LEADER 3D: Bayesian Statistics in Rare Disease Clinical Investigations

Belimumab (Benlysta)

Before reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. The small population affected by a rare disease presents additional considerations that must be addressed and also calls for appropriate flexibility. **Please note this case study is not intended or designed to provide specific strategies for obtaining product approval.** Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Learning Objectives

After reading this case study you will:

- Have a greater understanding of how Bayesian statistical methods can be used to borrow information from external sources (e.g., adult trials, natural history studies) to support efficacy determinations when traditional statistical approaches are not feasible due to small sample sizes in rare disease populations.
- Be aware of how pediatric extrapolation can be implemented through Bayesian analysis when there is sufficient evidence of similarity in disease course, pathophysiology, drug pharmacology, and treatment response between adult and pediatric populations.
- Have a greater understanding of how a robust mixture of prior approaches allows dynamic discounting of external information based on the degree of similarity between prior data and current trial data, ensuring findings remain robust even when external information differs from observed results.

To access FDA guidance documents for rare disease drug development organized by topic, please scan this QR code.

Case Study Summary

This case study describes the use of a Bayesian analysis design to determine the efficacy of belimumab for the treatment of systemic lupus erythematosus (SLE) in pediatric patients. Due to the rarity of childhood-onset SLE (cSLE), the Applicant was unable to enroll a sufficiently large patient population to effectively conduct formal statistical inference testing. FDA requested that the Applicant conduct a post hoc Bayesian analysis of the pediatric study (C1109) that borrowed information from the previous adult studies (C1056 and C1057) that supported approval of belimumab for adults with SLE. Importantly, the pediatric trial used the same primary endpoint as the adult trials, the SLE response index (SRI-4), which represents a novel composite endpoint.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics in the case study. For up-to date guidance documents please search Guidance Documents for Rare Disease Drug Development | FDA.

Key Concept: Bayesian Statistical Methods

Bayesian approaches combine prior knowledge relevant information with new data (e.g., clinical trial data) to yield probabilities that can be used to draw conclusions about efficacy or safety.[1] Bayesian approaches differ from traditional statistical approaches because classical statistical approaches are based only on new data and do not incorporate any prior beliefs.[2]

Prior knowledge can be based on many different sources (e.g., previous trials, registries, and natural history studies) and help address challenges such as limited number of participants and insufficient clinical trial data.[2] These Bayesian methods can also be beneficial for pediatric populations because we often have information from other source populations (e.g., adults, adolescents), which, when clinically appropriate, can be borrowed for pediatric assessment.[2,3] Bayesian methods, like the robust mixture prior approach used in this case study, are one way to implement such an analysis as they allow the amount of borrowing to be varied based on how similar the outcomes are.

When borrowing prior information, we have to consider evidence of similarity for the disease, drug pharmacology, and response to treatment between the two populations.[3] The degree of uncertainty about the effects in the target population also needs to be considered and addressed in the study design process before data collection begins. Assessments of the similarity and uncertainty are multidisciplinary and often complex. Borrowing too much information means the uncertainty about the effects in the target population may not be addressed; borrowing too little means the planned study will need more patients.

Bayesian approaches also offer viable solutions to rare disease drug product development because they are well suited for adaptive clinical trials.[4,5] These trials provide greater flexibility than traditional randomized controlled trials (RCTs) and have the potential to improve trial efficiency, shorten drug development timelines, and address unique challenges that limit an Applicant's ability to conduct rare disease treatment investigations.

Bayesian approaches can be applied across various scenarios of rare disease drug product development. Applicants are encouraged to consult with FDA on how Bayesian designs can be appropriately applied to their development program.

FDA Guidance Corner (Continued)

In this case study, the additional support for demonstrating efficacy of belimumab for treating pediatric SLE was obtained with the use of a post hoc Bayesian analysis conducted in consultation with FDA. Applicants are encouraged to consult with FDA on whether their proposed approaches to clinical trial design, including the use of Bayesian methodologies, can be beneficial to their development programs. This guidance represents the Agency's current thinking on drug development for rare diseases and provides important considerations for Applicants working in these areas.

Guidance for Industry Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023)

It is important that plans to use innovative clinical investigation designs be discussed in advance with the review division, ideally at the pre-investigational new drug application (pre-IND) meeting. Examples of innovative or nontraditional approaches in rare diseases include Bayesian methods, n-of-1 clinical investigations, randomized delayed-start designs, crossover designs, and master protocols (where a common placebo arm is shared among different drug arms).

For example, sponsors may be able to use Bayesian methods to maximize the use of information gleaned from early-phase studies or natural history studies. Bayesian methods also may inform pediatric clinical investigations through incorporation of adult clinical data.

The design of clinical investigations may allow early evidence to be used later in a clinical investigation, which may be especially helpful when there are limited numbers of participants to study, as is the case in rare diseases. If an adaptive clinical investigation design is under consideration, a detailed statistical analysis plan including the key features of the clinical investigation design and preplanned analyses (including interim analyses) should be discussed with the review division before clinical investigation initiation.

This guidance document, which, when final, will represent the Agency's current thinking, provides recommendations on the appropriate use of Bayesian methods in clinical trials, including their application in study design, interim analyses, and primary inference to support evaluation of effectiveness and safety.

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1 Using Bayesian statistical approaches to advance our ability to evaluate drug products

2 Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry

3 E11A Pediatric Extrapolation Guidance for Industry

4 Bayesian Methods in Human Drug and Biological Products Development in CDER and CBER

5 Bayesian Strategies in Rare Diseases

Introduction to the Rare Disease: Systemic Lupus Erythematosus

SLE is a chronic autoimmune disease characterized by autoantibody production with systemic inflammation due to immune dysregulation that may manifest as the disease flares, alternating with periods of remission. The estimated prevalence of SLE is 20 to 73 per 100,000 in adults and disease manifestation is most common between the ages of 15 and 40 years, with women at greater risk than men of developing SLE. 10-20% of SLE patients experience disease onset during childhood (cSLE), and the prevalence of cSLE is estimated to range between 1.1 to 9.7 per 100,000. SLE can affect various organ systems in the body (e.g., kidneys, heart, lungs, or brain) with a wide range of symptoms, including fatigue, joint pain, skin rashes, and fever. The exact cause of SLE is not fully understood but is believed to involve a combination of genetic, environmental, and hormonal factors. Diagnosis of SLE relies on a combination of clinical evaluation, laboratory tests, and the presence of specific criteria set by professional medical organizations.

Current Treatment Options

Although several treatments for SLE are approved for adult populations, no FDA-approved therapies existed for cSLE before belimumab received approval for pediatric patients ages 5 years to 17 years of age. Based on anecdotal reports and non-registrational studies, pediatric patients were typically managed with combinations of immunosuppressive medications. These regimens, which can include corticosteroids and hydroxychloroquine, are used off-label in children without well-characterized evidence of efficacy and safety. This gap highlights the unmet need for safe and effective therapies for cSLE.

Belimumab Mechanism of Action

Belimumab is a monoclonal antibody that inhibits the soluble human B-lymphocyte stimulator (BLyS) protein. BLyS promotes survival, maturation, and differentiation of B-cells, including autoreactive B-cells, by activating signaling pathways that increase antiapoptotic proteins.[6] Belimumab blocks soluble BLyS from binding to B-cell receptors, reducing antiapoptotic protein production. This action decreases B-cell survival and differentiation into antibody- and autoantibody-producing cells, leading to cell death via

Draft Guidance for Industry Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products (January 2026)

Pediatric extrapolation is defined in the ICH E11(R1) guideline as "an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population." Pediatric extrapolation can extend what is known about the characteristics of interest in the reference population (e.g., efficacy, safety, and/or dosing) to those of the target population based on an assessment of the relevant similarities of disease, drug pharmacology, and response to therapy of the two populations.

When some degree of pediatric extrapolation is justified, Bayesian methods can be considered to borrow data from adults in the analysis of a pediatric trial by using an informative prior distribution constructed based on results from previous adult trials.

Key Terminology: Robust Mixture Prior

A **robust mixture prior** is a Bayesian approach used to combine prior information from previous trials with new data in a way that allows dynamic discounting when the prior and current data differ. The prior consists of two components:

- **An informative component** that reflects the prior information intended to be borrowed, and
- **A minimally informative distribution** that is equivalent to observing a very small number of patients with no overall effect acts as a **robust component**.

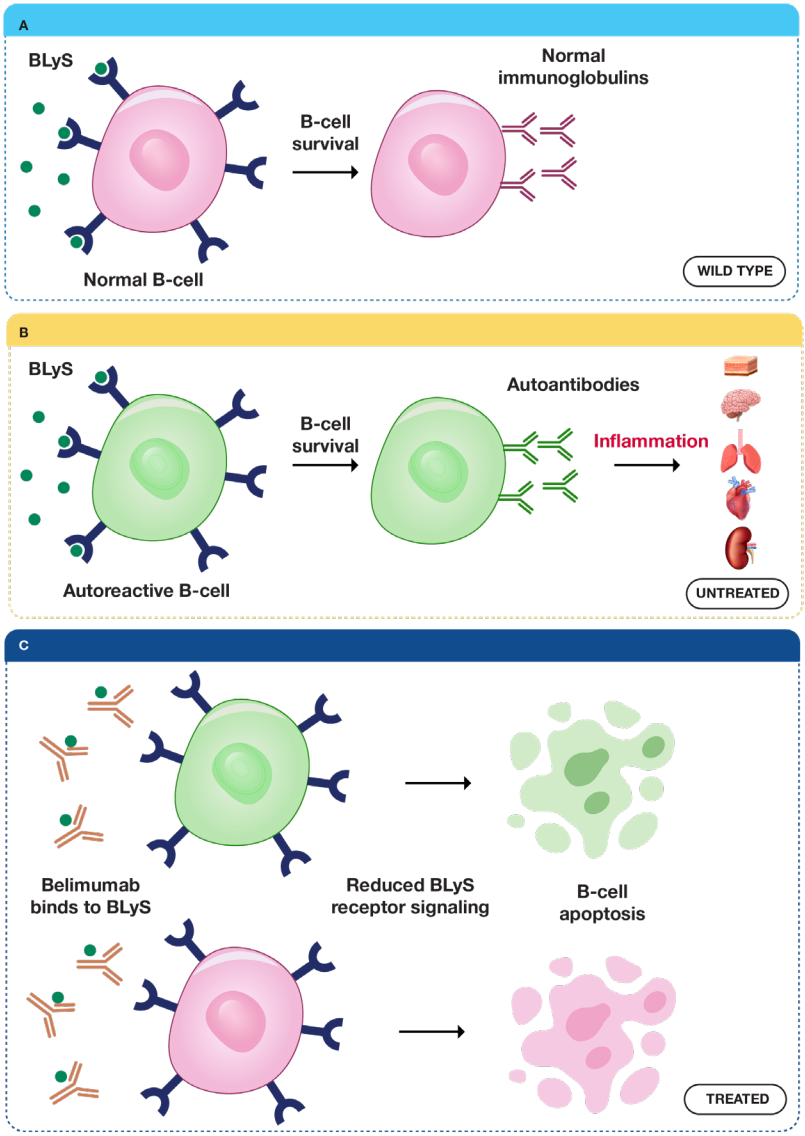
These components are blended using a prespecified borrowing weight (w) between 0 and 1, which allows variable levels of discounting and enables assessment of different degrees of borrowing. When w = 1, the prior relies entirely on the informative component; when w = 0, it relies entirely on the robust component. This structure allows the model to adapt the degree of borrowing based on the degree of similarity between the previous data and the current data, helping to ensure that findings remain robust even if external information differs from what is observed in the current study.

For more information on the use of robust mixture priors, please refer to Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States.

[6] Belimumab: a BLyS-Specific Inhibitor for the Treatment of Systemic Lupus Erythematosus

apoptosis. Thus, by inhibiting BLyS, belimumab facilitates apoptosis of autoreactive B-cells, limiting production of autoantibodies, and reducing systemic inflammation (**Figure 1**). Belimumab was approved by FDA as a therapeutic biologic product and has been marketed in the U.S. since 2011 as an intravenous (IV) formulation for the treatment of adult patients with SLE. In 2017, an alternative subcutaneous injection formulation packaged as a ready-to-use, pre-filled syringe and autoinjector was also approved for adults with SLE.

Figure 1: *Normal B-cell maturation, SLE pathophysiology and belimumab mechanism of action. Soluble human B-lymphocyte stimulator (BLyS) binds to receptors on both normal (pink) and autoreactive (green) B-cells. This interaction promotes B-cell survival, maturation, and differentiation via signaling pathways that upregulate antiapoptotic proteins. In SLE, immune dysregulation enhances autoantibody production by mature autoreactive B-cells, driving systemic inflammation. Belimumab blocks the binding of BLyS to receptors on autoreactive B-cells lowering autoantibody production and reducing systemic inflammation.*



Bayesian Analysis

A pediatric trial (C1109) was conducted to fulfill the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) trial related to the approval of belimumab for IV administration in adults with SLE. With this study, the Applicant proposed to expand the present belimumab IV administration indication to include the treatment of children 5 to 17 years of age with active, seropositive cSLE who were receiving standard therapy. Determination of efficacy was based on pharmacokinetic (PK) and efficacy results from this study, as well as PK exposure and extrapolation of the established efficacy of belimumab plus standard therapy from the previous adult studies (C1056 and C1057). Initially, 100 cSLE pediatric patients receiving standard of care (SOC) between the ages 5-17 were proposed to participate in the C1109 pediatric clinical trial. However, the Applicant encountered difficulties with patient recruitment due to the rarity of cSLE. Attempts to enhance enrollment among pediatric patients in C1109 included protocol amendments to broaden the inclusion and exclusion criteria.

Despite these modifications, the recruited sample size was smaller than planned and could not support an adequately powered phase 3 trial for formal statistical inference using traditional statistical approaches. Due to this statistical uncertainty, additional support for the efficacy findings of the pediatric trial was obtained from a post hoc Bayesian analysis, which borrowed information from the previous adult trials C1056 and C1057.[7] In Bayesian

[7] Please refer to the Integrated Review on page 99 for additional information on why Bayesian analysis was utilized for study C1109 - https://www.accessdata.fda.gov/drugsatfda_docs/pediatric/125370S64%20belimumab%20unireview%20prea.pdf

analysis, borrowing refers to incorporating information from external sources into the estimation of a treatment effect through the prior distribution. Bayesian methods allow data to be borrowed in a continuous fashion to strengthen inference when sample sizes are limited.[8]

The treatment responses to belimumab were expected to be similar between pediatric and adult patients, and thus, adult phase 3 trials of IV belimumab (C1056 and C1057) could be relevant to the expansion of IV belimumab administration in pediatric populations. In consultation with and at the request of the Agency, the Applicant performed a post hoc analysis using a Bayesian mixture prior approach where information from the adult trials (C1056 and C1057) was borrowed to supplement the comprehensive data obtained from the pediatric trial (C1109).[8] The decision to borrow information from adult studies was based on evidence of similarity between the pediatric and adult populations, with the trials sharing the same primary endpoint (SRI-4), similar inclusion criteria and disease characteristics, and comparable pharmacokinetic exposure profiles. These similarities supported the assumption that adult efficacy data were relevant to the pediatric population, providing a scientific basis for borrowing while acknowledging the uncertainty using a robust mixture prior. For this analysis, the Bayesian mixture prior approach combined the data from the placebo and 10 mg/kg dose treatment arms from the two adult trials (C1056 and C1057). Combined data from these two trials formed one component of the prior (i.e., when w = 1) and a minimally informative distribution (i.e., when w = 0 and borrowing relies entirely on the robust component), formed the other component. The degree of relative weighting between these two components is a key component of the Bayesian analysis because it controls the degree of borrowing from the adult trials and can be varied to yield different amounts of borrowing. The analysis explored the entire spectrum of borrowing strengths from no borrowing to full borrowing to give a complete picture of the possible outcomes.

Highlights

Clinical Development of Belimumab for Adults

Studies C1056 and Study C1057 were phase 3, multicenter, double-blind, placebo-controlled, randomized trials conducted in adult patients diagnosed with active seropositive SLE. All patients were receiving stable standard of care (SOC) immunosuppressive medication to manage their condition. Eligible participants were randomly assigned in a 1:1:1 ratio to one of three different treatment groups: 1 mg/kg IV, 10 mg/kg IV, or placebo IV.

Studies 1056 and 1057 both demonstrated superiority of belimumab 10 mg/kg IV over placebo plus SOC based upon the primary efficacy endpoint SLE response index (SRI-4) at week 52. FDA approved the IV formulation of belimumab for the treatment of adult patients with active, autoantibody positive SLE receiving standard therapy.

Engagement Tip

Work with FDA early in the drug development process to seek alignment on a statistical analysis plan

Bayesian statistical approaches can benefit rare disease drug development programs and are encouraged by FDA when appropriately justified. When assessing if your program is not well suited for frequentist statistical analyses, consider the Critical Thinking Questions on page 12. The Agency provides several types of engagement opportunities to advise sponsors seeking specific information on the development and review of investigational new drugs, biologics, and drug or biological product marketing applications, which are outlined in the draft guidance document, which, when final, will represent the Agency's current thinking, titled *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.*

Sponsors should discuss their statistical analysis plan with FDA prior to initiating a pivotal trial. For example, Type B end-of-phase (EOP) 2 meetings are intended to help sponsors evaluate phase 3 plans and protocols and the adequacy of current studies to assess safety and effectiveness. Sponsors may use these meetings to consult on fit-for-purpose statistical approaches that may benefit their development program and minimize the need for post hoc analyses of clinical trial data.

[8] For more information on how this approach contributed to FDA's decision to approve belimumab as the first treatment for cSLE, please refer to Pottackal, et al. "Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States." Lupus 34.9 (2025): 943-952

Use of Adult Clinical Trial Data to Inform the Pediatric Trial

To conduct the Bayesian analysis, it was essential that the Applicant selected the same clinically relevant endpoint in both populations.[9] Therefore, as shown in **Table 1**, the pediatric trial adopted the same primary efficacy endpoint as the adult trial (i.e., SRI-4 response rate at Week 52) and included all major secondary endpoints used in the adult trial (**Table 1**). The SRI-4 is a composite endpoint intended to capture both meaningful clinical improvement and the absence of disease worsening across key organ systems. In line with the ICH E9(R1) addendum, which emphasizes the importance of clearly defining the estimand as part of aligning clinical objectives, trial design, and analysis,[10] the use of the SRI-4 endpoint in both adult and pediatric trials supported a consistently defined treatment effect across studies. SRI-4 incorporates a composite strategy for addressing intercurrent events (e.g., disease worsening or flare), consistent with E9(R1) recommendations for handling such events when they are clinically meaningful and informative.[11]

In study C1109, an SRI-4 response required that a participant meet all the following criteria at Week 52:

1. Achieve a ≥4-point reduction from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) which quantifies global SLE disease activity across multiple organ systems, indicating clinically meaningful improvement in overall lupus disease activity. (Note: SELENA SLEDAI is a scoring system for SLE containing 24 descriptors across 9 organ systems, scored over the preceding 10 days, which is designed to assess disease activity and define disease flares).[12]
2. Have no worsening in the Physician's Global Assessment (PGA), defined as an increase of <0.30 points from baseline.
3. Have no new British Isles Lupus Activity Group (BILAG) A organ domain score and no more than one new BILAG B organ domain score compared with baseline; and
4. Not meet any protocol-defined treatment failure criteria and not drop out of trial before the Week 52 assessment.

In addition, the C1109 pediatric trial adopted the inclusion criteria, pharmaceutical form, route of administration, and dosing of belimumab (10 mg/kg) used in the two pivotal phase 3 adult studies (C1056 and C1057), with necessary modifications for pediatric treatment (**Table 1**). Like the adult SLE participants in the C1056 and C1057 trials, pediatric participants in the C1109 trial were required to have a clinical diagnosis of cSLE in accordance with the American College of Rheumatology (ACR) criteria and an Anti-Nuclear Antibody (ANA) titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL. The initial SELENA SLEDAI score requirement in the pediatric trial was higher (≥8) at screening but was later eased to match the score requirement of the adult trial (≥6 at screening) to improve recruitment.[13]

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[9] Please refer to the Integrated Review on page 100 for additional information on the Bayesian mixture prior approach utilized for study C1109 - https://www.accessdata.fda.gov/drugsatfda_docs/pediatric/125370S64%20belimumab%20unireview%20prea.pdf

[10] Please refer to Section A.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

[11] Please refer to Section A.3.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

[12] American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria, (2004, "The American College of Rheumatology response criteria for systemic lupus erythematosus clinical trials: measures of overall disease activity". Arthritis & Rheumatism, 50(11), 3418-3426

[13] Pottackal, et al. "Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States." Lupus 34.9 (2025): 943-952

***Table 1**: Study Design Features of Pediatric and Adult Studies Pertinent to Efficacy and Safety*

Trial Identity	Study Population	No. of Participants Enrolled	Trial Design	Regimen/ Schedule/ Route	Study Endpoints
C1109	Pediatric participants ≥ 5-17 years old with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 6 at screening with positive auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to day 0	N = 93 • n=13 participants 5-11 years old • n=80 participants 12-17 years old	Part A: Multicenter, randomized, double-blind, placebo controlled, parallel pediatric group study Part B: Long-term open-label safety follow-up for participants who completed Part A Part C: Long-term safety follow-up for participants who withdrew any time from Part A or Part B	Belimumab 10 mg/kg or placebo intravenous infusions on days 0, 14, 28, and every four weeks thereafter until week 52	SRI response at Week 52 defined as the proportion of participants with: • ≥ 4-point reduction from baseline in SELENA SLEDAI score, and; • No worsening (increase of ≥0.30 points from baseline in PGA) and; • No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline and; • Participant does not drop out before Week 52 and; • Does not meet treatment failure criteria
C1056	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with positive auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to day 0	N = 819 • Belimumab 1 mg/kg = 271 participants • Belimumab 10 mg/kg = 273 participants • Placebo = 275 participants	Multicenter, randomized, double-blind, placebo controlled, 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg, or placebo intravenous infusions on days 0, 14, 28, and every four weeks thereafter until week 52	SRI response at Week 52 defined as the proportion of participants with: • ≥ 4-point reduction from baseline in SELENA SLEDAI score, and; • No worsening (increase of ≥0.30 points from baseline in PGA) and; • No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline and; • Participant does not drop out before Week 52 and; • Does not meet treatment failure criteria
C1057	Adults age ≥ 18 years with SLE defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with positive auto-antibodies on stable SLE treatment regimen for ≥ 30 days prior to day 0	N = 865 • Belimumab 1 mg/kg = 288 participants • Belimumab 10 mg/kg = 290 participants • Placebo = 287 participants	Multicenter, randomized, double-blind, placebo controlled, 76-week comparative parallel group trial	Belimumab 1 mg/kg, 10 mg/kg, or placebo intravenous infusions on days 0, 14, 28, and every four weeks thereafter until week 52	SRI response at Week 52 defined as the proportion of participants with: • ≥ 4-point reduction from baseline in SELENA SLEDAI score, and; • No worsening (increase of ≥0.30 points from baseline in PGA) and; • No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline and; • Participant does not drop out before Week 52 and; • Does not meet treatment failure criteria

SLE: Systemic Lupus Erythematosus; ACR: American College of Rheumatology; SELENA SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index; SRI: SLE response index; PGA: Physician's Global Assessment; BILAG: British Isles Lupus Activity Group

Pediatric Trial and Bayesian Analysis Results

The pediatric trial C1109 was a multicenter, randomized, double-blind, placebo-controlled trial, evaluating the PK, safety, and efficacy of belimumab plus standard of care therapy in pediatric patients with cSLE. Unlike the adult phase 3 trials of IV belimumab (C1056 and C1057), pediatric study C1109 sample size calculations were based on enrollment practicality rather than statistical power considerations, due to rarity of the disease in children. Thus, no formal statistical hypothesis testing was conducted for the primary and major secondary endpoints. Rather, the trial presented the efficacy results using descriptive statistics and calculated odds ratios with 95% confidence intervals to compare the belimumab versus placebo groups. If applicable, the trial also noted whether these results were comparable to those observed in the previously reviewed adult IV belimumab trials, C1056 and C1057.

Table 2: *Primary Efficacy Analysis of SRI Response Rate at Week 52 from Studies C1109 (Part A, the pediatric trial), 1056, and 1057*

	Study C1109		Study 1056			Study 1057		
	Placebo N=40	Belimumab 10 mg/kg N=53	Placebo N=275	Belimumab 1 mg/kg N=271	Belimumab 10 mg/kg N=273	Placebo N=287	Belimumab 1 mg/kg N=288	Belimumab 10 mg/kg N=290
Response, n (%)	17 (43.6)	28 (52.8)	93 (34)	110 (41)	118 (43)	125 (44)	148 (51)	167 (58)
Observed difference	-	9.2%	-	7%	9%	-	8%	14%
Odds Ratio (95% CI)	-	2.5 (0.6, 3.5)	-	1.3 (0.9, 1.9)	1.5 (1.1, 2.1)	-	1.6 (1.1, 2.2)	1.8 (1.3, 2.6)

The proportion of pediatric participants who achieved the primary endpoint (the SRI-4 response at Week 52) was greater in the pediatric belimumab IV group (52.8%) compared to the pediatric placebo group (43.6%) [Odds Ratio (95% CI): 1.5 (0.6, 3.5)] (**Table 2**). This efficacy finding was consistent with the efficacy results observed in the adult belimumab IV studies C1056 and C1057 (**Table 2**). These results were also supported by consistent trends in analysis of the individual SRI components, major secondary endpoint (Pediatric Rheumatology International Trials Organization/American College of Rheumatology), and other secondary analyses, such as the sustained SRI response and sustained ParentGA. Additionally, pediatric participants randomized to belimumab had a lower risk of experiencing a severe flare compared to the placebo group, as well as a longer duration of time to severe flare (160 days versus 82 days, respectively).

The clinical pharmacology team also reviewed the available PK data and noted similar steady state exposure parameters (Cmax, Cmin, Cavg, and AUC)[14] between pediatric SLE and adult SLE patients, supporting the efficacy and safety findings in Study C1109.

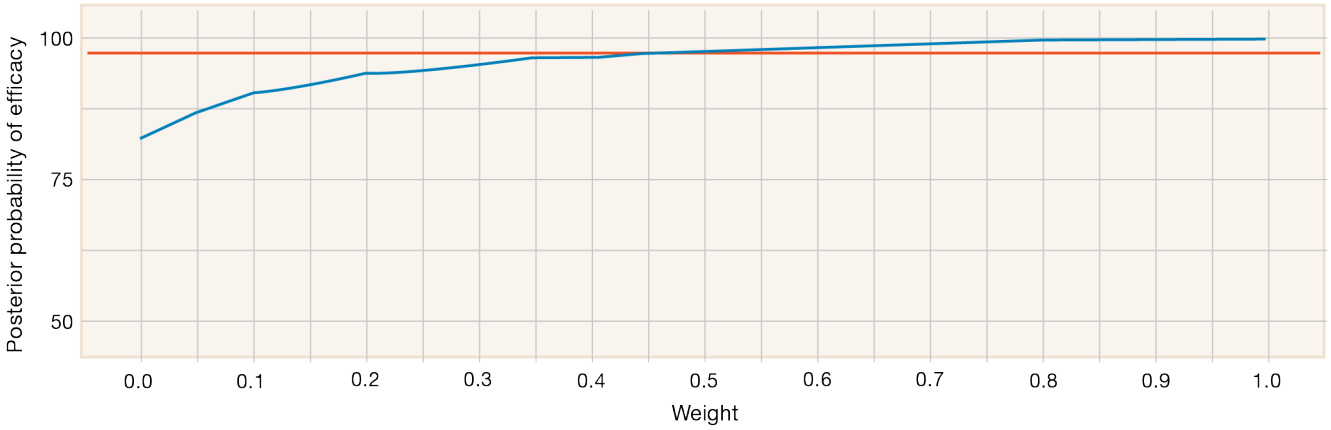
Bayesian analysis evaluating the primary endpoint (SRI-4 at Week 52) of the pediatric trial indicated that the posterior probability of efficacy (i.e., a positive treatment effect) was at least 97.5% when the prior weight was 0.55 or more (**Figure 2**). This posterior probability of efficacy was computed by calculating the percentage of posterior samples where the sampled treatment effect was greater than zero. Consistent with ICH E9(R1), which identifies sensitivity analysis as essential for evaluating the robustness of treatment effect estimates and introduces tipping-point logic as a structured method for this purpose,[15] the Bayesian analysis examined how the posterior probability of efficacy changed across a range of prior weights assigned to adult data. This approach ensured that conclusions were not unduly sensitive to any single set of assumptions. The review division determined that it was reasonable, based on a clinical assessment of the available supporting evidence on the disease and response similarity between adult and pediatric

[14] Belimumab (Benlysta) Label

[15] Please refer to Section A.5.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

patients, to assume a weight of at least 0.55 (corresponding to at least a 55% probability that efficacy in pediatric patients is similar to that in adults) to statistically conclude that the treatment effect of belimumab in the pediatric population favored belimumab compared to placebo.

Figure 2: *Bayesian Analysis of SRI-4 Endpoint. Posterior probability of efficacy across different weight values indicates there is at least a 97.5% posterior probability that belimumab 10 mg/kg has a positive effect in pediatric participants when at least a 55% weight on the relevance of the adult information to the pediatric population is assumed. (97.5% threshold displayed in red).*



FDA Guidance Corner

In this case study, a fully powered phase 3 trial was not feasible due to the rarity of cSLE. FDA's clinical review team believed that both the disease and patient response to treatment would be similar between adults and pediatric patients which would allow the implementation of Bayesian methods borrowing information from the previous adult trials (C1056 and C1057). The guidance documents below represent the Agency's current thinking on the use of Bayesian methodologies and important considerations for sponsors interested in applying these methods to their development programs.

Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics (December 2019)

The term Bayesian adaptive design has been used to refer to a wide variety of clinical trial designs that use Bayesian statistical reasoning and/or calculations in various ways.[16] Some examples of Bayesian adaptive design features are:

- Use of predictive statistical modeling, possibly incorporating information external to a trial, to govern the timing and decision rules for interim analyses
- Use of assumed dose-response relationships to govern dose escalation and selection
- Explicit borrowing of information from external sources, e.g., previous trials, natural history studies, and registries, via informative prior distributions to improve the efficiency of a trial
- Use of posterior probability distributions to form trial success criteria

In general, the same principles apply to Bayesian adaptive designs as to adaptive designs without Bayesian features. Trial designs that use Bayesian adaptive features may rely on frequentist or Bayesian inferential procedures to support conclusions of drug effectiveness. Frequentist inference is characterized by hypothesis tests performed with known power and Type I error probabilities and is often used along with Bayesian computational techniques that rely on non-informative prior distributions. Bayesian inference is characterized by drawing conclusions based directly on posterior probabilities that a drug is effective and has important differences from frequentist inference (Berger and Wolpert 1988). For trials that use Bayesian inference with informative prior distributions, such as trials that explicitly borrow external information, Bayesian statistical properties are more informative than Type I error probability.

[16] Berry, S. M., Carlin, B. P., Lee, J. J., & Muller, P. (2010). Bayesian adaptive methods for clinical trials. CRC press.

FDA Guidance Corner (continued)

Guidance for Industry Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products (December 2020)

Bayesian approaches may be well-suited for some complex innovative trial designs (CID) intended to provide substantial evidence of effectiveness because they can provide flexibility in the design and analysis of a trial, particularly when complex adaptations and predictive models are used. In addition, Bayesian inference may be appropriate in settings where it is advantageous to systematically combine multiple sources of evidence, such as extrapolation of adult data to pediatric populations, or to borrow control data from Phase 2 trials to augment a Phase 3 trial (see section IV of this guidance).

If a sponsor chooses to submit a Bayesian CID proposal, FDA's evaluation of the proposal relies on clear communication between the sponsor and FDA regarding two areas: the prior distribution and the study decision criteria for primary and key secondary endpoints. Bayesian approaches that formally borrow information external to a trial may not be appropriate for every development program. When submitting a Bayesian CID proposal with borrowing of external information, sponsors should include a rationale for the borrowing with specific details regarding how bias was avoided in the selection of the borrowed information.

Draft Guidance for Industry Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products (January 2026)

Use of a prior distribution is the main feature distinguishing Bayesian from frequentist approaches. Priors allow the analysis to reflect the available information in the particular situation, whether positive, negative, or neutral. With any Bayesian analysis, the prior construction process should be designed, implemented, and documented in a systematic and transparent manner. Sponsors should pre-specify and justify the full details of the proposed prior distribution in the protocol. This justification should address the appropriateness of the prior distribution's influence and the operating characteristics of the design, given the proposed prior.

When proposing to use an informative prior that borrows external information for inference on the primary estimand, sponsors should provide strong justification that considers feasibility (e.g., alternative approaches that do not involve borrowing) and the relevance of the available information. Areas where informative priors have been most often proposed include pediatrics and rare diseases. Additional areas can be considered on a case-by-case basis, and FDA advises early discussion of such proposals with the Agency.

Relevance: The information being leveraged should be relevant to the applicable regulatory question. When multiple information sources are used, not all information may be equally relevant. It is important to consider and discuss any planned approaches to reflect the different degrees of relevance. Factors that may influence relevance include:

- Similarity in estimand attributes such as the population (e.g., inclusion or exclusion criteria), endpoint, treatment conditions, or handling of intercurrent events
- Any differences in measurement or assessment (e.g., of the endpoint)
- Recency of data
- Any potentially important changes (e.g., in aspects of standard of care such as concomitant medications) over time

There is often a need to implement a discounting approach to reflect any residual uncertainty regarding the question of interest. For example, when using Bayesian methods to implement pediatric extrapolation, if the adult trial results were used to derive the prior without discounting, the evidence from the adults alone would already meet typically used success criteria and if a trial were conducted, the adult data would often overwhelm the pediatric data regardless of the results in the pediatric study. This would not be consistent with the uncertainty on the question of benefit in pediatric patients. Therefore, it will often be more reasonable to use a prior centered on a degree of benefit similar to what is observed in adults, but with a greater degree of variability and hence uncertainty.

There are many specific methods proposed in the scientific literature for implementing discounting. With any approach, the goal should be to identify parameter values that correspond to a reasonable degree of borrowing. What is reasonable will depend on the situation and the relevance of the borrowed data. A prior that is too informative risks overwhelming the data collected in the target population, regardless of what is observed. Leveraging too little information means not taking advantage of the available data and more information will be required in the target population, making the trial less efficient. Hence, finding the appropriate balance in the informativeness of the prior is crucial.

Conclusion

To address the limitation imposed by small sample sizes, FDA recommended a post hoc Bayesian analysis, combining data from the pediatric trial with two adult trials. This approach enabled pediatric extrapolation, allowing efficacy evidence from adult populations to strengthen the pediatric dataset and support a robust evaluation of belimumab's efficacy in the pediatric population. The evaluation of risks and benefits supported the approval of the 10 mg/kg dosing regimen of belimumab IV as a treatment for pediatric patients with active, seropositive, cSLE who have undergone standard care, based on:

1. Comprehensive findings from the well-conducted pediatric trial C1109 (an international, multicenter, randomized, double-blind, placebo-controlled trial);
2. Efficacy and safety results from two adequate and well-controlled adult trials (C1056 and C1057) previously assessed under the original marketing application; and
3. Consideration of the unmet medical need for safe and effective treatments for pediatric patients with cSLE.

Borrowing the adult information using Bayesian methods provided the statistical power necessary to overcome the limitations of a small sample size and was appropriate because:

- The disease course is sufficiently similar in adults and pediatric patients.
- There were similar PK data such as steady state exposure parameters between pediatric and adult SLE patients, supporting the efficacy and safety findings in trial C1109.
- Most of the baseline disease characteristics were similar in the pediatric and adult trial populations.
- The pediatric and adult trials had the same primary endpoint (Week 52 SRI-4 response rate), allowing for comparison across trial populations.
- Pediatric primary efficacy results were consistent with the efficacy results observed in the adult trials C1056 and C1057.
  - Like adults, pediatric participants randomized to the treatment group demonstrated a lower risk of experiencing a severe flare and a longer duration of time to severe flare compared to placebo.
- Adequate data existed to determine a prior and a posterior probability.

Key Takeaways

- When clinically appropriate, Bayesian approaches allow explicit borrowing of information from external sources, which may offer more flexibility compared to traditional statistical methods and help address unique challenges, such as small trial populations and low statistical power, that can limit an applicant's ability to conduct rare disease investigations.
- Pediatric clinical investigations can borrow data from relevant adult clinical investigations if they are designed and conducted in a similar manner (e.g., use of the same endpoints) and the disease course, pathophysiology, and the drug's pharmacologic activity are similar in both the pediatric and adult populations.
- Bayesian extrapolation analyses should be planned prospectively rather than applied retrospectively after observing the data. Applicants are encouraged to consult with FDA to determine whether, and to what extent, Bayesian methodologies can be applied to their drug development program.

Critical Thinking Questions for a Rare Disease Drug Development Program

Rare disease drug developers should engage FDA early to discuss the selection of endpoints and the statistical methods planned for their analysis. When preparing for and designing a clinical investigation for a rare disease medical product, consider the following questions:

1. If your development program is expected to face challenges not well suited for frequentist statistical analyses (e.g., small patient population and inadequate statistical inference), **would alternative statistical methodologies, such as Bayesian approaches, be suitable (or fit-for-purpose) for the development program?**
2. Is there adequate and sufficient data to establish informative priors and generate posterior probabilities?
3. Is the source of external data scientifically justifiable?
   a. To what extent do the disease course, pathophysiology, and drug's pharmacologic activity align between trial populations?
   b. How similar are the patient populations, endpoints, eligibility criteria, dosing, and trial designs across the investigations?
4. Is the level of borrowing ethically justifiable given patient risk and trial feasibility?
   a. Does your statistical analysis plan clearly outline how assumptions and special considerations will be evaluated?
   b. What criteria and statistical judgements will be used to determine the degree of borrowing, as well as to assess and quantify the degree of similarity and uncertainty?
5. How might FDA interpret the strength and supportability of the data analysis assessed using Bayesian methodology?

We recommend meeting with the Agency early[17] in the drug development program to reach alignment regarding endpoint selection, trial design, and the approach to demonstrate substantial evidence of effectiveness.

[17] Please refer to the Additional Resources section for guidance on how to engage early with FDA, including information on Critical Path Innovation Meetings, INTERACT Meetings, and Pre-IND Meetings

Additional Resources

1. Focus Area: Complex Innovative Trial Design. https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-complex-innovative-trial-design
2. Complex Innovative Trial Design Meeting Program. https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program
3. Guidance for industry: Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products (December 2020). https://www.fda.gov/media/130897/download
4. Pottackal, Ginto, et al. "Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States." Lupus 34.9 (2025): 943-952. https://journals.sagepub.com/doi/abs/10.1177/09612033251349930
5. CDER Small Business and Industry Assistance Chronicles, Using Bayesian statistical approaches to advance our ability to evaluate drug products. https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/audio-transcript-using-bayesian-statistical-approaches-advance-our-ability-evaluate-drug-products
6. BEST (Biomarkers, EndpointS, and other Tools) Resource web page (https://www.ncbi.nlm.nih.gov/books/NBK338448/)
7. Guidance for Industry: Critical Path Innovation Meetings. https://www.fda.gov/media/89497/download
8. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. https://www.fda.gov/media/172311/download
9. Draft Guidance for Industry: Early Drug Development and the Role of Pre-IND Meetings. https://www.fda.gov/media/117322/download

Case Study References by Order of Appearance

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- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.

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- See Using Bayesian Statistical Approaches to Advance our Ability to Evaluate Drug Products, available at https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/audio-transcript-using-bayesian-statistical-approaches-advance -our-ability-evaluate-drug-products
- See guidance for industry Adaptive Designs for Clinical Trials of Drugs and Biologics (2019), available at https://www.fda.gov/media/78495/download
- See guidance for industry E11A Pediatric Extrapolation (2024), available at https://www.fda.gov/media/161190/download
- See Ionan, A. C., Clark, J., Travis, J., et al, 2023, Bayesian methods in human drug and biological products development in CDER and CBER. Therapeutic Innovation & Regulatory Science, 57(3), 436-444, available at https://doi.org/10.1007/s43441-022-00483-0
- See Garczarek, U., Muehlemann, N., Richard, F., Yajnik, P., & Russek-Cohen, E, 2023, Bayesian strategies in rare diseases. Therapeutic innovation & regulatory science, 57(3), 445-452, available at https://doi.org/10.1007/s43441-022-00485-y
- See Guidance for Industry Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023) https://www.fda.gov/media/119757/download

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- See Dennis, G. J., 2012, Belimumab: a BLyS-specific inhibitor for the treatment of systemic lupus erythematosus. Clinical Pharmacology & Therapeutics, 91(1), 143-149, available at https://doi.org/10.1038/clpt.2011.290
- Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products (January 2026), available at https://www.fda.gov/media/190505/download. When final, this guidance will represent the Agency's current thinking on this topic
- See Pottackal, G., Travis, J., Nie, L., et al, 2025, Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States. Lupus, 34(9), 943-952, available at https://doi.org/10.1177/09612033251349930

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- See page 99 of the Integrated Review document for Belimumab (Benlysta), available at https://www.accessdata.fda.gov/drugsatfda_docs/pediatric/125370S64%20belimumab%20unireview%20prea.pdf

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- See Pottackal, G., Travis, J., Nie, L., et al, 2025, Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States. Lupus, 34(9), 943-952, available at https://doi.org/10.1177/09612033251349930

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- See page 100 of the Integrated Review document for Belimumab (Benlysta), available at https://www.accessdata.fda.gov/drugsatfda_docs/pediatric/125370S64%20belimumab%20unireview%20prea.pdf
- See draft guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (2023), available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic
- See Section A.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials of guidance for industry E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (2021), available at https://www.fda.gov/media/148473/download
- See Section A.3.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials of guidance for industry E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (2021), available at https://www.fda.gov/media/148473/download
- See American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria, (2004), "The American College of Rheumatology response criteria for systemic lupus erythematosus clinical trials: measures of overall disease activity". Arthritis & Rheumatism, 50(11), 3418-3426, available at https://doi.org/10.1002/art.20628
- See Pottackal, G., Travis, J., Nie, L., et al, 2025, Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States. Lupus, 34(9), 943-952, available at https://doi.org/10.1177/09612033251349930

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- See the Belimumab (Benlysta) product label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761043s034lbl.pdf
- See Section A.5.2 of the E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials of guidance for industry E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (2021), available at https://www.fda.gov/media/148473/download

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- See guidance for industry Adaptive Designs for Clinical Trials of Drugs and Biologics (2019), available at https://www.fda.gov/media/78495/download
- See Berry, S. M., Carlin, B. P., Lee, J. J., & Muller, P. (2010). Bayesian adaptive methods for clinical trials. CRC press, available at https://doi.org/10.1201/EBK1439825488

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- See guidance for industry Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products (2020), available at https://www.fda.gov/media/130897/download
- See draft guidance for industry Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products (January 2026), available at https://www.fda.gov/media/190505/download. When final, this guidance will represent the Agency's current thinking on this topic