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Applying the Estimand Framework to Dose-Ranging Trials: A Case Study

A practical illustration for Phase 2 dose selection using a cutaneous lupus erythematosus case study

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Key message: in dose-ranging trials, the estimand should target the dose to take forward - not only treatment differences at tested doses.

WHY THIS MATTERS

- ICH E9(R1) was developed for confirmatory trials, but it remains underutilized for phase 2 dose-ranging studies
- Problem seen in reviewed examples: methods such as Bayesian Emax or MCP-Mod were described, but the estimand often stayed at "mean difference from placebo for each tested dose".
- That misses the dose-selection question: "Which dose(s) should be studied in Phase 3?"

OBJECTIVES

- Applied the estimand thinking process retrospectively to a phase 2 dose-ranging trial of litifilimab in moderate or severe cutaneous lupus erythematosus, using publicly available information, as a case study
- Dosing range considered: 50-450 mg SC, every 4 weeks, with an additional Week 2 loading dose.
- Efficacy endpoints: CLASI-A reduction from baseline and CLASI-50 response at Week 16.
- Goal: choose a dose to optimize efficacy while maintaining an acceptable safety profile. A dose not directly tested, but within the tested range, may be considered.

THE SHIFT IN THE QUESTION

Conventional summary measure
Treatment difference from placebo at each tested dose

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Decision-oriented summary measure
Dose giving 80% of maximum efficacy while staying below a 10 percentage-point safety-risk increase

ESTIMAND-THINKING PROCESS

A seven-step thinking process in ICH E9(R1) Training Materials converts the trial objective into estimands, design choices, and analyses.

1 Objective | 2 ICEs | 3 Strategies | 4 Estimand | 5 Design + estimation | 6 Sensitivity | 7 Document

Step 1: Trial objectives and clinical questions the trial should answer

Primary efficacy
What dose gives 80% of the estimated maximum therapeutic effect within 50 - 450 mg SC?
Endpoint: percent reduction from baseline in CLASI-A at Week 16.

Safety
What dose has <10 percentage-point absolute risk increase for a composite safety event vs. placebo by Week 16?
Composite Safety Endpoint: SAE, AESI, or discontinuation due to AE.

Supplementary efficacy
CLASI-50 response at Week 16, using intercurrent-event handling aligned to phase 3 expectations.

Steps 2/3: Intercurrent event strategies

ICE strategy choice is driven by the clinical question. The same event can be handled differently for primary efficacy, safety, and supplementary efficacy.

Methods are illustrative and should be tailored for each trial.

ICE: Treatment discontinuation due to lack of efficacy or safety concerns

Estimand	Strategy	Motivation
Primary efficacy	Hypothetical	Estimate the pure treatment effect: what would happen if discontinuation did not occur?
Safety	While-on-treatment / composite	For discontinuations due to lack of efficacy, count AEs while exposed. For discontinuation due to safety, the event is itself part of the safety question.
Supplementary efficacy	Treatment policy (or composite)	Align with phase 3 expectations; some authorities may request non-response/composite handling after discontinuation.

ICE: Start/increase concomitant therapy or corticosteroids

Estimand	Strategy	Motivation
Primary efficacy	Hypothetical	Avoid attributing improvement from rescue/standard-of-care changes to the investigational treatment.
Safety	Treatment policy	Composite safety endpoint (SAE, AESI, or discontinuation due to AE) is sufficiently specific; attribution is difficult once new medication is introduced, so count events regardless.
Supplementary efficacy	Treatment Policy (or composite)	Use ICE handling aligned with phase 3 expectations

Step 4: Construct dose-ranging estimands

Primary efficacy
Treatment: litifilimab 50-450 mg SC + SoC vs placebo + SoC
Population: moderate/severe CLE patients (CLASI-A ≥8)
Endpoint: percent reduction from baseline in CLASI-A at Week 16
ICE handling: hypothetical for discontinuation and therapy changes
Population-level summary: dose corresponding to 80% of maximum placebo-adjusted mean percent reduction within the tested range

Safety
Endpoint: composite safety event - SAE, AESI, or treatment discontinuation due to AE by Week 16
ICE handling: while-on-treatment for lack-of-efficacy discontinuation; composite for safety discontinuation; treatment policy for therapy changes
Population-level summary: dose with <10 percentage-point absolute risk increase vs. placebo

Supplementary efficacy
Endpoint: CLASI-50 response at Week 16
ICE handling: treatment policy for discontinuation and therapy changes
Population-level summary: dose corresponding to 80% of the increase in proportion of patients achieving response vs. placebo within the tested range

Step 5: Design + Estimation

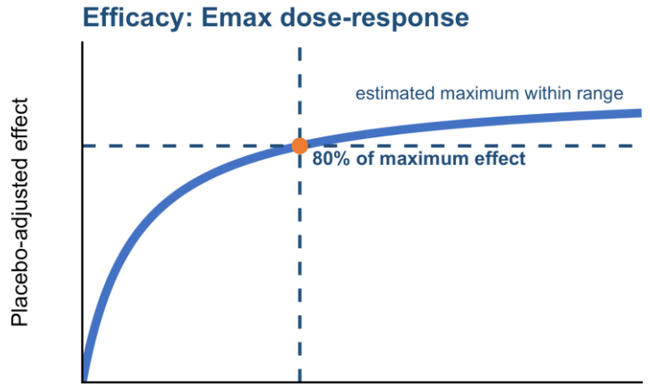
Primary efficacy model
Use Emax dose-response model to calculate the dose giving 80% of estimated maximum effect within the tested range on Week 16 estimates from an MMRM model. Uncertainty of the estimated dose is quantified via bootstrap.

Safety model
Use logistic regression to model the probability of composite safety event vs. dose and calculate the highest dose below the risk threshold.

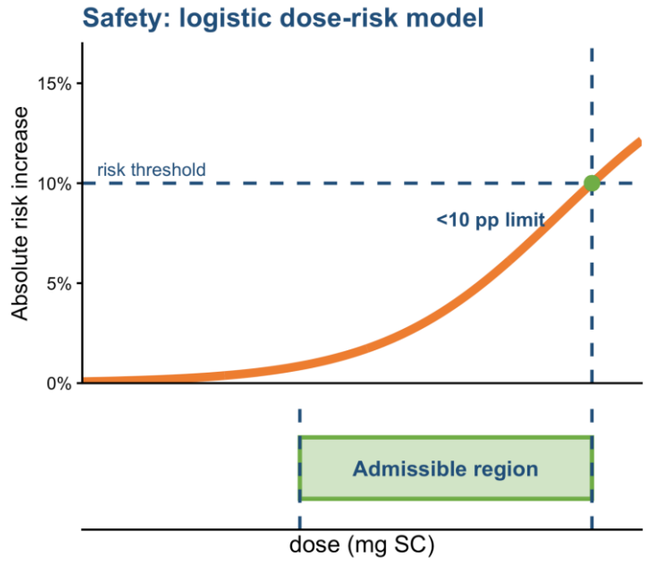
Select a Phase 3 dose(s) in the window:

Charts are illustrative and not observed trial results.

Efficacy: Emax dose-response



Safety: logistic dose-risk model



Step 6: Assumptions and sensitivity analyses

Primary efficacy
The Emax model assumes monotonicity of efficacy. Alternative dose-response models that do not enforce monotonicity can be used.

Safety
The logistic regression model assumes that the log-odd of the safety event is linear with respect to dose. Alternative models with fewer assumptions, such as isotonic regression, can be used.

RECOMMENDATIONS

- Define population-level summaries in terms of dose, not only pairwise treatment differences.
- Separate primary efficacy, supplementary efficacy, and safety questions because their intercurrent-event strategies differ.
- State whether untested doses within the studied range can be selected.
- Split treatment discontinuation by reason so ICE strategies match the clinical question.

TAKEAWAY

- Phase 2 dose-ranging estimands should make dose selection explicit: ask which dose on the curve should be taken forward.
- This improves coherence between objective, design, data collection, and analysis - and creates a clearer bridge to the next development decision.

References: Werth et al. NEJM 2022; Furie et al. J Clin Invest 2019; ICH E9(R1) Training Materials. All study information obtained from public sources. The authors have no affiliation with the sponsor of the study.

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