Supplementary Materials for ‘Applying the Estimand Framework to Dose-Ranging Trials: A Case Study’ poster

Abstract

ICH E9 (R1) arose in the context of confirmatory trials to quantify the efficacy for a selected dose (or doses) that was identified based on prior dose-response studies. There are limited worked examples on the application of this framework in the context of dose response (2b) trials where the clinical question of interest is the efficacy and safety of dose response over a range of doses.

In a few examples of dose ranging studies reviewed, we found that although the analysis methods to estimate the dose-response curve (e.g., Bayesian Emax, MCP-Mod) were described, the estimand instead described the treatment difference in means from placebo for each dose tested, and did not consider the dose-ranging nature of the study.

We use a case study of a phase 2b dose-ranging trial of litifilimab for cutaneous lupus erythematosus (NCT02847598) [1] to provide an illustration of considerations when applying the estimand framework to a dose-response study.

The specific estimands proposed are for illustrative purposes; the key takeaway is the application of the estimand thinking process in a dose-ranging context.

The authors have no affiliation with the sponsors of this study. All study information obtained was from public sources.

Introduction

We used a case study of a phase 2b dose-ranging trial of litifilimab for cutaneous lupus erythematosus (NCT02847598) [1] to provide considerations when applying the estimand framework to a dose-response study during development. This was done retrospectively, based on the information available in the literature. This phase 2b trial was conducted after a phase 1 trial (NCT02106897) [2] that evaluated safety, tolerability, and PK in healthy volunteers and patients. The Phase 2b trial led to a pivotal phase 2/3 trial (NCT05531565) [3].

The seven steps of the Estimand Thinking Process from the ICH E9(R1) training slides [4] were followed in arriving at an estimand for the dose-response study.

- Step 1: Therapeutic setting and intent of treatment determining a trial objective
- Step 2: Identify intercurrent events

- Step 3: Discuss strategies to address intercurrent events
- Step 4: Construct the estimand
- Step 5: Align choices on trial design, data collection and method of estimation
- Step 6: Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
- Step 7: Document the estimand

Step 1: Therapeutic setting and intent of treatment determining a trial objective

Therapeutic setting

Cutaneous lupus erythematosus (CLE) is an autoimmune disease with various skin manifestations. First-line therapies for cutaneous lupus erythematosus include topical glucocorticoids and antimalarial medications. The intent of the treatment is to modulate disease activity, quantified by CLASI-A (CLASI Activity Score), which is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. A 50% decrease reflects a major improvement in disease activity.

Intent of treatment

Litifilimab is a humanized monoclonal antibody which binds to BDCA2 (Blood Dendritic Cell Antigen 2), a protein expressed on plasmacytoid dendritic cells (pDCs), which are major producers of type I interferons (IFN-I) that play a key role in CLE pathogenesis. BDCA2 is internalized (pulled from the surface) into the interior of the pDC, which allows co-localization with Toll-like receptors 7 and 9 (TLR7/9) in the intracellular compartment where TLR signaling normally occurs. This co-localization inhibits the TLR7/9 signaling pathway that initiates IFN-I production.

In the phase 1 study, the BDCA2 levels on pDCs reached peak internalization at 14 days after a single 20 mg/kg IV dose of litifilimab in patients with systemic lupus erythematosus (SLE) with skin manifestation. BDCA2 levels on pDCs maintained internalized until day 56, before recovering on days 84 and 112 in some patients. The terminal half-life (t1/2) of a litifilimab 20 mg/kg IV dose in SLE patients (n=8) was 18 days.

To guide doses to be tested in the phase 2 study, population PK/PD modeling [5] based on phase 1 study data (NCT02106897) was conducted, which suggested that a threshold serum concentration of 1 µg/mL was required to ensure internalization of BDCA2 exceeding 90%.

The dose ranged tested was from 50 mg to 450 mg SC. A dose of 50 mg SC ensures BDCA2 internalization for the majority of a dosing interval of 4 weeks. The long 18-day half-life, along with the PK/PD modeling, supported the selection of an "every 4 weeks" (Q4W) dosing frequency for the Phase 2 trial. To ensure target concentrations were reached quickly, an additional loading dose was administered at Week 2.

Trial objective

Given the public materials that were available to the authors, the main objective could be envisaged as to select a dose that has high efficacy and is also safe. The selected dose will be brought forward to confirmatory phase 3 trials.

It is assumed that the dose selected for the pivotal trial can include doses not directly tested but within the range tested in the study without extensive reformulation work, given litifilimab is a biologic.

While there is sufficient safety coverage based on phase 1 data, safety information gathered in phase 1 is inherently limited due to the shorter duration of exposure and limited number of participants, and thus safety will be a consideration for dose selection.

Possible high-level questions and outcomes from the trial

Possible high-level questions, each will require an estimand

- For primary efficacy, what is the lowest dose (continuous within the dose range tested) that gives most (e.g., 80%) of the estimated maximum effect within the dose range under consideration, assuming the intercurrent events do not occur, to understand the pure pharmacological effect
- For supplementary efficacy, what is the lowest dose (continuous within the dose range tested) that gives most (e.g., 80%) of the estimated maximum effect within the dose range under consideration, assuming the intercurrent event handling **and endpoints** are defined like in phase 3.
    - Different health authorities may require different handling strategies.
- For safety, what is the highest dose (continuous within the dose range tested) that corresponds to an increase of <10 percentage-points in absolute risk for a composite safety event (a SAE, an AESI, or treatment discontinuation due to an AE) vs. SoC, while patients are on treatment?

Possible outcomes from the trial:

- Efficacy plateau reached within the tested range
- Efficacy still on the up-slope at the top dose tested
- Safety limits the dose before full efficacy

Step 2: Identify intercurrent events

The intercurrent events are as follows:

- Treatment discontinuation due to lack of efficacy or safety concerns
- Initiate disallowed concomitant therapy; initiate or increase SLE/CLE standard of care therapy; or initiate or increase corticosteroid dose above baseline

Step 3: Discuss strategies to address intercurrent events

Treatment discontinuation due to lack of efficacy and Treatment discontinuation due to safety concerns

- Estimand (primary efficacy): **Hypothetical**: to get the pure effect of the treatment
- Estimands (supplementary efficacy): To follow similar handling strategies as in phase 3 trials.
    - Most likely: **Treatment Policy** strategy

    - Also plausible request: **composite** strategy. In this case two separate estimands may be created to cover both cases.
- Estimand (safety): Via the **While-on-Treatment strategy** for 'lack of efficacy' as interest is in AEs in relation to exposure to treatment; and via **composite** for 'lack of safety', because this is an event of interest.

Intercurrent events of initiate disallowed concomitant therapy, initiate or increase SLE/CLE standard of care therapy, or initiate or increase corticosteroid dose above baseline

They indicate both a lack of efficacy and also the use of new medication that may improve outcomes

- Estimand (primary efficacy): **Hypothetical**: to get the pure effect of the treatment.
- Estimands (supplementary efficacy): To follow similar handling strategies in phase 3 trials.
- Estimands (safety): **Treatment Policy** – two reasons: (1) definition of endpoint (a SAE, an AESIs, or discontinuation due to AEs) is sufficiently specific (e.g., AESI can be targeted towards viral infections like Herpes Zoster that may result from inhibiting type I interferon production) and (2) difficult to know whether an AE is from the new medication or due to the study drug.

The specific intercurrent event handling methods proposed are for illustrative purposes and should be tailored for each trial. The key takeaway is the application of the estimand thinking process in a dose-ranging context.

Step 4: Construct the estimands

The primary efficacy clinical question of interest is:

In patients with moderate or severe cutaneous lupus erythematosus, what is the dose of litifilimab (mg SC) that gives 80% of the estimated maximum therapeutic effect within the dose range, measured by percent reduction from baseline in CLASI-A score at week 16, if all participants adhered to the investigational treatment without discontinuation due to lack of efficacy or safety concerns, and without initiating disallowed concomitant therapies or increasing baseline SoC/corticosteroid doses?

The primary efficacy estimand is defined by the five attributes:

- Treatment: litifilimab in doses ranging from 50 mg to 450 mg SC on top of SOC, compared to placebo on top of SoC
- Population: patients with moderate or severe cutaneous lupus erythematosus (CLASI-A score >= 8)
- Endpoint: Percent reduction from baseline in CLASI-A score at Week 16.
- Intercurrent events and strategies: A hypothetical strategy is used for treatment discontinuation due to lack of efficacy or safety concerns, initiation of disallowed concomitant therapy, initiation or increase of SLE/CLE standard-of-care therapy, and initiation or increase of corticosteroid dose above baseline.
- Population-level summary: the dose of litifilimab, in mg SC, corresponding to 80% of the maximum placebo-adjusted mean percent reduction within the dose range under consideration.

The safety clinical question is:

In patients with moderate or severe cutaneous lupus erythematosus, what is the dose that corresponds to an increase of <10 percentage-points in absolute risk for a composite safety event (defined as SAE, AESI, or treatment discontinuation due to an AE) vs. SoC by Week 16 within the dose range under consideration, while participants are on treatment, and regardless of whether participants initiated/increased concomitant therapies?

The safety estimand is defined by the five attributes:

- Treatment: litifilimab in doses ranging from 50 mg to 450 mg SC on top of SOC, compared to placebo on top of SoC
- Population: patients with moderate or severe cutaneous lupus erythematosus (CLASI-A score >= 8)
- Endpoint: A composite safety event (defined as a SAE, AESI, or treatment discontinuation due to an AE)
- Intercurrent events and strategies: A while-on-treatment strategy is used for treatment discontinuation due to lack of efficacy, so that safety events are considered while participants are exposed to the assigned investigational treatment. A composite strategy is used for treatment discontinuation due to safety concerns, because treatment discontinuation due to an AE is itself included in the composite safety endpoint. A treatment policy strategy is used for initiation of disallowed concomitant therapy, initiation or increase of SLE/CLE standard-of-care therapy, and initiation or increase of corticosteroid dose above baseline; safety events are counted regardless of these concomitant therapy changes.
- Population-level summary: the dose of litifilimab, in mg SC, corresponding to an absolute risk increase of <10 percentage-points for a composite safety event vs. SoC within the dose range under consideration.

The supplementary efficacy clinical question of interest (aligned to likely regulatory expectation) is:

In patients with moderate or severe cutaneous lupus erythematosus, what is the dose of litifilimab (mg SC) that gives 80% of the estimated maximum therapeutic effect, measured by CLASI-50 response (at least a 50% reduction from baseline in the CLASI-A score) at week 16, regardless of whether participants discontinued treatment due to lack of efficacy or safety concerns, or initiated disallowed concomitant therapies?

The CLASI-50 binary endpoint is more closely aligned to late-phase trials.

The supplementary efficacy estimand is defined by the five attributes:

- Treatment: litifilimab in doses ranging from 50 mg to 450 mg SC on top of SOC, compared to placebo on top of SoC
- Population: patients with moderate or severe cutaneous lupus erythematosus (CLASI-A score >= 8)
- Endpoint: CLASI-50 response (at least a 50% reduction from baseline in the CLASI-A score) at week 16
- Intercurrent events and strategies: A treatment policy strategy is used for treatment discontinuation due to lack of efficacy or safety concerns, initiation of disallowed concomitant therapy, initiation or increase of SLE/CLE standard-of-care therapy, and initiation or increase of corticosteroid dose above baseline.
- Population-level summary: the dose of litifilimab, in mg SC, corresponding to 80% of the increase in proportion of patients achieving CLASI-50 response vs. SoC within the dose range under consideration.

Step 5: Align choices on trial design, data collection and method of estimation

Trial design

Number of doses tested: To enable flexibility of fitting models with up to four parameters, at least five doses (four active and one placebo dose) should be used. The dosing frequency will be every four weeks, with an additional dose at week 2.

Data collection:

Participants are to remain in the study after all intercurrent events, because the Treatment Policy strategy is applied in at least one estimand for all intercurrent events identified.

Method of estimation:

Primary efficacy estimand:

A two-step approach will be used.

First, an MMRM model will be fitted to generate Least Square Means (marginal means) at week 16 for various treatments (placebo and doses tested) and associated uncertainty (in the form of variance-covariance matrix of the LS means at each dose level and placebo). Data collected after the intercurrent events handled by the hypothetical strategy will be set to monotone missing.

Second, a EMax model will be fitted based on the estimated LS Means and associated uncertainty (in the form of a variance-covariance matrix of the LS Means.) Based on the EMax model, the dose (continuous within the dose range tested) that gives 80% of the estimated maximum effect within the dose range under consideration (ED80) can be calculated.

Uncertainty of ED80 can be quantified via bootstrapping participants with replacement.

Safety estimand

A logistic regression model will be used to model the dose-dependent relationship with safety.

The dose that corresponds to an absolute risk increase of <10 percentage-points for a composite safety event (defined as a SAE, an AESI, or treatment discontinuation due to an AE) vs. SoC Week 16 within the dose range under consideration will be calculated from the logistic regression model.

Step 6: Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions

Primary efficacy estimand:

The primary analysis used the Emax model, which assumes monotonicity of efficacy. Alternative dose-response models that do not enforce monotonicity can be used.

Furthermore, the observed value, rather than the model-estimated value, can be used to determine the “maximum therapeutic effect.”

Safety estimand

The logistic regression model assumes that the log-odds of the safety event are linear in log dose. Alternative models, such as isotonic regression, can be used, with linear interpolation to determine the probability of a composite safety event between tested doses.

Step 7: Document the estimand

The estimand will be documented in the protocol and SAP.

Additional information related to safety for contextualization

In the phase 2 trial's 450 mg litifilimab group (N=48) (AE results unknown when designing the phase 2 study), 3 participants (6%) had SAEs, 4 (8%) discontinued due to AEs, and 1 (2%) experienced oral herpes. Accounting for potential overlap between these categories, between 4 and 8 unique individuals (~ 8% to 17%) experienced an SAE, discontinued due to an AE, or had oral herpes (a potential AESI) by week 16.

The maximum dose tested in Phase 1 (20 mg/kg IV) is higher than the maximum dose in Phase 2 (450 mg SC). It is also noted in the protocol that “Cumulative exposure of 450 mg SC Q4W with additional dose at week 2 in Phase 2 is comparable or lower, than the highest dose tested in Phase 1 (20 mg/kg IV).” “Furthermore, this dose regimen with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45 is expected to result in cumulative exposure comparable to or lower than that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers”

References

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