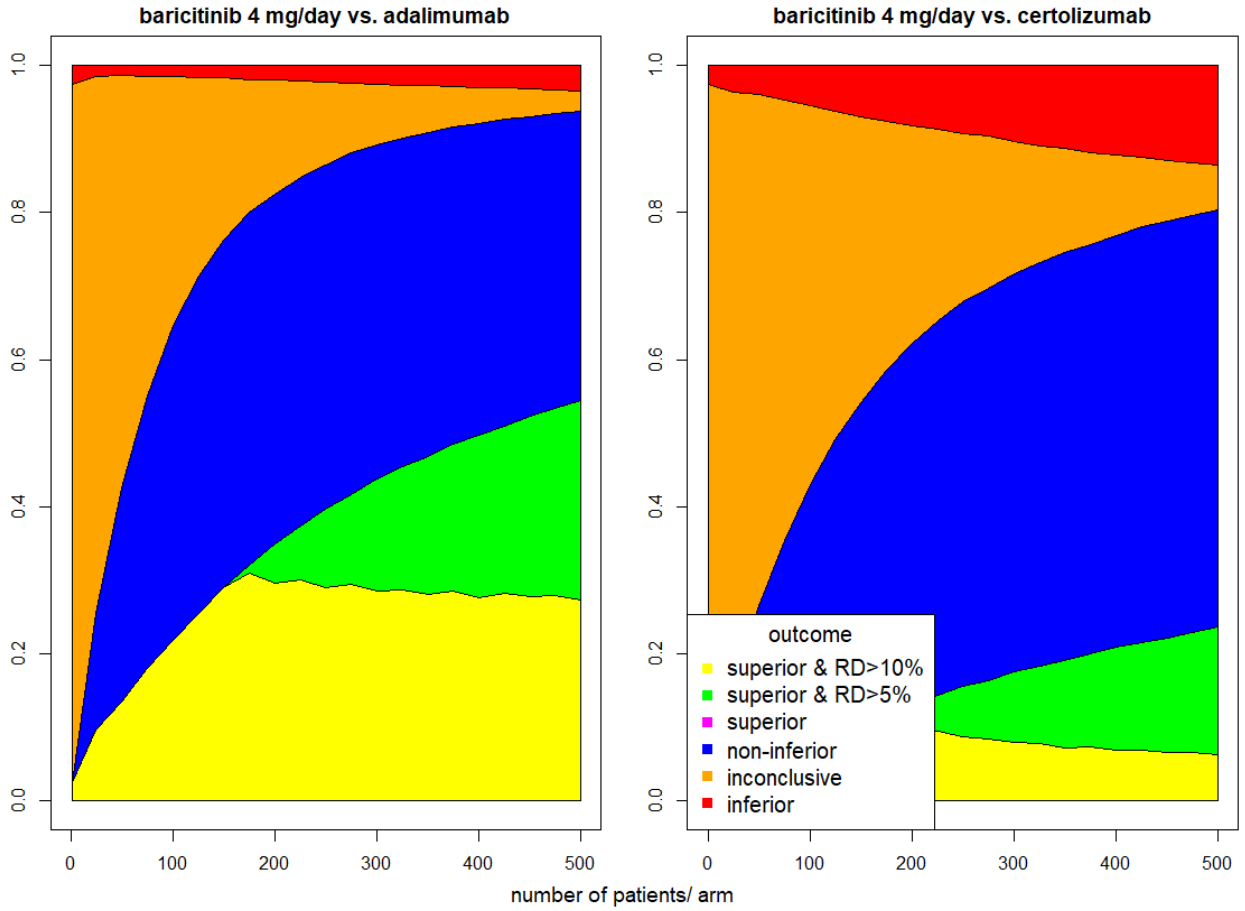
# What is the optimal endpoint or comparator for phase III?




## ACR20 or ACR50?

## Adalimumab or certolizumab?



# Probability of trial outcome conditional on effect size and probability of baricitinib to achieve effect size