Avalglucosidase alfa-ngpt (Nexviazyme) and Seladelpar (Livdelzi)

Use of Biomarkers as Surrogate Endpoints for Approval

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. 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.

Introduction

This case study examines the use of biomarkers as a component of demonstrating substantial evidence of effectiveness to support U.S. Food and Drug Administration (FDA) drug approvals. In the case of avalglucosidase alfa-ngpt (Nexviazyme), the Applicant used a biomarker as a validated surrogate endpoint for traditional approval, and in the case of seladelpar (Livdelzi), the Applicant used biomarkers in a composite biochemical endpoint as a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval.

Surrogate Endpoints

In rare diseases, selecting an endpoint for a clinical trial can be challenging, as the endpoint is often novel, or without precedent, in the condition being studied. Clinical investigations, including rare disease drug trials, can have endpoints that are either direct measures of the way a patient feels, functions, or survives (e.g., many clinical outcome assessments) or surrogate endpoints that are thought to indirectly measure the way a patient feels, functions, or survives. A clinical endpoint is a characteristic or variable that directly measures, or reflects, a therapeutic effect of a drug in humans—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.[1] A surrogate endpoint is a clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives.[2] A surrogate endpoint is generally a biomarker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit but is not itself a measure of clinical benefit.[1] Depending on the strength of the evidence supporting the ability of a biomarker to predict clinical benefit, the biomarker may be a surrogate endpoint that is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or a surrogate endpoint that is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in

Table of Surrogate Endpoints

The Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure on the FDA website includes surrogate endpoints that sponsors have used as primary efficacy clinical trial endpoints for approval of new drug applications (NDAs) or biologics license applications (BLAs). The table also includes surrogate endpoints that may be appropriate for use as a primary efficacy clinical trial endpoint for drug or biological product approval, although they have not yet been used to support an approved NDA or BLA.

This table serves as a reference guide to help facilitate but not replace discussions between sponsors and the relevant review divisions of potential surrogate endpoints for a specific development program.

Use of a Surrogate Endpoint

The FDA notes it is important for applicants to understand that the acceptability of surrogate endpoints for use in a particular drug or biological product development program will be determined on a case-by-case basis. It is context-dependent, relying in part on the disease, studied patient population, therapeutic mechanism of action, and availability of current treatments. A particular surrogate endpoint that may be appropriate for use in a particular drug or biological product clinical development program, should not be assumed to be appropriate for use in a different program that is in a different clinical setting.[3]

[1] Draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) which, when final, will represent the Agency's thinking on this topic.

[2] See the FDA Surrogate Endpoint Resources for Drug and Biologic Development webpage.

[3] See the Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure webpage.

accordance with section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[4] Surrogate endpoints that are known to predict clinical benefit are called validated surrogate endpoints, and those that are reasonably likely to predict clinical benefit are referred to as reasonably likely surrogate endpoints (RLSEs).

Biomarkers can act as surrogate endpoints, providing an alternative to traditional clinical endpoints when a direct measurement of clinical benefit may be impractical. A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics.[5]

According to the FDA, "validated surrogate endpoints are supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit."[6] Validated surrogate endpoints are accepted by the FDA as evidence of clinical benefit and therefore can be used to support traditional approval of a drug or biological product.

In contrast, RLSEs can be used to support accelerated approval, which provides for the approval of drugs that treat a serious condition, offer a meaningful advantage over available therapies, and demonstrate an effect on a surrogate endpoint. Accelerated approval has been used in settings in which the disease course is too long to provide more rapid access to promising therapies. Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship. Such empirical evidence may include "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."[7] Because RLSEs used for accelerated approval have not been validated, sponsors must verify the predicted clinical benefit of their products with a post-approval confirmatory trial.

Intermediate clinical endpoints that are reasonably likely to predict clinical benefit may also support accelerated approval. An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality (IMM). Approvals based on clinical endpoints (other than IMM) will be considered under accelerated approval only when it is critical to confirm the effects on IMM or other clinical benefit.

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.

In these two development programs, one Applicant used a biomarker as a validated surrogate endpoint for a traditional approval, and the other applicant used a composite biochemical surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval.

This guidance which, when final, will represent the Agency's current thinking, provides important considerations for designing a drug development program that will result in the demonstration of substantial evidence of effectiveness:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

One of the characteristics of an adequate and well-controlled clinical investigation is that "the methods of assessment of [participants'] response are well-defined and reliable." Such a method of assessment can be a clinical endpoint or, where appropriate, a surrogate endpoint. The Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit) as the basis for traditional approval. In contrast to traditional approval, accelerated approval can be based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint. Effects on intermediate clinical endpoints can also be a basis for accelerated approval. For drugs granted accelerated approval, FDA requires post-approval trials to verify the predicted clinical benefit.

Note that for accelerated approval, the evidentiary standard still applies – that is, there must be substantial evidence that the drug has a meaningful effect on the surrogate or intermediate clinical endpoint.

4 See 21 U.S.C. 356.

5 See the BEST (Biomarkers, EndpointS, and other Tools) Resource.

6 See the FDA Surrogate Endpoint Resources for Drug and Biologic Development webpage.

7 See section 506(c)(1)(B) of the FD&C Act.

Avalglucosidase alfa-ngpt (Nexviazyme)

This example highlights the use of a validated surrogate endpoint for the traditional approval of avalglucosidase alfa-ngpt as an enzyme replacement therapy (ERT) for the treatment of patients one year of age and older with late-onset Pompe disease (LOPD). Avalglucosidase alfa-ngpt is a hydrolytic lysosomal glycogen-specific enzyme created by conjugating bis-mannose-6-phosphate (bis-M6P) to oxidized sialic acid residues on alglucosidase alfa[8] (a recombinant human acid alpha-glucosidase, a previously approved ERT); this modification is hypothesized to improve its cellular uptake.

The Disease

Pompe disease (PD) is an autosomal recessive, lysosomal storage disease that results in deficient activity of lysosomal alpha-glucosidase (GAA), the enzyme that degrades glycogen to glucose in lysosomes. The GAA deficiency results in intralysosomal accumulation of glycogen in skeletal and cardiac muscle cells. This accumulation results in myopathy, respiratory weakness, physical disability, and may lead to premature death. The disease spectrum ranges from severe, rapidly progressive infantile-onset PD (IOPD) to slowly progressive, heterogeneous LOPD. The characteristics of IOPD include severe left ventricular hypertrophy and a high mortality rate within the first year of life. The characteristics of LOPD include limb girdle and respiratory muscle weakness, and premature death (in the fifth and sixth decade of life) due to respiratory insufficiency.

Drug Mechanism of Action

Avalglucosidase alfa-ngpt provides an exogenous source of GAA. The M6P on avalglucosidase alfa-ngpt mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased GAA enzymatic activity. Avalglucosidase alfa-ngpt then exerts enzymatic activity in cleaving glycogen.

FDA Guidance Corner

In this case study, the Applicant engaged with the FDA early to develop avalglucosidase alfa-ngpt as an ERT for the treatment of patients with a confirmed diagnosis of PD and designed a clinical development program to demonstrate benefit. FDA encourages applicants to engage early in the planning for the new drug application for discussion on considerations specific to the drug development plans.

This guidance highlights important considerations in rare disease drug and biologics development:

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

FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition. Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the specific challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

Biomarker Supporting Effectiveness of Avalglucosidase alfa-ngpt

The Applicant established substantial evidence of effectiveness for avalglucosidase alfa-ngpt in patients with LOPD using data from one adequate and well-controlled investigation with confirmatory evidence. The primary endpoint of the single adequate and well-controlled investigation was the effect of avalglucosidase alfa-ngpt treatment on the biomarker, Forced Vital Capacity (FVC) (% predicted), compared to alglucosidase alfa (see **Use of a Surrogate Endpoint**).[9] FVC is the total amount of air that a person can exhale after a full inhalation and is an important measurement of lung function. FVC (% predicted) was selected as the surrogate endpoint biomarker for the traditional approval of avalglucosidase alfa-ngpt because previous clinical studies conducted for the approval of the comparator, alglucosidase alfa, demonstrated that changes in FVC (% predicted) correlated with clinically meaningful outcomes.[10]

[8] See the FDA Integrated Review for alglucosidase alfa (Lumizyme).

[9] See the FDA Integrated Review for avalglucosidase alfa-ngpt (Nexviazyme).

[10] See the FDA Integrated Review for alglucosidase alfa (Lumizyme).

FVC Biomarker Results

The efficacy of avalglucosidase alfa-ngpt was evaluated in a randomized, double blind, comparator-controlled study in treatment-naïve patients with LOPD (i.e., Trial EFC14028 [COMET]). The primary objective of this trial was to determine the effect of avalglucosidase alfa-ngpt treatment on lung function as measured by the primary endpoint, FVC (% predicted) in the upright position, compared to alglucosidase alfa.

One hundred patients were randomized based on baseline FVC (% predicted; <55% or ≥55%), and other criteria (e.g., age)[11] to receive 20 mg/kg of avalglucosidase alfa-ngpt or alglucosidase alfa administered intravenously once every two weeks for 49 weeks. The estimated mean change from baseline to Week 49 in FVC (% predicted) was higher in the avalglucosidase alfa-ngpt arm (Table 1): 2.9% and 0.5% for avalglucosidase alfa-ngpt and alglucosidase alfa, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring avalglucosidase alfa-ngpt, which met pre-established noninferiority criteria (Table 1). Figure 1 depicts the mean change in FVC (% predicted) over time by the treatment arms. The difference between the two groups was observed at week 13 (i.e., the time of the first post-baseline assessment) and maintained through week 49.

Table 1: *Summary Results of FVC (% predicted) in Upright Position in ERT Naïve Participants with LOPD in Trial EFC14028 (COMET).*[12]

		Avalglucosidase alfa-ngpt (n=51)	Alglucosidase alfa (n=49)
Pretreatment baseline	**Mean (SD)**	62.5 (14.4)	61.6 (12.4)
Week 49	**Mean (SD)**	65.5 (17.4)	61.2 (13.5)
Estimated change from baseline to Week 49	**Least Square (LS) mean (SE)**	2.9[a] (0.9)	0.5[a] (0.9)
Estimated difference between groups in change from baseline to Week 49	**LS mean (95%CI)**	2.4[b] (-0.1, 5.0)	

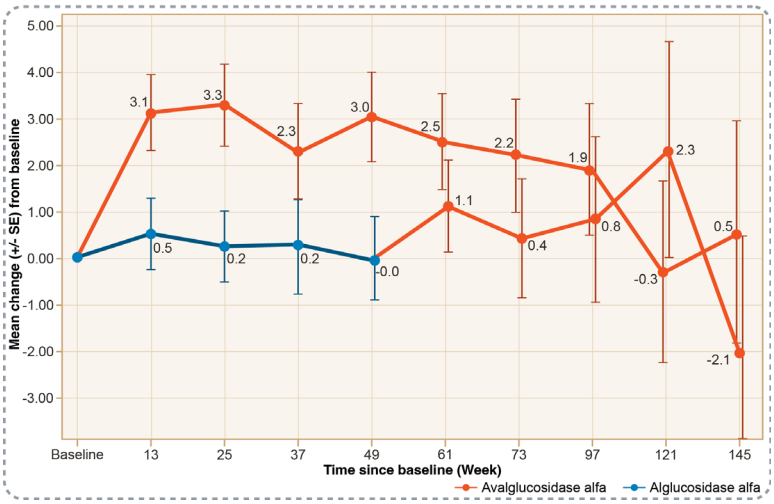
[a] *Estimated using a mixed model for repeated measures (MMRM) including baseline FVC (% predicted, as continuous), sex, baseline age (years), treatment group, visit, and treatment-by-visit interaction term as fixed effects (please refer to the Integrated Review for information on the statistical analysis plan and analyses).*

[b] *Noninferiority margin of 1.1% (p=0.0074). Statistical superiority of avalglucosidase alfa-ngpt over alglucosidase alfa was not achieved (p=0.06).*

Conclusion

A large and clinically meaningful numerical improvement in lung function, measured by the primary biomarker endpoint, FVC (% predicted), supported the effectiveness of avalglucosidase alfa-ngpt in treatment-naïve patients greater than 16 years of age with LOPD. Previous clinical studies conducted for the approval of the comparator, alglucosidase alfa, demonstrated that changes in FVC (% predicted) correlated with clinically meaningful outcome (i.e., survival).

Figure 1: *Mean (±SE) change from baseline in FVC (% predicted) over time (all randomized). At each time point, the vertical bar presents ± standard error (SE). The red and blue lines represent the mean change from baseline over time in the avalglucosidase alfa-ngpt arm and the alglucosidase alfa arm, respectively.*[13]



[11] For more information on trial design, please refer to pg. 26 of the Integrated Review for avalglucosidase alfa-ngpt (Nexviazyme).

[12] Table 1 was generated using information provided on page 35 of the Integrated Review for avalglucosidase alfa-ngpt (Nexviazyme), BLA 761194.

[13] Figure 1 was generated using information provided on page 36 of the Integrated Review for avalglucosidase alfa-ngpt (Nexviazyme), BLA 761194.

Seladelpar (Livdelzi)

In this example, the Applicant used a biomarker-based composite endpoint as a surrogate endpoint that is reasonably likely to predict clinical benefit for the accelerated approval of seladelpar. Seladelpar is a peroxisome proliferator-activated receptor PPAR-δ agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

The Disease

PBC is a rare, autoimmune, chronic liver disease characterized by progressive damage to the intrahepatic bile ducts, leading to impaired bile flow in the liver (i.e., cholestasis), liver inflammation, and eventual cirrhosis if left untreated. PBC predominantly affects women (approximately 90%), with a mean age of 52 years at diagnosis. The prevalence of PBC is estimated to be between 19 and 402 cases per million.

Drug Mechanism of Action

Seladelpar is a PPAR-δ agonist. However, the mechanism by which seladelpar exerts its therapeutic effects in patients with PBC is not well understood. Pharmacological activity that is potentially relevant to therapeutic effects includes the inhibition of bile acid synthesis through activation of PPAR-δ, which is a nuclear receptor expressed in most tissues including the liver. Published studies show that PPAR-δ activation by seladelpar reduces bile acid synthesis through Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol. [14]

Biomarkers Supporting Effectiveness of Seladelpar

Substantial evidence of effectiveness for seladelpar in patients with PBC was established using data from one adequate and well-controlled

FDA Guidance Corner

In this case study, the Applicant was granted accelerated approval. Sponsors must meet specific qualifying criteria and agree to the conditions of the accelerated approval.

FDA's policies for accelerated approval as well as threshold criteria generally applicable to concluding that a drug is a candidate for accelerated approval can be found here:

Draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024). When final, this draft guidance will represent the Agency's current thinking on this topic.

The accelerated approval pathway has been used in settings in which the disease course is long or the clinical outcome events intended to be reduced by the drug are infrequent. FDA's accelerated approval regulations state that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments, and the FD&C Act was subsequently amended to require that FDA consider "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments" when approving a product under accelerated approval.

At the time a product is granted accelerated approval, FDA has determined that an effect on the endpoint used to support approval—a surrogate endpoint or an intermediate clinical endpoint—is reasonably likely to predict clinical benefit. The risks of this approach include that patients may be exposed to safety risks from a drug that ultimately does not demonstrate clinical benefit. In addition, because there generally may be smaller or shorter clinical trials than is typical for a drug receiving traditional approval, there may be less information available at the time of accelerated approval about the occurrence of rare or delayed adverse events. These risks inform the Agency's decision-making regarding use of accelerated approval.

Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship...Evidence of pharmacologic activity alone is not sufficient. Clinical data should be provided to support a conclusion that an effect on the surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit.

The extent to which the pathophysiology of a disease and the role of the surrogate endpoint is understood [is an important factor in determining whether an endpoint is reasonably likely to predict clinical benefit]. [I]f the disease process is complex, has multiple pathophysiologic or causal pathways, or is poorly understood, it may be difficult to determine whether an effect on a surrogate endpoint would be reasonably likely to translate into a meaningful clinical effect.

FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and planning and conduct of confirmatory trials.

[14] See the FDA Integrated Review for seladelpar (Livdelzi).

clinical investigation (i.e., Trial CB8025-32048) with confirmatory evidence (i.e., Trial CB8025-31735). The primary endpoint in Trial CB8025-32048 was a composite biochemical response based on two blood circulating biomarkers – alkaline phosphatase (ALP) and total bilirubin (TB) levels.

FDA accepted the endpoint constructed using ALP and TB as an RLSE to support accelerated approval of seladelpar based on the following information:

- One of the hallmark features of PBC is persistently elevated ALP levels in the blood, indicating bile duct damage or obstruction; and elevated ALP and TB levels, along with antimitochondrial antibodies, strongly support a diagnosis of PBC.
- Data collected and analyzed from multiple retrospective studies demonstrated that a reduction in the levels of ALP and TB was associated with clinical outcomes, such as longer transplant-free survival after treatment with UDCA.[15]

There is unmet medical need for PBC treatments, especially for those with more advanced liver fibrosis/cirrhosis and those who have an incomplete response or are intolerant of UDCA. Due to the slow and progressive nature of PBC, long-term clinical trials are required to evaluate clinical endpoints and liver transplantation. Therefore, there were benefits to using surrogate biochemical markers, such as ALP and TB, to demonstrate a reasonable likelihood of clinical benefit to support accelerated approval.

Biomarker-Based Composite Endpoint Results

The efficacy of seladelpar was evaluated in a 12-month, randomized, double-blind, placebo-controlled trial (i.e., Trial CB8025-32048). The study included 193 adult patients with PBC with an inadequate biochemical response (as assessed by ALP) or intolerance to UDCA. Patients were included in the trial if their ALP was greater than or equal to 1.67-times upper limit of normal (ULN) and TB was less than or equal to 2-times the ULN.[16] Participants were randomized to receive seladelpar 10 mg (N=128) or placebo (N=65) once daily for 12 months. Seladelpar or placebo was administered in combination with UDCA (181 [94%] patients), or as a monotherapy (12 [6%] patients) for participants who were unable to tolerate UDCA.

The primary endpoint was a composite biochemical response assessed at Month 12, where biochemical response was defined as achieving: (1) ALP less than 1.67-times ULN; (2) an ALP decrease of greater than or equal to 15% from baseline, and; (3) TB less than or equal to ULN. The threshold of at least 15% reduction in ALP was added to the endpoint to ensure that reductions were related to treatment effect and not due to variability arising from potential spontaneous fluctuations in ALP. The normalization of TB was also included in the endpoint to ensure that there was no worsening of TB during the clinical trial. The ULN for ALP was defined as 116 U/L. The ULN for TB was defined as 1.1 mg/dL.[17]

Table 2 presents results at Month 12 for the percentage of patients who achieved biochemical response and achieved each component of biochemical response. Overall, 87% of patients had a baseline TB concentration of less than or equal to ULN. Therefore, the improvement in ALP was the main contributor to the biochemical response rate results at Month 12. Seladelpar demonstrated greater improvement on biochemical response at Month 12 compared to placebo.

[15] Lammers, WJ, et al., 2014, Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study, Gastroenterology, 147(6), 1338 – e15.

[16] For more information on inclusion and exclusion criteria, please refer to the Integrated Review for seladelpar (Livdelzi).

[17] See the FDA Integrated Review for seladelpar (Livdelzi).

Table 2: *Percentage of Adult Participants with PBC Achieving Biochemical Response and ALP Normalization at Month 12 in Trial CB8025-32048.* [18]

	Seladelpar 10 mg Once Daily (n=128)	APlacebo (n=65)	Treatment Difference % (95% CI)[c]
Biochemical Response Rate, n (%) [a,b]	**79 (62)**	13 (20)	42 (28, 53)
Components of Biochemical Response			
ALP less than 1.67-times ULN, n (%)	**84 (66)**	17 (26)	39 (25, 52)
Decrease in ALP of at least 15%, n (%)	**107 (84)**	21 (32)	51 (37, 63)
TB less than or equal to ULN, n (%)	**104 (81)**	50 (77)	4 (-7, 17)

[a] Biochemical response is defined as ALP less than 1.67-times ULN, an ALP decrease of greater than or equal to 15%, and TB less than or equal to ULN.

[b] tp<0.0001 for seladelpar 10 mg versus placebo. P-values were obtained using the Cochran–Mantel-Haenszel test stratified by baseline ALP level (<350 U/L versus ≥350 U/L) and baseline pruritus NRS (<4 versus ≥4).

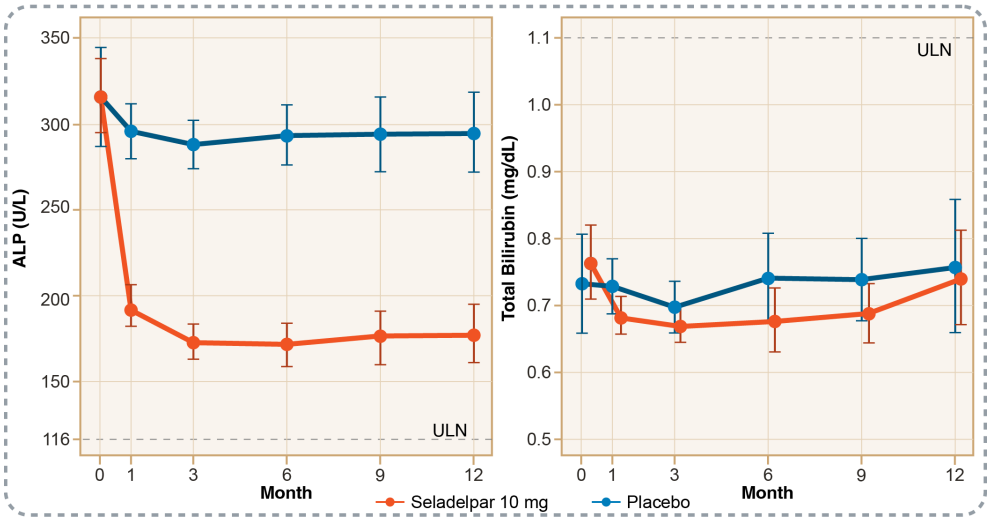
[c] 95% unstratified Miettinen and Nurminen confidence intervals (CIs) are provided.

Participants who discontinued treatment prior to Month 12 or who had missing data were considered as non-responders.

Figure 2 shows the mean (95% CI) levels of ALP and TB over 12 months. A separation between the treatment groups was observed for ALP with a trend of lower ALP in the seladelpar arm compared to the placebo arm starting at Month 1 through Month 12. A separation between the treatment groups was not observed for TB, which remained lower than ULN (i.e., 1.1 mg/dL) for both treatment groups.

The RLSE (i.e., biochemical response at Month 12) supported the demonstration of effectiveness for the accelerated approval of seladelpar. Results were statistically significant with robust treatment effect sizes.

Figure 2: *Mean ALP and TB in Adult Participants with PBC over 12 Months in Trial CB8025- 32048. Refer to Integrated Review for information on how means and CI were computed.*[19]



Confirmatory evidence included Week 12 results from Trial CB8025-31735. The same biochemical response outcome was assessed in Trial CB8025-31735 as in Trial CB8025-32048, except evaluated at Week 12 instead of Month 12. The biochemical response rate at Week 12 in Trial CB8025-31735 was consistent with the biochemical response rate at Month 12 in Trial CB8025-32048.

Postmarketing Requirements: The Confirmatory Trial

Because the FDA approved seladelpar under accelerated approval, the Applicant must conduct an adequate and well-controlled confirmatory trial to verify and describe clinical benefit. Trial CB8025-41837, is an ongoing, randomized, double-blind, placebo-controlled trial that will enroll participants with compensated cirrhosis and will evaluate seladelpar's effect on development of clinical outcomes (i.e., liver decompensation, transplant, and death).

[18] Table 2 was generated using information provided on page 40 of the Integrated Review for seladelpar (Livdelzi), NDA 217899.

[19] Figure 2 was generated using information provided on page 43 of the Integrated Review seladelpar (Livdelzi), NDA 217899.

Key Takeaways

- In cases where changes in symptoms and disease status occur slowly, surrogate endpoints may be considered.
- It is particularly important to understand the pathophysiology and natural history of the disease to help identify potential surrogate endpoints.
- It is important to understand the distinction between validated surrogate endpoints and RLSEs and their regulatory considerations. Validated surrogate endpoints are accepted by the FDA as evidence of clinical benefit and, therefore, can be used to support traditional approval of a drug or biological product.
- For RLSEs the amount of clinical data available is not sufficient to show that they are a validated surrogate endpoint. RLSEs can be used to support an accelerated approval. Determining whether an endpoint is reasonably likely to predict clinical benefit depends on the biological plausibility of the relationship between the disease, endpoint, and the desired effect, and the empirical evidence to support that relationship.
- The specific clinical evidence needed to support a conclusion that a particular surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit or IMM [irreversible morbidity or mortality] is case-specific and is not readily generalizable.
- FDA may grant accelerated approval to a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit.
- Under accelerated approval, drug companies conduct trials to confirm the anticipated clinical benefit of their product. If the confirmatory trial shows that the product provides a clinical benefit, then the application converts to traditional approval. If the confirmatory trial does not show that the product provides clinical benefit, FDA has procedures in place that could lead to withdrawal of FDA approval. FDA has the authority to require, as appropriate, that a confirmatory trial be underway prior to accelerated approval or within a specified time period after the date of accelerated approval. [20]
- The acceptability of surrogate endpoints for use in a particular drug or biologic development program will be determined on a case-by-case basis. It is context-dependent, relying in part on the disease, studied patient population, therapeutic mechanism of action, and availability of current treatments. A particular surrogate endpoint that may be appropriate for use in a particular drug or biologic clinical development program, should not be assumed to be appropriate for use in a different program that is in a different clinical setting.

FDA Guidance Corner

In this case study, the Applicant was granted accelerated approval and must complete a confirmatory trial with due diligence.

This draft guidance, which when final, will represent the Agency's current thinking on considerations for sponsors conducting postapproval confirmatory trials:

Draft guidance for industry *Expedited Program for Serious Conditions—Accelerated Approval of Drugs and Biologics* (December 2024)

For drugs granted accelerated approval, sponsors conduct confirmatory trials that must be completed postapproval and are intended to verify and describe the anticipated effect on irreversible morbidity or mortality (IMM) or other clinical benefit.

Section 506(c) of the FD&C Act was most recently amended by the Consolidated Appropriations Act, 2023 (Public Law 117-328), which granted FDA additional authorities and imposed on FDA additional obligations regarding accelerated approval. Among other revisions, section 3210 of the Consolidated Appropriations Act, 2023 provides that not later than the date of approval of a product under accelerated approval, FDA will specify conditions for the confirmatory study or studies sponsors are required to conduct under this section, which "may include enrollment targets, the study protocol, and milestones, including the target date of study completion."

Section 506(c)(3)(A) of the FD&C Act, as amended by section 3210 of the Consolidated Appropriations Act, 2023, provides that FDA may use expedited procedures to withdraw approval of a drug that has received accelerated approval if:

1. the sponsor fails to conduct any required post-approval study of the product with due diligence, including with respect to conditions specified by the Secretary under paragraph (2)(C) [of section 506(c)];
2. a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit;
3. other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use; or
4. the sponsor disseminates false or misleading promotional materials with respect to the product.

[20] Draft guidance for industry *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway* (January 2025).

Critical Thinking Questions for a Rare Disease Drug Development Program

Does the Development Plan Include Surrogate Endpoints?

Rare disease drug developers should discuss the rationale for using biomarkers as surrogate endpoints with FDA early in the development of the therapy. When planning for and designing a clinical investigation(s) for a rare disease medical product, consider the following questions:

1. **Is the biomarker(s) appropriate as a surrogate endpoint in the development program?**
   - Is there a good understanding of the pathophysiology and the natural history of the disease for which the product is intended to treat?
   - Does the biomarker(s) reflect the underlying disease pathophysiology?
   - Is there evidence the biomarker is on the causal pathway of disease?
   - Is the biomarker(s) supported by a clear mechanistic rationale?
2. **Are the bioanalytical assays used to measure the biomarkers validated, if applicable?**
3. **Can the biomarker(s) be considered a validated surrogate endpoint for traditional approval?**
   - Do clinical data provide strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit?
4. **Can the biomarker be considered a RLSE to support accelerated approval?**
   - Is the condition intended to treat with the medical product serious or life threatening?
   - Is there a meaningful therapeutic benefit of the investigational product over available therapy?
   - Is the biomarker supported by strong mechanistic and/or epidemiologic rationale, but the amount of clinical data available is not sufficient to show that it is a validated surrogate endpoint?
   - What is the feasibility of conducting a confirmatory trial to support the clinical benefit of the medical product if a RLSE for accelerated approval is used?

We recommend meeting with the Agency early in the drug development program to reach alignment regarding endpoint selection, trial design, the approach to demonstrate substantial evidence of effectiveness and the confirmatory post approval trial when accelerated approval is being considered.

Case Study References by Order of Appearance

Page 1

- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See the FDA Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure webpage available at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.
- See draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) available at https://www.fda.gov/media/184120/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See the FDA Surrogate Endpoint Resources for Drug and Biologic Development webpage available at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.
- See the FDA Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure webpage available at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.

Page 2

- See the FDA Guidance Documents for Rare Disease Drug Development webpage available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See section 506(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356) available at https://www.govinfo.gov/content/pkg/USCODE-2023-title21/pdf/USCODE-2023-title21-chap9-subchapV-partA-sec356.pdf.
- See the FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK326791/.
- See the FDA Surrogate Endpoint Resources for Drug and Biologic Development webpage available at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

Page 3

- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) available at https://www.fda.gov/media/119757/download.
- See the FDA Integrated Review document for alglucosidase alfa (Lumizyme) available at https://www.accessdata.fda.gov/drugsatfda_docs/bla/2014/125291orig1s136.pdf.
- See the FDA Integrated Review document for avalglucosidase alfa-ngpt (Nexviazyme) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761194Orig1s000IntegratedR.pdf.
- See the FDA Integrated Review document for alglucosidase alfa (Lumizyme) available at https://www.accessdata.fda.gov/drugsatfda_docs/bla/2014/125291orig1s136.pdf.

Page 4

- See page 26 of the avalglucosidase alfa-ngpt (Nexviazyme) FDA Integrated Review document for more information on the trial design available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761194Orig1s000IntegratedR.pdf.

Page 5

- See draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) available at https://www.fda.gov/media/184120/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See the FDA Integrated Review for seladelpar (Livdelzi) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217899Orig1s000IntegratedR.pdf.

Page 6

- See Lammers, WJ, HR van Buuren, GM Hirschfield, HL Janssen, P Invernizzi, AL Mason, CY Ponsioen, A Floreani, C Corpechot, MJ Mayo, PM Battezzati, A Parés, F Nevens, AK Burroughs, KV Kowdley, PJ Trivedi, T Kumagi, A Cheung, A Lleo, MH Imam, K Boonstra, N Cazzagon, I Franceschet, R Poupon, L Caballeria, G Pieri, PS Kanwar, KD Lindor, and BE Hansen, Global PBC Study Group, 2014, Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study, Gastroenterology, 147(6), 1338 – e15 available at https://doi.org/10.1053/j.gastro.2014.08.029.
- See the FDA Integrated Review document for more information on inclusion and exclusion criteria for seladelpar (Livdelzi) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217899Orig1s000IntegratedR.pdf.
- See the FDA Integrated Review for seladelpar (Livdelzi) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217899Orig1s000IntegratedR.pdf.

Page 8

- See draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) available at https://www.fda.gov/media/184120/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway Guidance for Industry* (January 2025) available at https://www.fda.gov/media/184831/download. When final, this guidance will represent the Agency's current thinking on this topic.