

Competitive Landscape Model Using Meta-analysis and Simulation-based Evaluation for Phase IIb Study Design of MRL-1 Being Developed for the Treatment of Rheumatoid Arthritis

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Background and Objectives

MRL-1 is being evaluated in two Phase II studies for the treatment of rheumatoid arthritis (RA) in methotrexate inadequate and anti-TNF inadequate responders.

1. Comparator Landscape

- Benchmark efficacy database for the MRL-1 and competitor was created through literature on compounds approved or evaluated for treatment of RA.
- Objective:* To assess a competitive landscape for MRL-1 by comparing with market leaders and key competitors (disease-modifying antirheumatic drugs [DMARDs] and anti-tumour necrosis factor [TNF]) and define relative advantages of MRL-1.

2. Clinical Trial Simulation (CTS) to Support Phase IIb Study Design and Dose Selection

- 5 doses (6 arms including placebo) were originally selected for Phase IIb based on exposure-biomarker response (*Presented at Acop in 2013*).
 - 25, 100, 200 mg QD, and 25, 100 mg BID
- Objective:* To compare different study designs and optimize sample size through a simulation-based approach to provide confidence that the Phase IIb design offers high probability of demonstrating a robust dose-response relationship.

Comparator Landscape

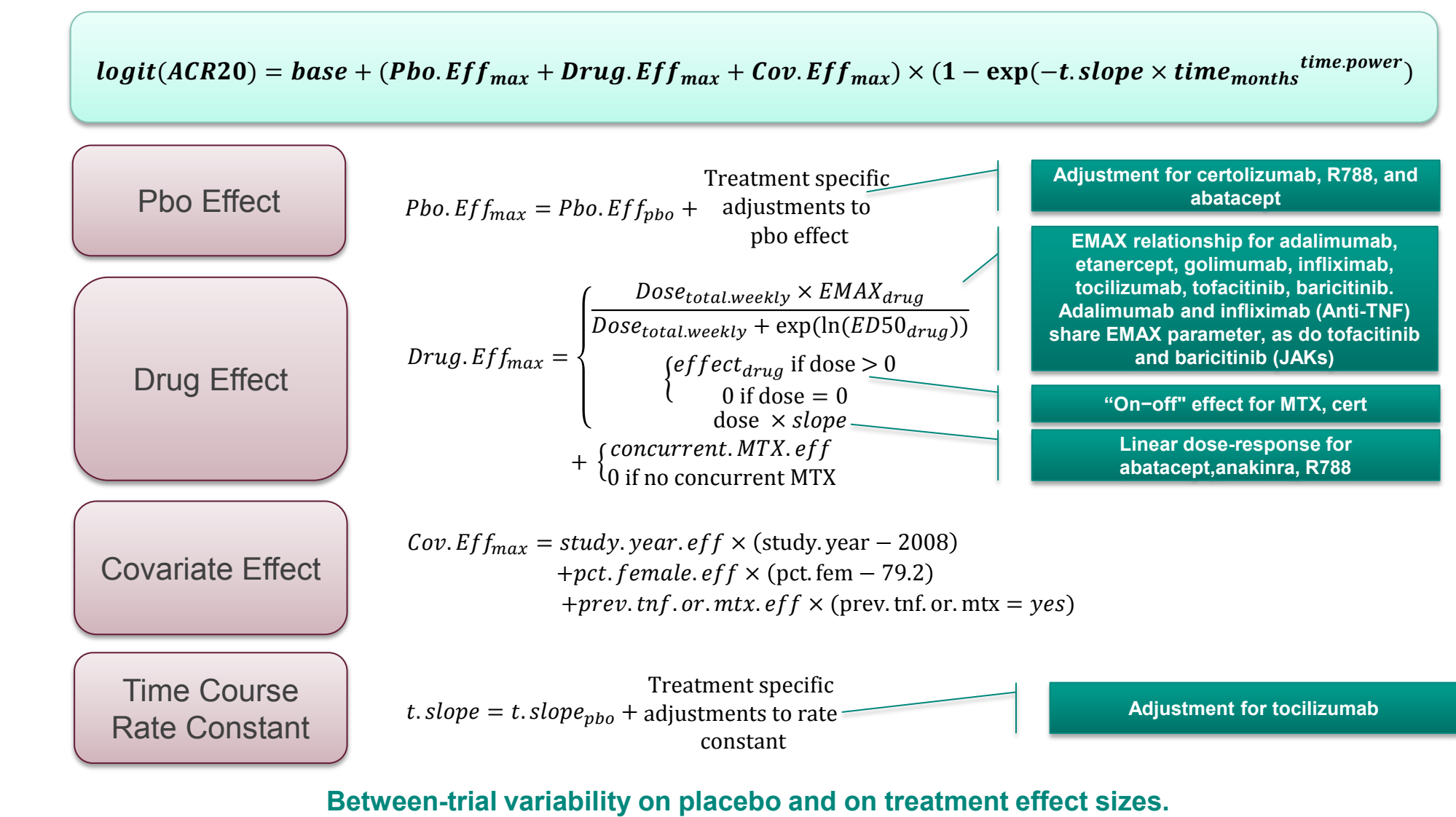
Methods

Table 1: The final modeling dataset contained the subset of the meta-analysis database.

Drug	Mechanism of Action	Trials	Total Arms	Total Patients
abatacept	anti-CD28	5	9	19,316
adalimumab	anti-TNF	11	23	34,379
anakinra	anti-IL-1	4	10	7,447
baricitinib	JAK	1	4	1,932
certolizumab	anti-TNF	4	6	23,714
etanercept	anti-TNF	11	17	19,568
golimumab	anti-TNF	5	16	15,699
infliximab	anti-TNF	10	22	14,549
placebo	n.a.	82	82	75,825
R788	SYK	6	12	8,316
tocilizumab	anti-IL-6	4	11	21,070
tofacitinib	JAK	2	7	2,672

ACR20: The database included longitudinal summary-level information at different dose levels and patient characteristics (covariates) for 31 drugs (12 used) tested in 88 controlled clinical trials (85 were used) in more than 200,000 patients.

Figure 1: Mathematical form of final model



The model-based meta analysis including time course observations for efficacy endpoints were conducted using NONMEM and R to characterize the probability that MRL-1 would be greater, similar, or worse on efficacy endpoints given uncertainty in the literature, which also enabled comparison of onset of action relative to competitors.

Key Assumptions and Limitations

- For comparisons, clinically meaningful criteria were assumed; change from PBO ACR20 of >10%.
- Competitor models were built from multiple studies with very large sample sizes, compared to the relatively small dataset available from two MRL-1 phase IIa studies.
- Relatively more comparator data are available for ACR20 compared to DAS28 (DAS28: limited data, less confident in comparator model, not included in this poster).
- The expected level of MRL-1 efficacy (ACR20) was predicted using a comparator model based on a DMARD.

Results

- ACR20 time-course by treatment – there were ample data with which to characterize the speed of onset of the various therapies, how quickly they reach maximum effect, dose-response and patient population effects.

Variability

- Between-trial effects (ETAs) supported on placebo and treatment effects.

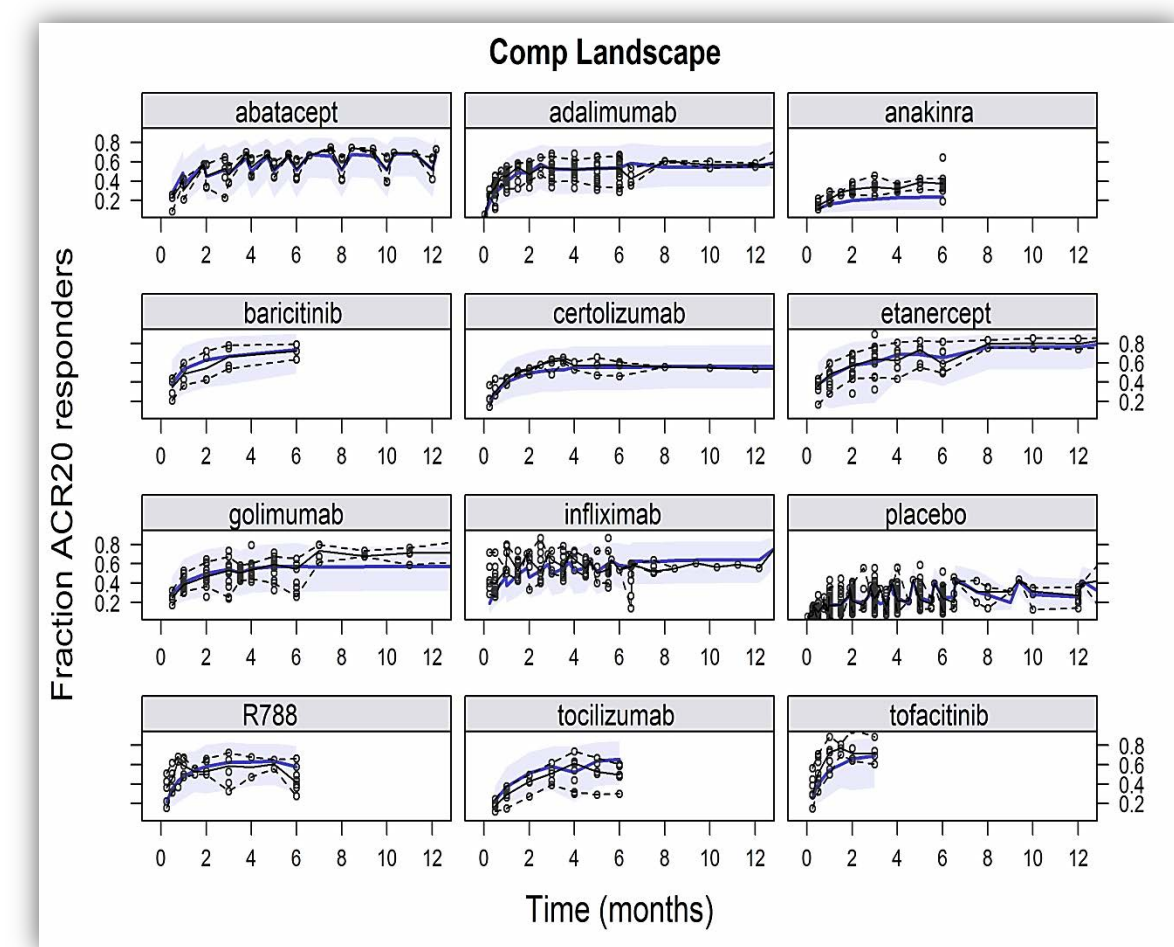
Structural

- Time-Course
 - Exponential time-course for all.
 - Unique effects for tocilizumab (onset rate is slower).
- Dose-Response
 - Linear for abatacept, anakinra, R788.
 - Adalimumab and Infliximab (Anti-TNFs) share Emax, as do tofacitinib and baricitinib (JAKs).

Covariates

- Three covariates were significant
 - Previous treatment with TNF or MTX, publication year, and % of female patients.

Figure 2: ACR20 Goodness of Fit (VPC)



Comparator Landscape (continued)

Summary

- Based on 12 week data, simulations suggest that 100-mg BID MRL-1 has ~50-70% probability of being similar or better on ACR20 vs. all competitors, including the anti-TNFs (Figure 3).

Figure 3: Probability MRL-1 would be better, worse, or similar versus competitors. Effects at 12 weeks (3 months) ACR20 change from placebo

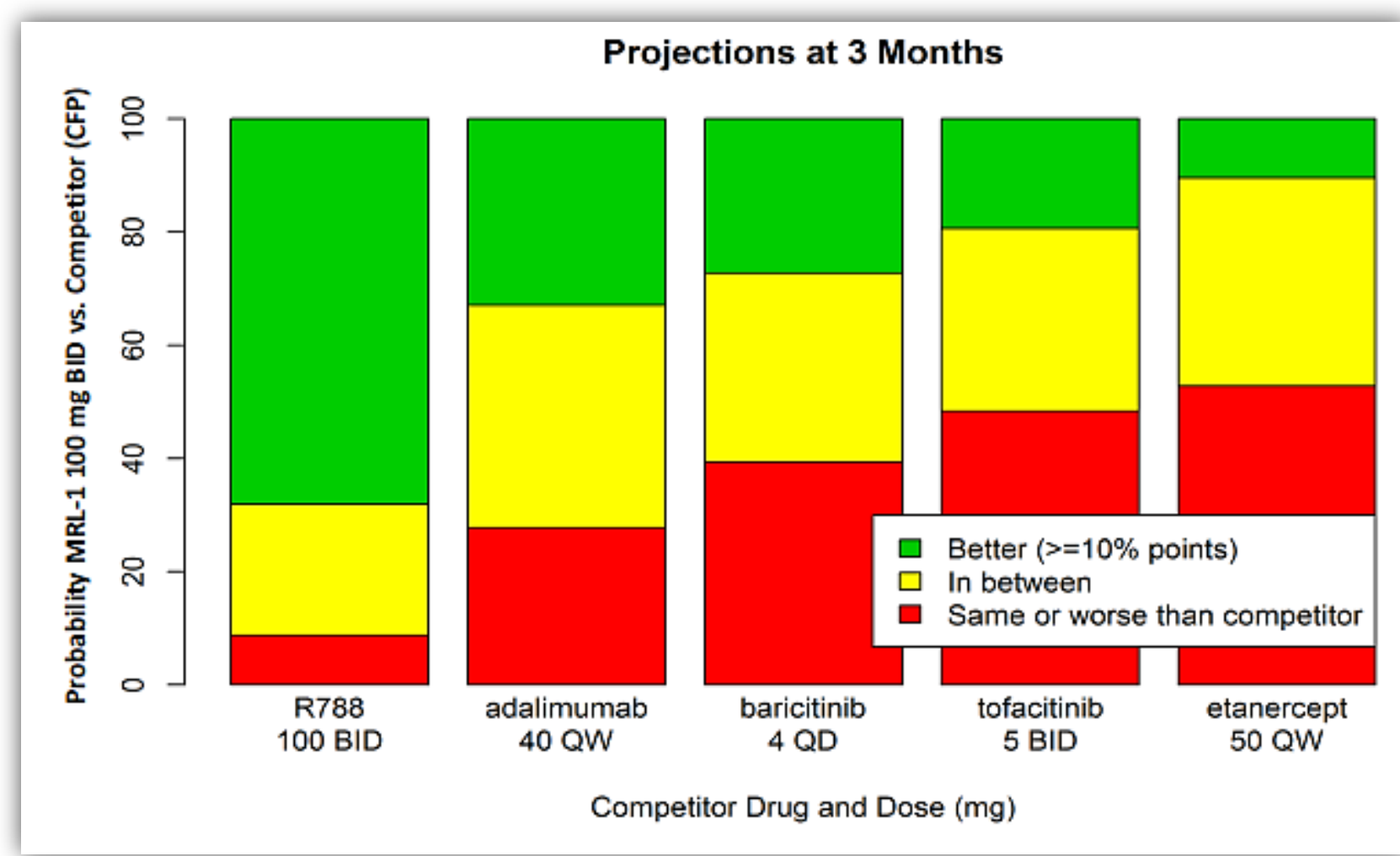
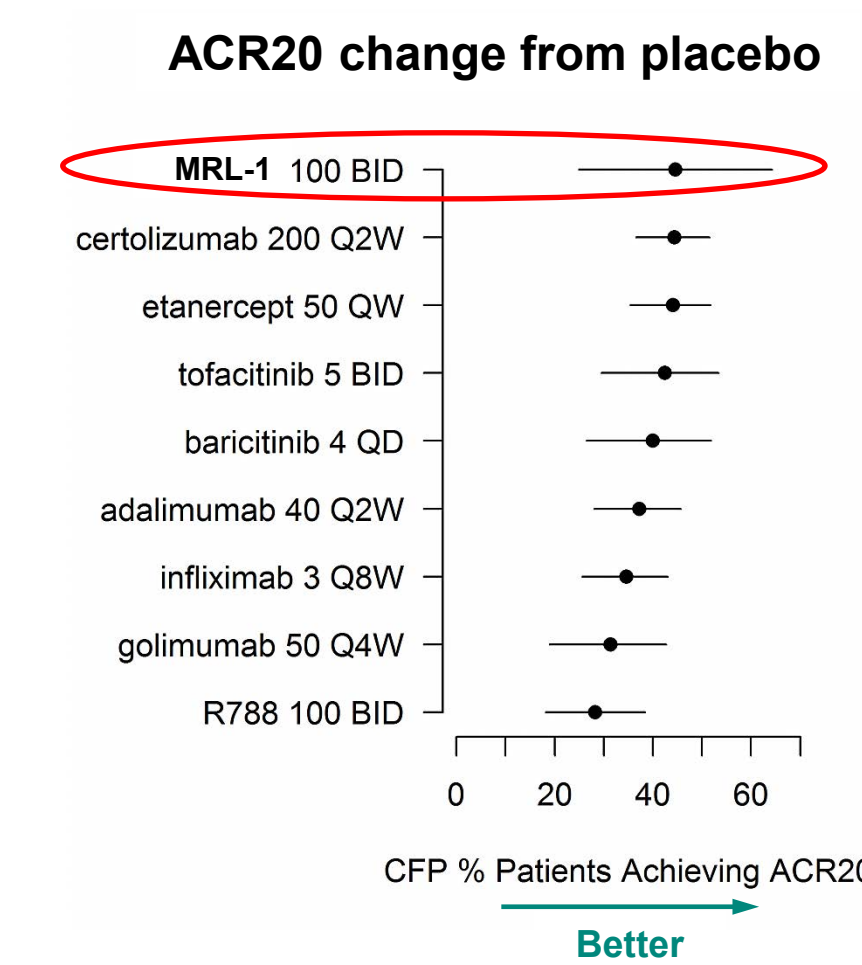


Figure 4: MRL-1's observed ACR20 change from placebo (CFP) performance vs. summarized performance of competitors. Effects at 12 weeks (3 months)



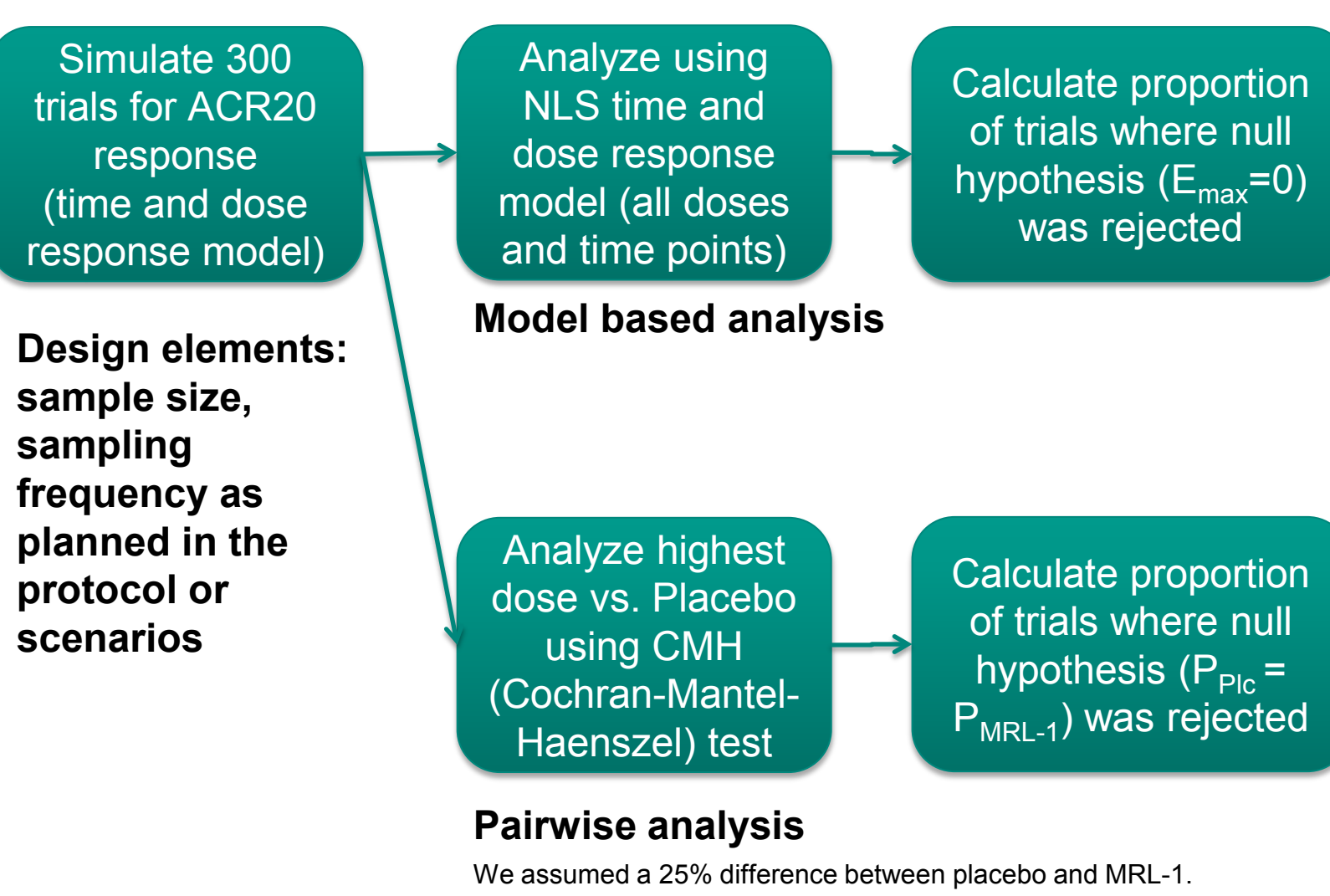
CTS to Support Phase IIb Study Design and Dose

Methods

Table 2: MRL-1 dosing options considered and subjects needed for Phase IIb

Dose groups	Subjects Per Arm		
	Scenario 1	Scenario 2	Scenario 3
100 BID	62	62	62
150 QD	62	62	62
75 QD	62	62	40
25 BID	0	62	40
25 QD	62	62	40
PBO	62	62	62
Subject Total	310	372	306
*Total still needed to recruit for Ph2b	248	310	244

Figure 5: Power calculation



Results

Table 3: Quantitative basis for choosing Scenario 3

	Scenario 1 PBO, 25, 75, 150 QD; 100 BID (5 arms)	Scenario 2 PBO, 25, 75, 150 QD; 25, 100 BID (6 arms)	Scenario 3 PBO, 25, 75, 150 QD; 25, 100 BID (6 arms)
Dose levels			
Sample Size	N=62 All Treatment Arms	N=62 All Treatment Arms	N=62 (150 QD, 100 BID); N=40 (25 QD, 25 BID, 75 QD)
C _{ave} Drives ACR20	90%	98%	98%
C _{ave} Drives ACR20 (but MRL-1 has 20% less %CD63 effect)	81%	96%	96%
C _{ave} Drives ACR20 (with 50% less efficacy than predicted by competitor model)	93%	99%	97%
C _{trough} Drives ACR20	50%	67%	67%

Numbers represent power to establish dose response (Emax parameter being statistically significant)

- Higher power for Scenario 3 to detect dose-response (similar to the original design).
- The power is also maintained under different sensitivity assumptions.
- Higher power for Scenario 3 is largely an improvement to define BID dose response.

Summary

- Scenario 3 was suggested;** PBO, 25, 75, 150 QD and 25, 100 BID (6 arms)
 - To better characterize dose- and exposure-response for QD and BID regimens in most efficient manner with respect to sample size
 - This scenario allows for evaluation of the efficacy PK driver (i.e. C_{ave} vs. C_{trough}) which may be critical to choose and justify either dosing regimen.
 - The primary and interim analysis plans will remain unchanged.
 - Both traditional statistical and model-based (time and dose response) analysis will be used and allows for lower sample size to pick commercially viable and most effective dose/regimen for Phase III.

Conclusions

A comparator model supported the decision to continue with clinical development of MRL-1 based on the efficacy comparison. Further, the modeling efforts were pivotal to select Phase IIb doses and the sample size needed to fully characterize the exposure-response for efficacy parameters.

References

- JW Mandema, DH Salinger, SW Baumgartner, MA Gibbs; A Dose-Response Meta-Analysis for Quantifying Relative Efficacy of Biologics in Rheumatoid Arthritis, Clin Pharmacol Ther. 2011 Dec;90(6):828-35.
- I Demin, B Hamrén, O Luttringer, G Pillai, T Jung; Longitudinal Model-Based Meta-Analysis in Rheumatoid Arthritis: An Application Toward Model-Based Drug Development, Clin Pharmacol Ther. 2012 Sep;92(3):352-9.