Delivering Transformative Medicines to Patients by Leveraging Complex Innovative Designs
AMG 592 SLE Case Study

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on Behalf of AMG 592 Team

Amgen

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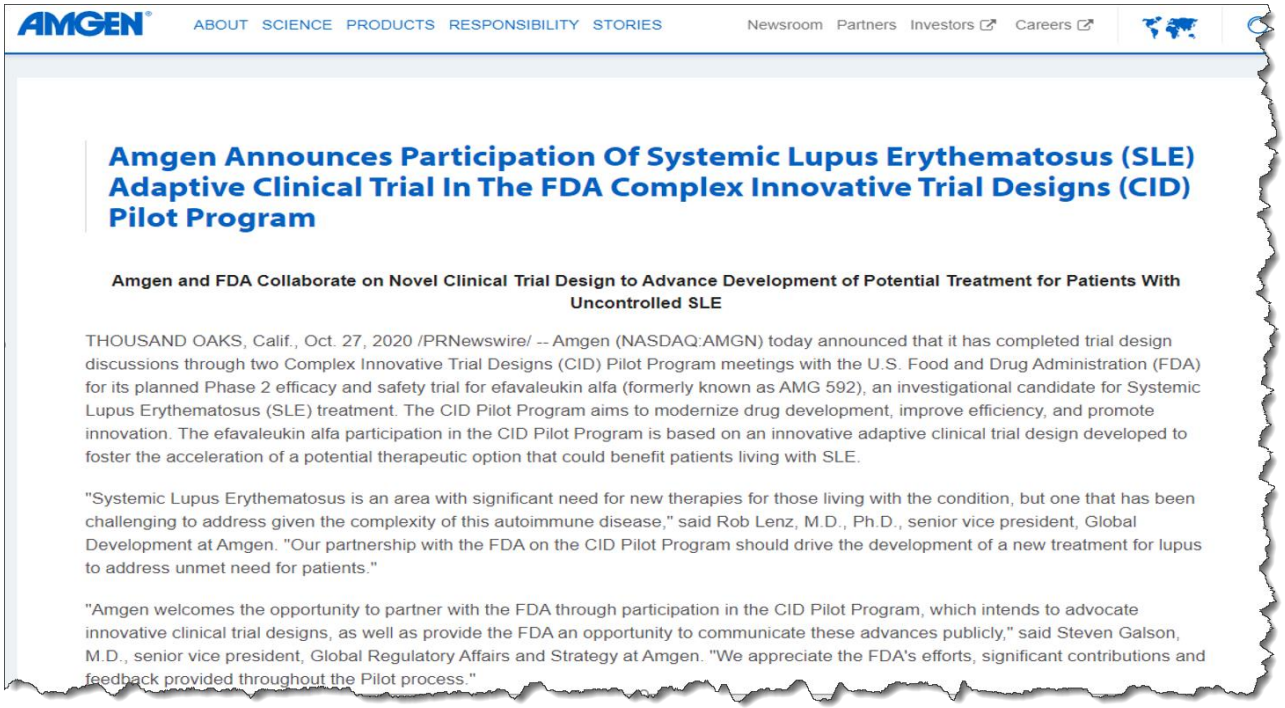
OUTLINE

- **Introduction and Background – Amy Xia**
- **Study Design and 4 Principles – May Mo**
- **Simulation and Shiny Tool – Tony Jiang**

FDA Complex Innovative Design (CID) Pilot Program

- **Under PDUFA VI, FDA launched the CID pilot program in 2018, aiming to facilitate and advance the use of complex adaptive, Bayesian, and other novel clinical trial designs which often require simulations to determine the statistical properties of the trial**
- **The program provides two additional meetings to discuss a specific CID proposal**
- **FDA can select up to 2 CID proposals per quarter for 5 years**
- **This program will continue under PDUFA VII**

Press Releases



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Amgen Announces Participation Of Systemic Lupus Erythematosus (SLE) Adaptive Clinical Trial In The FDA Complex Innovative Trial Designs (CID) Pilot Program

Amgen and FDA Collaborate on Novel Clinical Trial Design to Advance Development of Potential Treatment for Patients With Uncontrolled SLE

THOUSAND OAKS, Calif., Oct. 27, 2020 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that it has completed trial design discussions through two Complex Innovative Trial Designs (CID) Pilot Program meetings with the U.S. Food and Drug Administration (FDA) for its planned Phase 2 efficacy and safety trial for efavaleukin alfa (formerly known as AMG 592), an investigational candidate for Systemic Lupus Erythematosus (SLE) treatment. The CID Pilot Program aims to modernize drug development, improve efficiency, and promote innovation. The efavaleukin alfa participation in the CID Pilot Program is based on an innovative adaptive clinical trial design developed to foster the acceleration of a potential therapeutic option that could benefit patients living with SLE.

"Systemic Lupus Erythematosus is an area with significant need for new therapies for those living with the condition, but one that has been challenging to address given the complexity of this autoimmune disease," said Rob Lenz, M.D., Ph.D., senior vice president, Global Development at Amgen. "Our partnership with the FDA on the CID Pilot Program should drive the development of a new treatment for lupus to address unmet need for patients."

"Amgen welcomes the opportunity to partner with the FDA through participation in the CID Pilot Program, which intends to advocate innovative clinical trial designs, as well as provide the FDA an opportunity to communicate these advances publicly," said Steven Galson, M.D., senior vice president, Global Regulatory Affairs and Strategy at Amgen. "We appreciate the FDA's efforts, significant contributions and feedback provided throughout the Pilot process."

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Lupus is a Complex, Heterogeneous Autoimmune Disease

What is lupus?

Systemic Lupus Erythematosus (SLE), or lupus, is a chronic, inflammatory autoimmune disease[1] which affects approximately five million people globally[2]

5m

In SLE the body produces antibodies that attack its own healthy cells and tissues in addition to producing antibodies to protect against infection[2,3]

BRAIN | HEART | KIDNEYS | MUSCULO-SKELETAL

Signs and symptoms

Symptoms can vary greatly. Some of the most common symptoms of lupus are:[1]

- Painful and swollen joints (arthritis)
- Extreme fatigue
- Skin rashes
- Anaemia
- Kidney problems

It is estimated that

70-90%

of lupus cases are in females

with the highest incidence during a woman's most productive childbearing and professional development years[4]

Persistent SLE disease activity is associated with a higher risk of organ damage and mortality[5]

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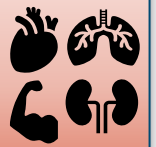
Top Barriers to Lupus Drug Development

- Challenges in understanding the biology of the chronic autoimmune disease
- Heterogeneity of clinical symptomatology defining the patient population

Disease Heterogeneity



- Lack of user-friendly, sensitive and accurate outcome measures
- Lack of stand-alone domain specific assessments of organ systems or symptoms

Outcome Measures

- Under-represented disease populations and many competing trials
- Suboptimal outcome measures
  - High variability
  - High control response rate

Clinical Trial Design

Heterogeneity of the disease is a foundational barrier

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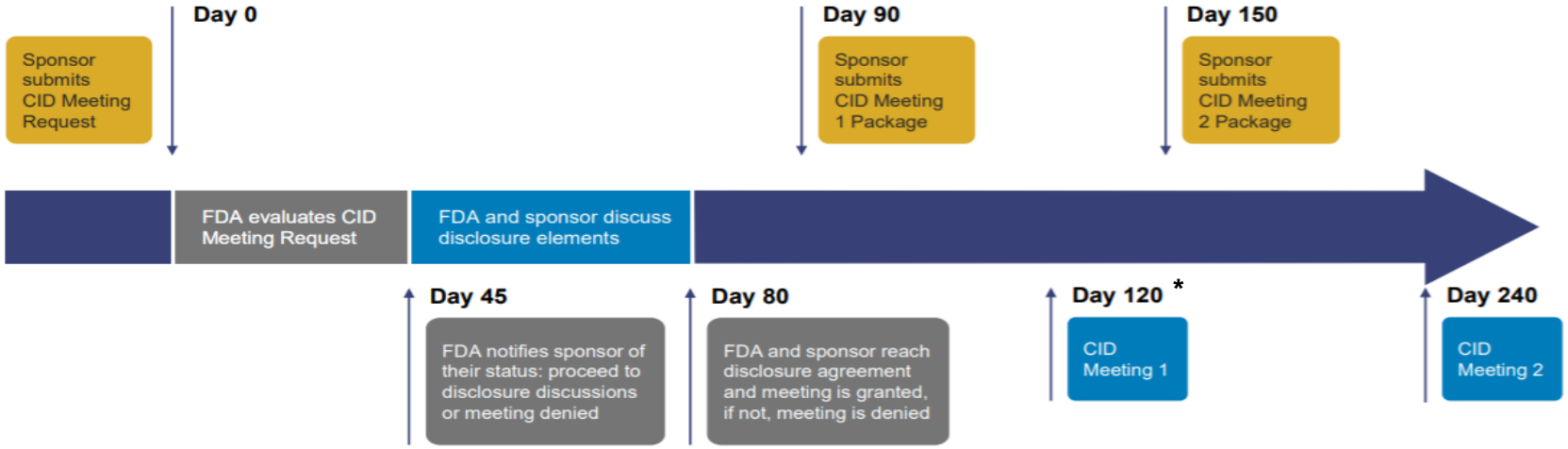
Rationale for Proposed CID

These challenges have led to a high development failure rate of potential therapeutics and highlight the need for innovative clinical trial design to improve development efficiency and probability of success compared with the traditional development approach:

- make the most efficient use of clinical trial data to simultaneously inform dose selection, generate adequate and well-controlled evidence on efficacy and quality safety data
- reduce the probability of inconclusive trial, and enable early and accurate decision-making
- shorten the time to bring new therapies to patients

CID PILOT PROGRAM: *PROCESS AND TIMELINE*



***Note:** *If sponsor believes that feedback received at the first CID meeting is sufficient and does not want a second meeting before initiating a trial, the sponsor may choose to finalize the protocol, submit it to the IND, and begin enrolling patients*

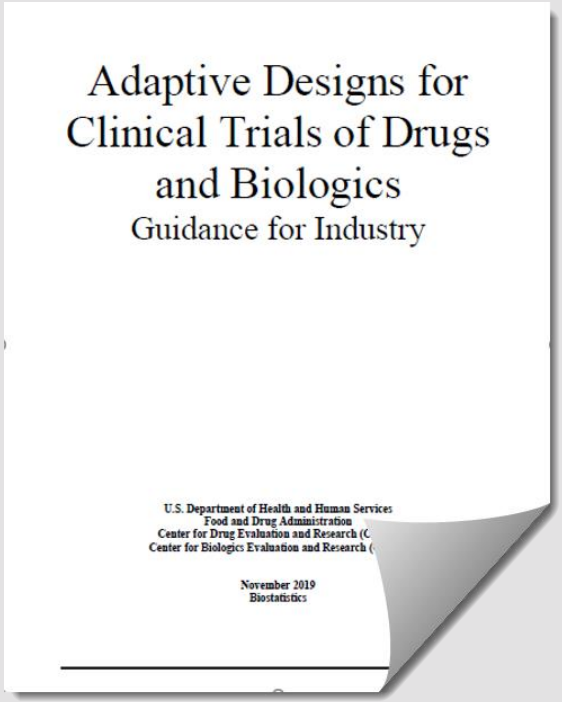
AMGEN US FDA EXPERIENCE THROUGH THE CID PILOT PROGRAM

Amgen participated in two meetings with FDA to engage in scientific discussions and reach agreement on an innovative study design that is appropriate for a study supporting registration

Meeting Request	Meeting 1	Meeting 2
➢ Requested discussion of the clinical relevance of the potential primary endpoints and formal definition of their estimands ➢ Recommended removing some proposed adaptive elements to reduce the dimensions to be explored in simulation for feasibility and interpretability considerations ➢ Suggested arm-dropping as an alternative to RAR* ➢ Set expectations on operating characteristics, simulation replicates, and nuisance parameters to be explored	➢ Discussed in detail the space of plausible nuisance parameters and combinations required to provide convincing evidence of type I error control and other operating characteristics ➢ Confirmed that BHM* and RAR would not preclude the study from being registrational, however, requested evaluations against multiple alternative designs, analysis methods, and simulation scenarios to demonstrate advantages of the proposed design ➢ Provided feedback on primary endpoint selection and recommended additional criteria to maintain trial conduct and integrity	➢ Confirmed that Amgen had largely addressed concerns and implemented suggestions to demonstrate that the proposed study design was appropriate as a registrational study ➢ Requested further comparison to alternative methods (NDLM, Dunnett) to establish BHM as the favorable method ➢ Requested information to justify for range of control response rate and concordance between adjacent visits ➢ Requested data access plan to be submitted

*RAR: Response Adaptive Randomization
BHM: Bayesian Hierarchical Model

Regulatory Guidance & 4 Principles



An adaptive trial intended to provide substantial evidence of effectiveness should satisfy:

1. Adequate control of the chance of erroneous conclusions
2. Sufficiently reliable estimation of treatment effects
3. Pre-specification of trial planning
4. Maintenance of trial integrity

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How We Benefitted from CID Regulatory Engagement

FEEDBACK

Direct feedback from large multidisciplinary team from the agency

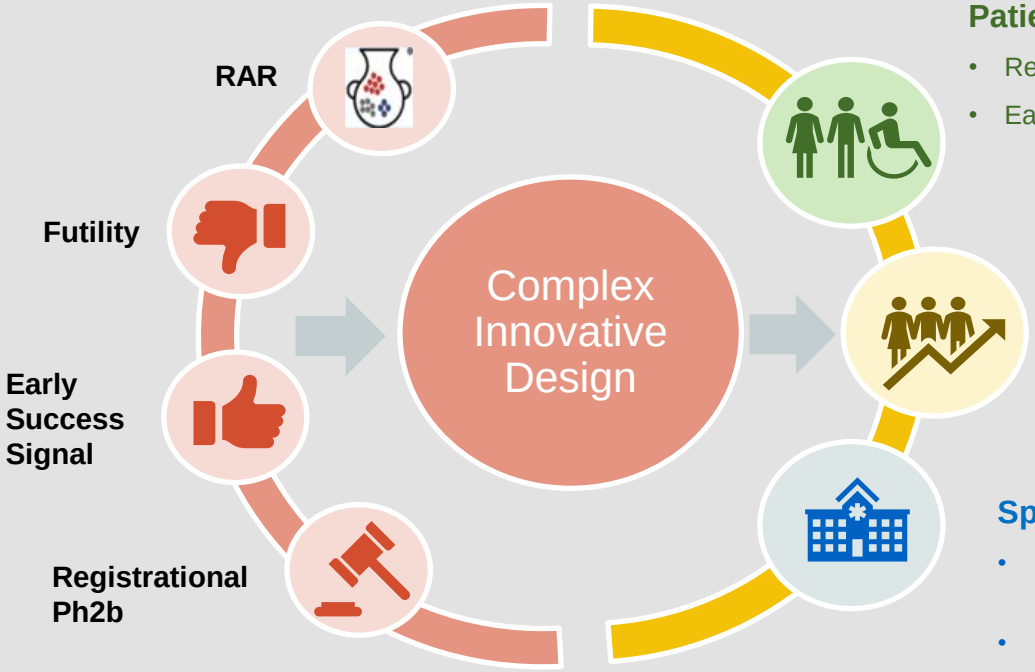
KNOWLEDGE SHARE

Opportunity to share innovative tools to evaluate complex innovate designs

GUIDANCE

Clear guidance on missing pieces of the evaluation

What Do We Gain from the CID Program?



Patients

- Reduced exposure to treatment that is not effective
- Early access to new treatment options

AMG 592 Program

- Cut 1 phase 3 study from the development program
- Streamlined development program
- Improve probability of success
- Reduce the cost of failure

Sponsor

- Collaborate with regulatory agencies to improve drug development efficiency
- Build capabilities in innovative trial design, modeling & simulation, and execution

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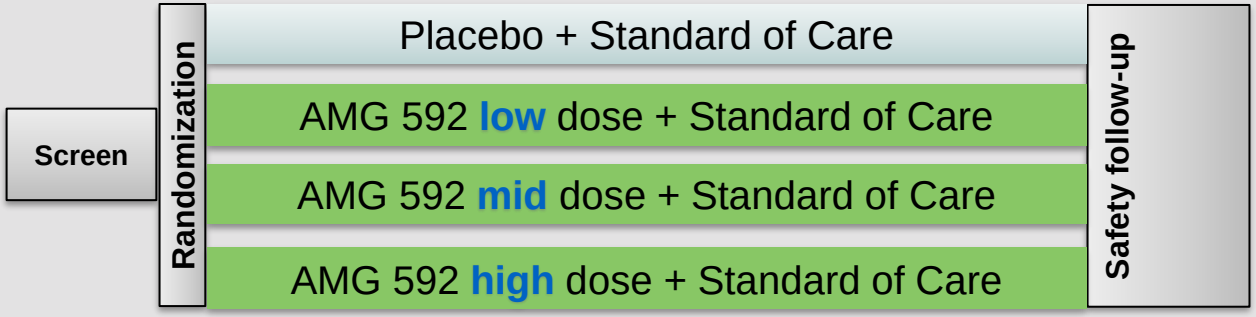
Study Schema

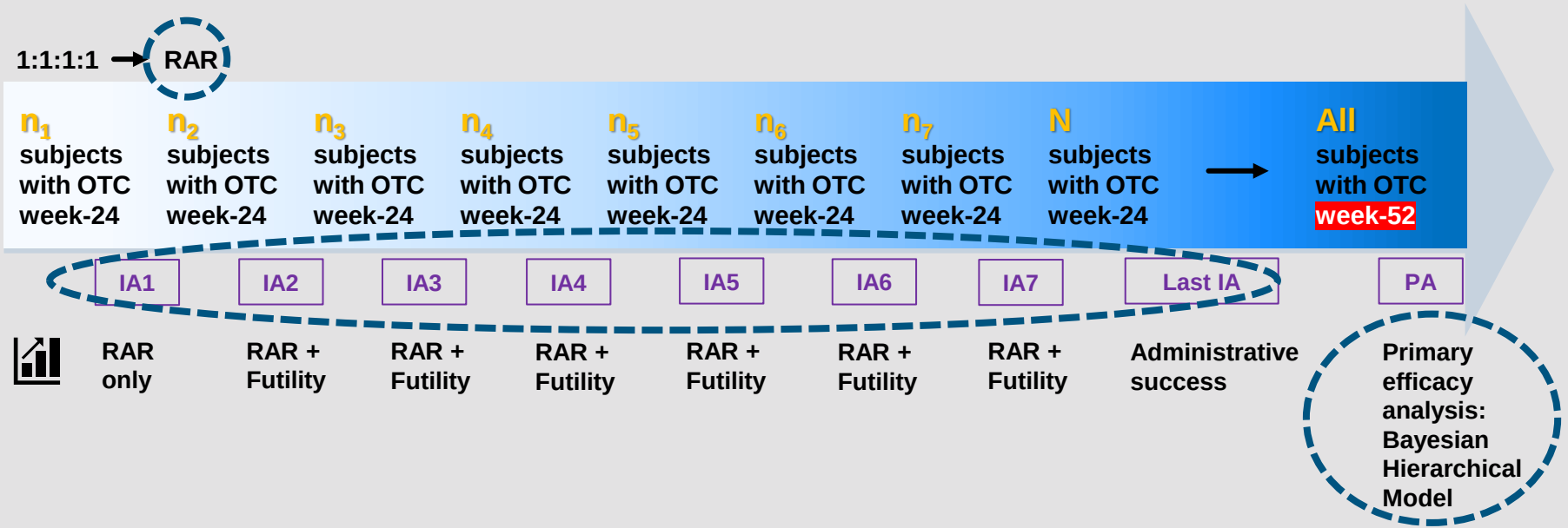


N:	320
1ºEdpt:	Response at W52
Summary Measure:	Difference in response rates

Objectives

1. Dose Selection
2. Qualify as an adequate and well-controlled study

Interim Analysis Schedule



OTC: opportunity to complete

Rationale for the Adaptive/Innovative Design Features

Response Adaptive Randomization

- Learn from accumulating data from ongoing trial
- Patient centric: reduce exposure to less effective treatment
- Increase efficacy & safety data collection on effective treatment

Interim Analyses for futility

- Stop patient exposure to non-effective treatment
- Reduce the cost of failure / shorten development timeline
- Redirect resources to other promising programs

Final Analysis Bayesian Hierarchical Model

- Dynamic borrowing across the active treatment arms improves estimation of treatment effect
- No underlying dose-response assumptions to reduce bias

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Response Adaptive Randomization

- **The randomization ratio to each active treatment group is based on the posterior probability that each group has the highest response rate at week 52 among the three active treatment groups.**

$$Allocation_d \propto \Pr\left(p_d = \max_c p_c \,|\text{interim data}\right) \; c, d \in \{low, medium, high\}$$

- **The posterior probability is calculated based on the Bayesian independent model**

$$X_d \sim Binomial(p_d, N_d)$$

$$\log\left(\frac{p_d}{1-p_d}\right) = \alpha_d$$

for $d \in \{low, medium, high\}$

Bayesian Hierarchical Model

Leverage information across all doses without a prior understanding of expected dose response

- **The number of responders in each group is modeled using a binomial distribution:**

$$X_d \sim Binomial(p_d, N_d)$$

where p_d is the week 52 response rate in group d.

- **Each response rate is modeled independently using a logistic model:**

$$\log\left(\frac{p_d}{1-p_d}\right) = \alpha_d$$

- **The log-odds of response in the treatment groups is modeled using a hierarchical prior:**

$$\alpha_d \sim \mathcal{N}(\alpha_{treatment}, \sigma^2) \text{ for } d \in \{low, medium, high\}$$

- **BHM is used in futility and primary efficacy analyses**

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Principle 1: Control of Erroneous Conclusion

Type 1 Error (Global Null)

What is Global Null?

- There is no treatment effect in any of the 3 treatment arms
- There is no treatment effect at any timepoint during the 52-week treatment period

How is Type 1 Error Defined?

- Reject null for any of the treatment arms using Bayesian Hierarchical Model (BHM) and longitudinal modeling for:
  - any plausible control response rate
  - any plausible enrollment rate
  - any plausible correlation (concordance) within subject over time by treatment arms

Nuisance Parameters

- 3 Nuisance Parameters:
  - Enrollment rate: a plausible range
  - Control response: 30%, 40%, 50%
  - Correlation (concordance) patterns:
    - 0.5-0.9 same or different across visits by arms
- Full factorial combinations simulated 100K each

Type 1 Error Rate

Type I Error is controlled across the plausible Global Null scenarios

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Principle 1: Control of Erroneous Conclusion

Type 1 Error (Local Null)

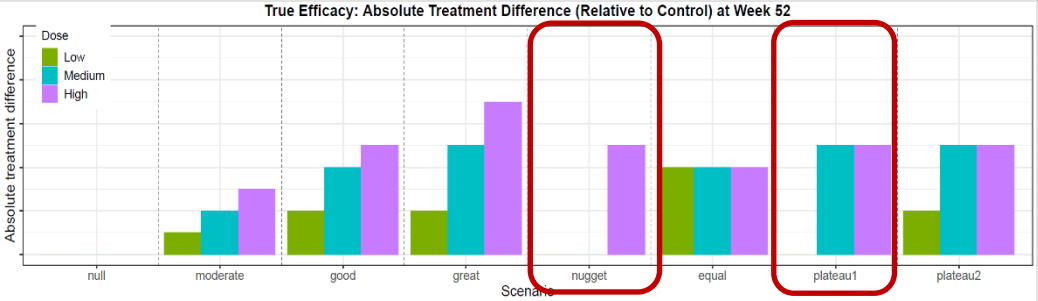
What is Local Null?

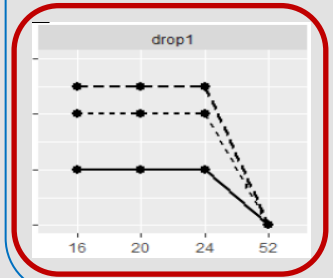
1. There is no treatment effect for 1 or 2 treatment arms, while at least one is effective
2. There is no treatment effect at week 52 assessment for the primary endpoint, while there are treatment effects at earlier visits (ie, “Drop1” Scenario)

Are these Type I error?

1. Reject null for any of the ineffective dose levels and select the dose for phase 3
2. Reject null for any treatment arm in “Drop 1” scenario

Scenarios Simulated





1. “Nugget” and “Plateau1” with either 1 or 2 ineffective dose(s) are evaluated across the nuisance parameter factorial combinations
2. The “Drop1” scenarios with efficacy at week 16-24 and none at week 52 is evaluated for selected nuisance parameter combinations

Each scenario was simulated 100k each

Type I Error is controlled across the plausible Local Null scenarios

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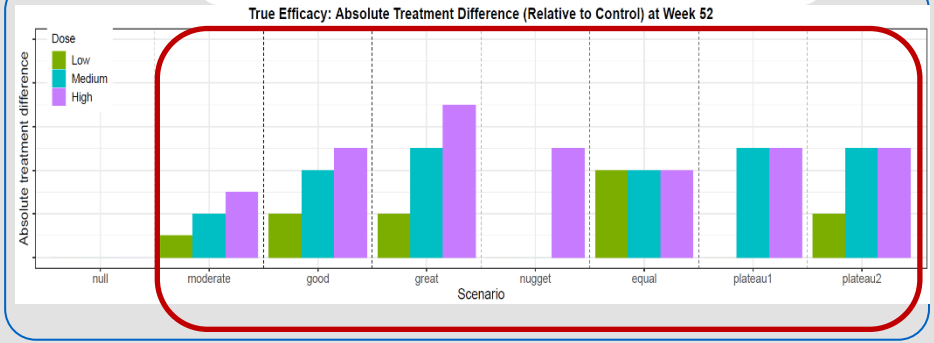
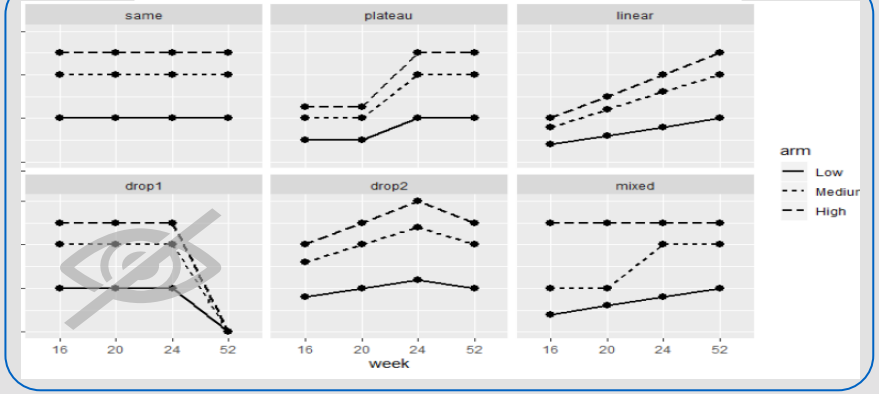
Principle 1: Control of Erroneous Conclusion

Type II Error

Efficacy Scenarios (n=7)



Longitudinal Patterns (n=5)



How is Type II Error Evaluated

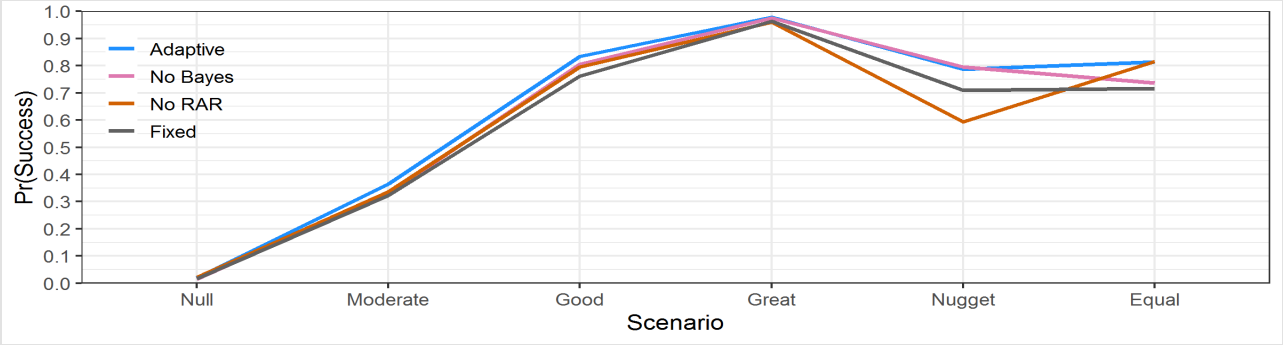
- The nuisance parameter space is reduced by fixing 2 parameters at the most plausible value, and varying the third parameter univariately across its plausible range resulting in reduced set of combinations
- Each of the 12 combinations is then evaluated across the **7** efficacy scenarios and **5** longitudinal patterns, which results in hundreds of total efficacy factorial combinations

Principle 1: Control of Erroneous Conclusion

Type II Error

Power – Pr(Success) of Any of the Treatment Arms

- Power estimates from 4 study designs are compared below based on the most plausible nuisance parameters and longitudinal pattern



- The operating characteristics (OCs) across simulated scenarios provide sensitivity analysis of the robustness of the study design to the underlying assumptions and identify worst case scenarios

Some Other OCs

- ***Pr(Futility)*** - probability of stopping the study early for futility
- ***Pr(Adm.Success)*** - probability of achieving the administrative success criteria
- ***Pr(Select Best Dose)*** - probability of selecting the best dose
- ***Avg.Randomized*** - Average randomized subjects across all treatment groups

Proposed design elements (RAR and BHM) improve study power

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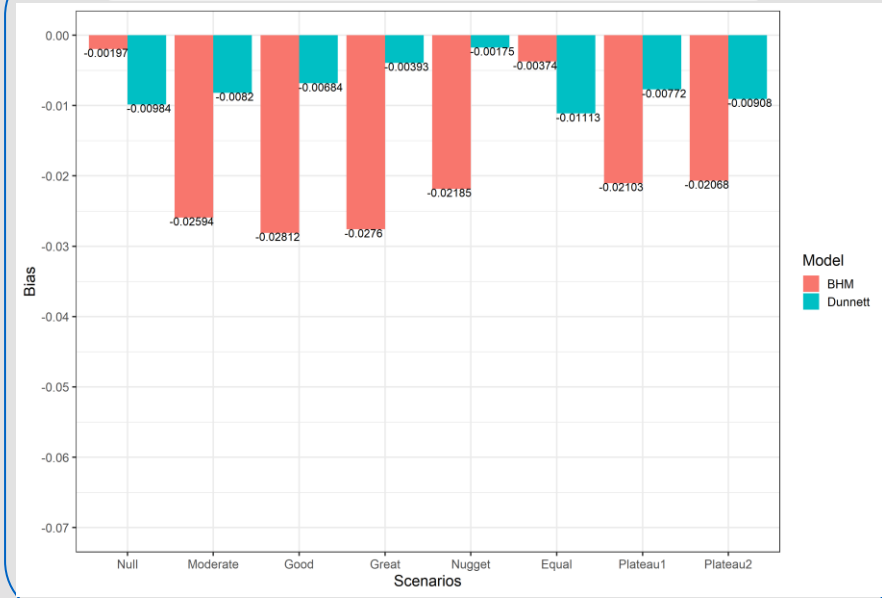
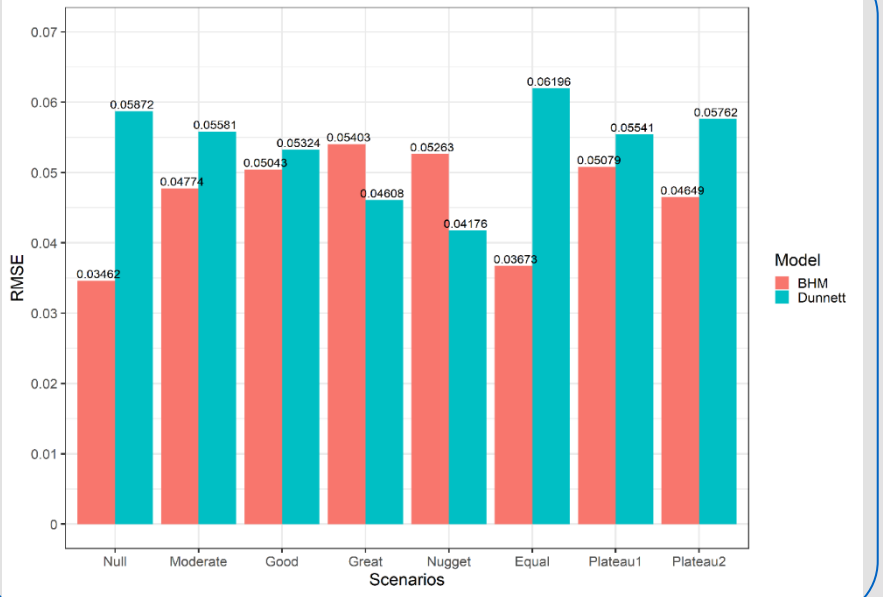
Principle 2:
Sufficiently Reliable Estimation of Treatment Effects

Bias



RMSE



BHM has lower RMSE of treatment effect estimates than Dunnett's

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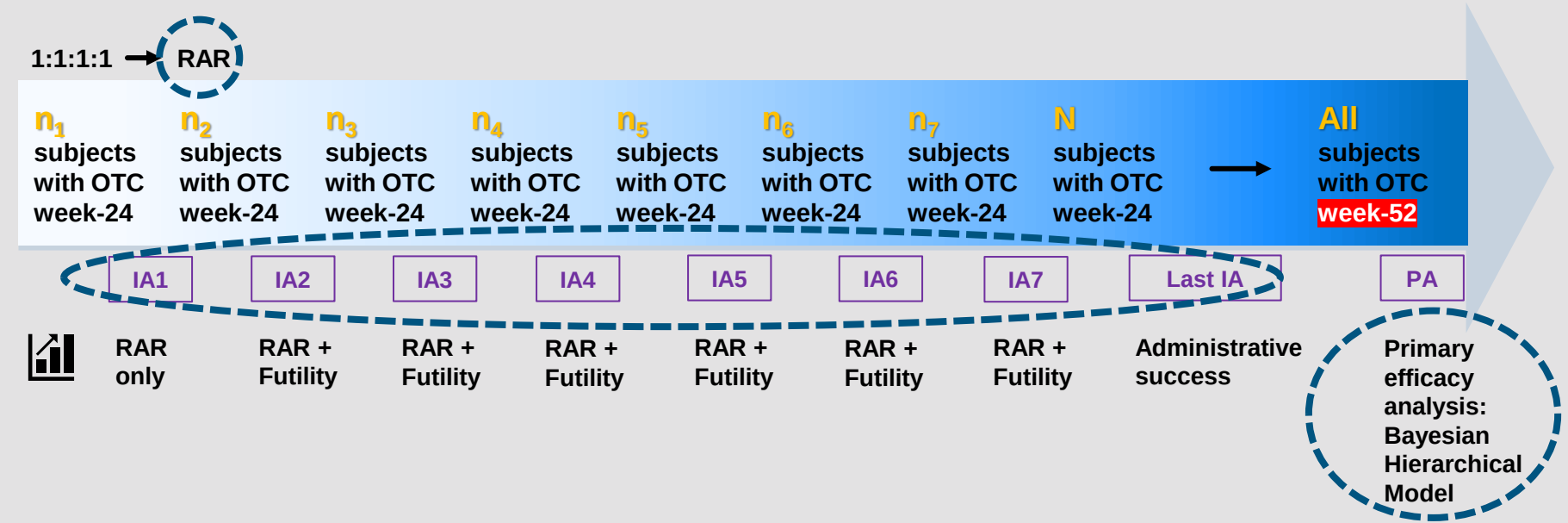
Principle 3:

Pre-Specification of Interim Analysis and RAR Algorithm



OTC: opportunity to complete

Principle 3:
Pre-Specified Decision Rules

- ***Futility Stopping***

  Enrollment to the study may be stopped for futility if

  $$\max \Pr\left(p_d - p_{placebo} > \textbf{\textit{target treatment effect}} \mid \text{Interim Data}\right) < \textbf{\textit{low value threshold}}, d \in \{low, medium, high\}$$

- ***Administrative Success***

  BHM will be fit to compute the **predictive probability of success** in **a hypothetical, future phase 3 study**, with a frequentist final analysis tested at the 2.5% one-sided level. The threshold of administrative success is the predictive probability of success in this hypothetical future study is larger than **a cutoff value**.

- ***Primary Analysis Success***

  The null hypothesis will be rejected if the posterior probability of superiority in any group is above a threshold:

  $$\Pr(p_d > p_{placebo} \mid \text{Data}) > \textbf{\textit{high value threshold}}, \text{ for } any\ d \in \{low, medium, high\}$$

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Principle 4:
Maintaining Trial Conduct & Integrity

Adaptive design adds logistical challenges to trial conduct and trial integrity

- Limit access to comparative interim results provides confidence in design modification and assurance of quality trial conduct
  - **External:** Independent Data Monitoring Committee (DMC)
    - Implement a **carefully designed and prespecified adaptation plan**, in addition to its primary responsibility to maintain patient safety and trial integrity
  - **Internal:** Data Access Plan (DAP) to document limited access of sponsor
    - Individuals to perform interim analysis or access interim results
    - Procedures to control access and evaluate compliance
    - Processes for adaptive decision making and dissemination
- Ensure high-quality interim data for adaptive decision-making

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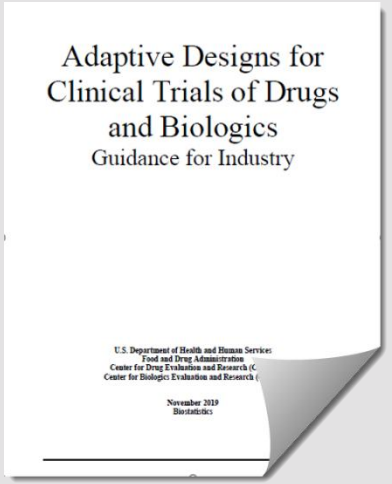
SIMULATION EXPERIENCE

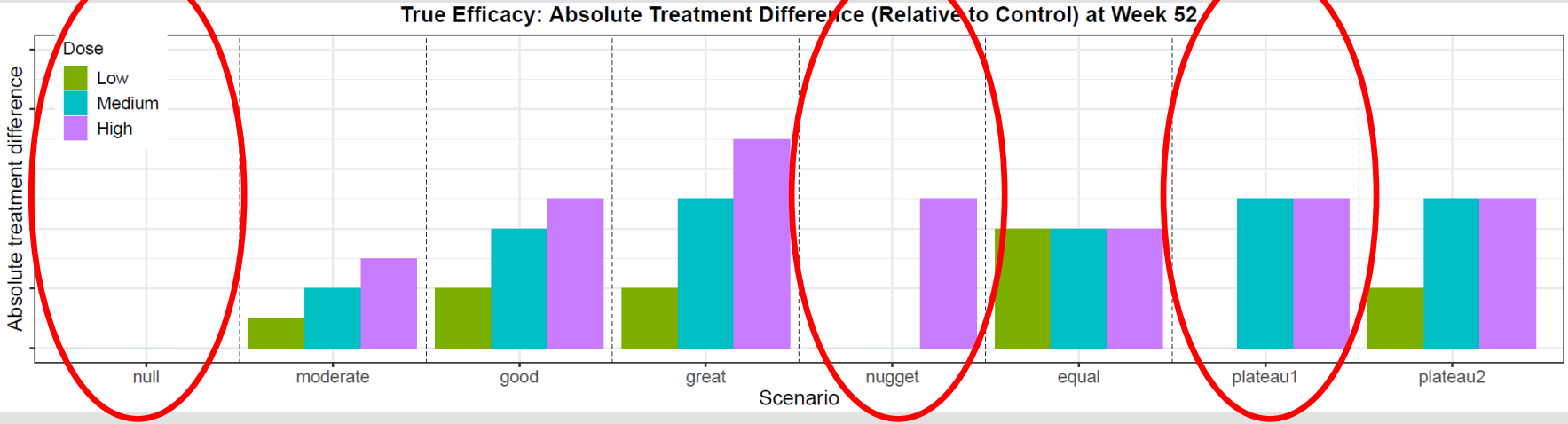
- Amgen team, in consultation with the FDA, has conducted an extensive simulation study to evaluate the CID design
- A comprehensive simulation report along with full results and code files have been submitted to the FDA according to the adaptive design guidance recommendation

SIMULATION REPORT – TABLE OF CONTENTS



SIMULATION SCOPE – CLINICAL SCENARIOS

Efficacy Scenarios on week 52 primary endpoint



Global Null

Local Null

SIMULATION SCOPE – NUISANCE PARAMETERS

Control Arm Response

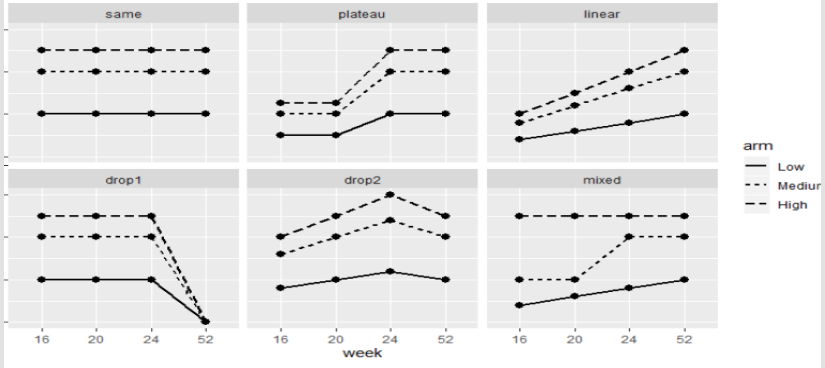
- A meta-analysis was done on historical SLE studies
- Based on the meta-analysis result, control response rates of (30%, 40%, 50%) is considered the most plausible scenarios

Accrual Rate

- Three scenarios are included to cover the plausible range of accrual rate
- For all simulations, enrollment is assumed to have a 10-week ramp-up period followed by a constant accrual rate

Longitudinal Pattern

- Longitudinal response pattern with respect to W52 response



Concordance

- Concordance of SRI-4 Response Between Adjacent Visits

Scenario	Value											
	Same concordance across visits and treatment arms											
#1	0.5											
#2	0.6											
#3	0.7											
#4	0.8											
#5	0.9											
	Different across visits, but same across treatment arms											
#6	Week 16-20			Week 20-24			Week 24-52					
	0.8			0.8			0.5					
	Same across visits, but different across treatment arms											
#7	Control Arm			Low Dose			Med Dose			High Dose		
	0.5			0.6			0.7			0.8		
	Different across visits and treatment arms											
#8	Control Arm			Low Dose			Med Dose			High Dose		
	16-20	20-24	24-52	16-20	20-24	24-52	16-20	20-24	24-52	16-20	20-24	24-52
	0.5	0.5	0.5	0.6	0.6	0.5	0.7	0.7	0.6	0.8	0.8	0.7

SIMULATION ITERATIONS

Type I Error

- For type I error evaluation, the results were based on 100k simulations per scenario, which provides type I estimation accuracy of approximately ± 0.001 with 95% confidence

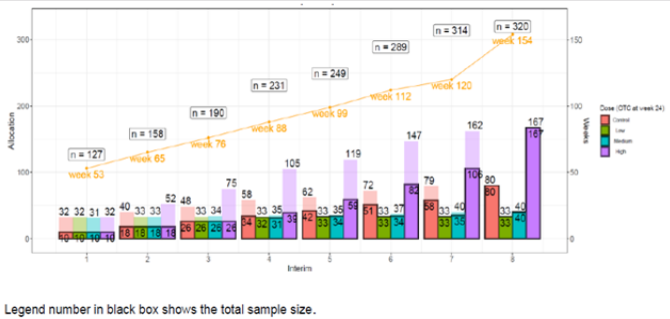
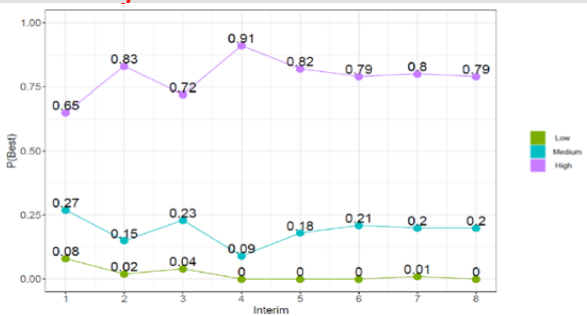
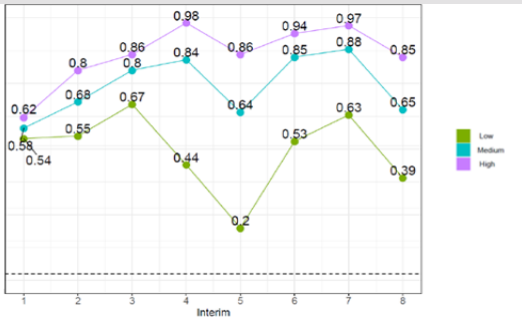
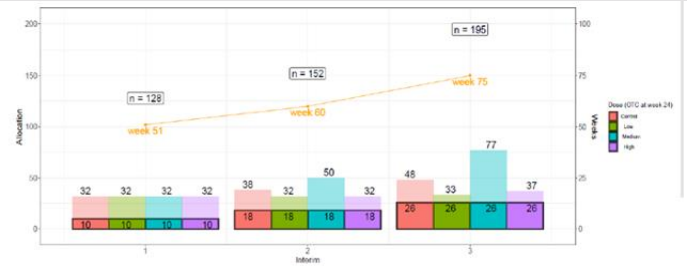
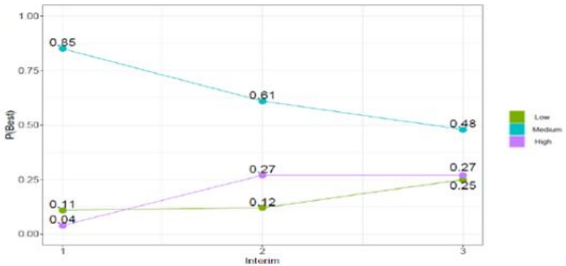
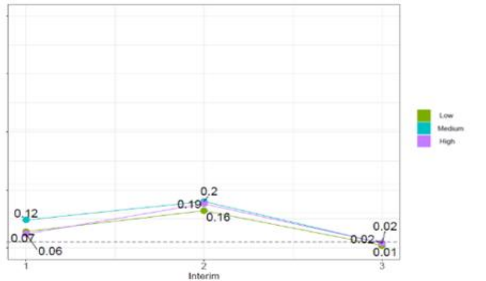
Power and Estimation / Bias

- For efficacy scenarios, the results are based on 10k simulations per scenario, which provides estimation accuracy of ± 0.01 for probabilities and ± 2 subjects for subject allocation with 95% confidence

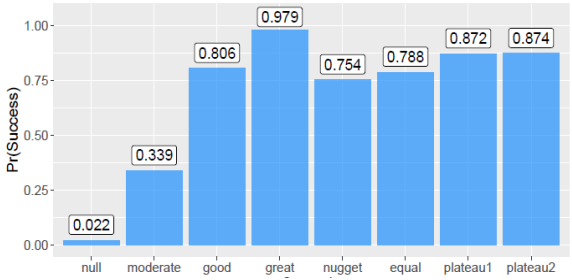
Consistent with FDA adaptive design guidance

EXAMPLE TRIAL

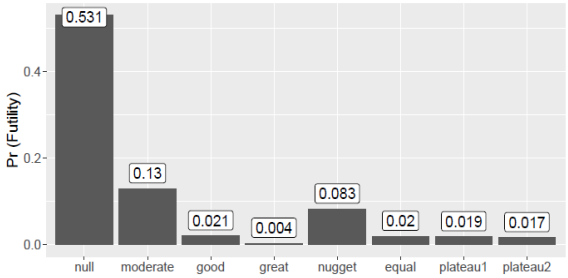
- Example trials have been submitted in the simulation report and a shiny app has been created to visualize example trials with complete transparency

Sample Size and Allocation	Prob. of Being Best Dose (BAR)	Posterior Probability (Futility)
Example trial 1: a successful trial		
		
Legend number in black box shows the total sample size.		
Example trial 2: a futile trial		
		
Legend number in black box shows the total sample size.		

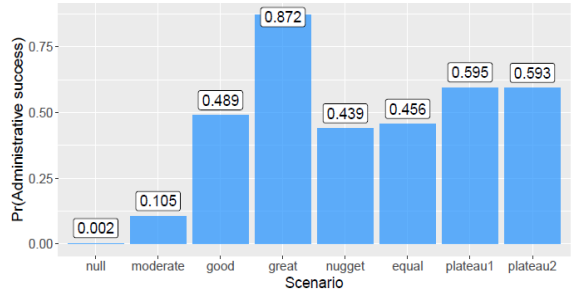
Probability of Success



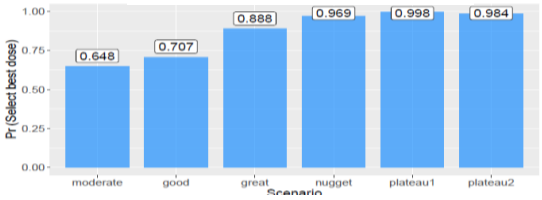
Probability of Futility



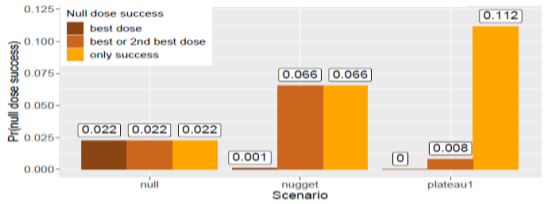
Probability of Administrative Success



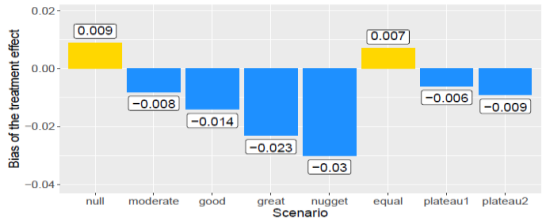
Probability of Selecting Best Dose



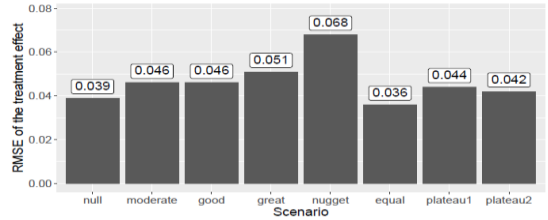
Probability of Null Dose Success



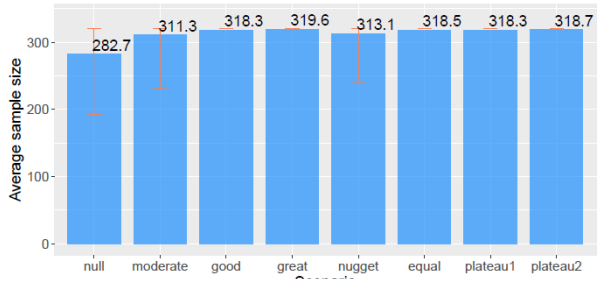
Bias of the Treatment Effect Estimate on Best Selected Dose



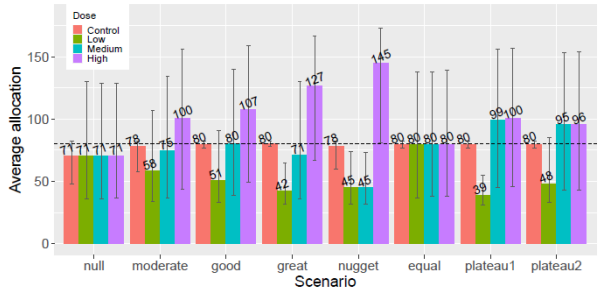
RMSE of the Treatment Effect Estimate on Best Selected Dose



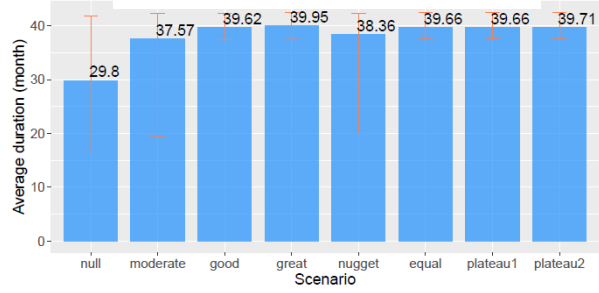
Average Total Sample Size in Each Scenario



Average Allocation by Dose in Each Scenario



Average Duration (Month) in Each Scenario



Closing Remarks

- ✓ PDUFA VI and 21st Century Cures Act provide exciting opportunities for industry to collaborate with regulatory agencies in promoting use of CIDs and providing the FDA an opportunity to communicate these advances publicly
- ✓ CIDs can help improve efficiency in clinical programs throughout the drug development cycle
- ✓ Our partnership with the FDA on the SLE CID Pilot Program should drive the development of a new treatment for lupus to address unmet need for patients
- ✓ We appreciate the FDA's efforts, significant contributions and feedback provided throughout the Pilot process

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THANK YOU!