FDA Complex Innovative Trial Design (CID) Pilot Program Experience

AMG 592 SLE Case Study

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CID Pilot Meeting Program

- Joint effort of the Center for Drug Evaluation and Research and Center for Biologic Evaluation and Research
- Sponsors
  - submit designs
  - have the opportunity to engage with **regulatory team** on designs via two meetings
- Agency
  - will select up to 2 submissions per quarter
  - uses the design as a case study for continuing education and information sharing
- Meetings led by statistical units with participation from all relevant disciplines
- Five year duration

Dionne Price, Oct 5, 2021, https://www.efpia.eu/media/636514/day-1-master-v3.pdf

Progress to date

- 5 accepted submissions span several therapeutic areas
  - Neurology
  - Analgesia
  - Rheumatology
  - Oncology
- Designs incorporated
  - Bayesian hierarchical modeling
  - Use of formal priors
  - Formulation of a master protocol

Dionne Price, Oct 5, 2021, https://www.efpia.eu/media/636514/day-1-master-v3.pdf

Complex Innovative Trial Design Pilot Meeting Program

New! CID Pilot Program Trial Design Case Studies

The description of each CID Pilot Meeting Program case study focuses on the single clinical trial design that was the focus of the Pilot Program submission. The description does not discuss other potentially important aspects of the development program for the respective drug or biologic, such as any plans to conduct additional adequate and well-controlled trial(s) and/or to obtain confirmatory evidence to help establish substantial evidence of effectiveness. Please refer to draft guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

- Master Protocol Case Study
- Lupus Case Study
- DLBCL Case Study

Learn More about CID

- New!Publication: The U.S. Food and Drug Administration's Complex Innovative Trial Design Pilot Meeting Program: Progress to date
- Guidance Snapshot: Interacting with FDA on Complex Innovative Trial Designs for Drugs and Biological Products Guidance For Industry

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program#case%20studies

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Lupus is a Complex, Heterogeneous Autoimmune Disease

What is lupus?

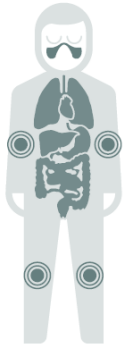
Systemic Lupus Erythematosus (SLE), or lupus, is a chronic, inflammatory autoimmune disease[1] which affects approximately five million people globally[2]

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]

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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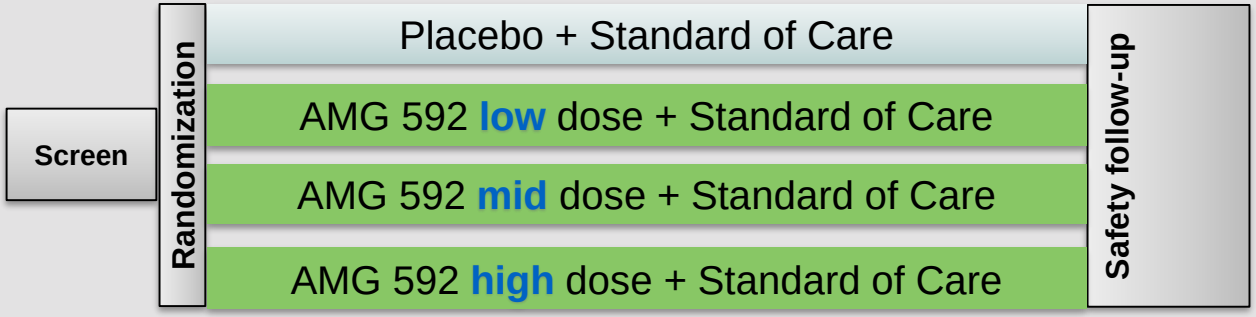
Rationale for Proposed CID

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

Study Schema

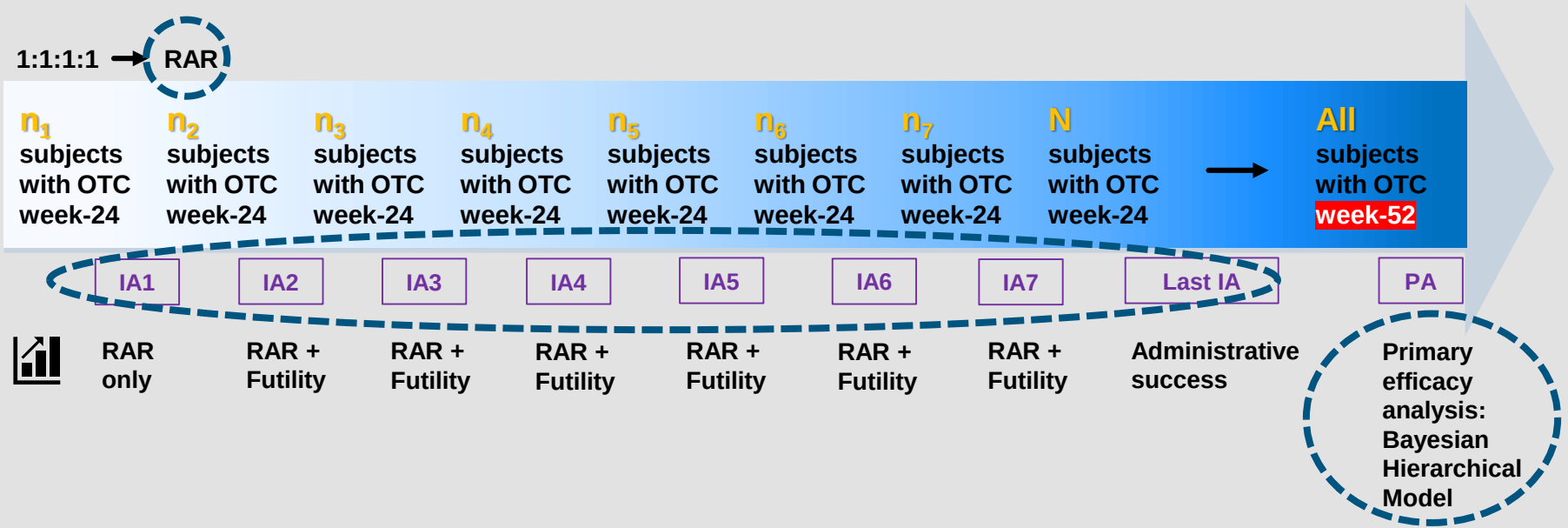


N:	320
1ºEdpt:	Response at W52
Summary Measure:	Difference in response rates

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

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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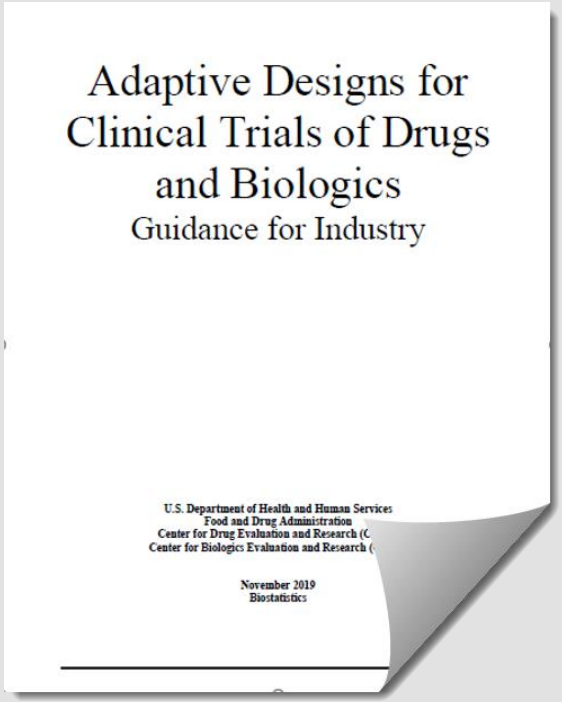
Regulatory Guidance & 4 Principles



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

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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BACK-UP SLIDES

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

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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**

Pre-Specified Decision Rules

- ***Futility Stopping***

  Enrollment to the study may be stopped for futility if

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

- ***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:

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

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Modeling & Simulation Visualization Tool

RAR algorithm at each IA
- Allocation on each arm
- Number of subj with OTC week 52
- Probability of being best dose
- Dynamic update of Randomization ratio

Bayesian sequential monitoring at IA
- Futility analysis
- Administrative success
- Primary analysis
- Posterior prob
- Model est. response rate

Design OC
- Total allocation, duration
- Probability of success
- Probability of futility
- Probability of admin. success
- Bias/RMSE, etc.

Null space exploration
- Global Null
  - Accrual rate
  - SoC control rate
  - Concordance
- Non-Global null
  - Longitudinal pattern
  - Nugget/plateau 1 efficacy scenarios

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