FDA Issues Complete Response Letter for Biohaven's VYGLXIA (troriluzole) New Drug Application for Spinocerebellar Ataxia

November 5, 2025

- *The troriluzole clinical development program encompassed the first industry clinical trials to generate data showing therapeutic potential in patients with spinocerebellar ataxia (SCA), a rare genetic, inherited, life-threatening neurodegenerative disease with no treatment options.*

    - *Compelling data from troriluzole's new drug application (NDA) included: a 3-year real-world evidence study (Study 206-RWE) showing slowing of SCA disease progression by 50-70% in troriluzole-treated patients compared to matched untreated external controls; > 50% risk reduction in AEs of falls in troriluzole-treated subjects compared to placebo from the safety analysis of the 1-year, double-blind, placebo controlled Study -206; and multiple supportive analyses showing a delay in becoming wheelchair bound or losing the ability to walk, decreased gait impairment as measured by f-SARA and objective video-based kinematic analysis, and improvement in overall functioning as assessed by the clinician global impression (CGI) scale.*

    - *The FDA issued a complete response letter (CRL) despite Study 206-RWE being reviewed by FDA and achieving statistical significance in the study's prespecified primary and secondary outcome efficacy endpoints. FDA cited issues that can be inherent to real-world evidence and external control studies including potential bias, design flaws, lack of pre-specification and unmeasured confounding factors.*

        - *Prior to 206-RWE protocol finalization, study approval and topline data analysis, the FDA provided feedback on the study's statistical analysis plan and study protocol that were incorporated into the IRB approved study. The FDA official meeting minutes (March 8, 2024) from discussion of the RWE study included the statement, "a large and robust treatment effect would be needed to overcome the biases of an externally controlled trial, in order for it to be used as the primary basis for substantial evidence for effectiveness."*
        - *Biohaven believes the statistical significance and clinical meaningfulness achieved on the primary endpoint and eight consecutive secondary endpoints in 206-RWE, which included consistent results across two separate, independent, third-party run, multi-center, external controls from the largest natural history studies of SCA in the United States and Europe, clearly met criteria of "a large and robust treatment effect."*

    - *Troriluzole received Orphan and Fast Track designation as well as a Priority Review acceptance of the NDA; FDA subsequently delayed the PDUFA date by 3 months during the review period. There was no communication of the need for an Advisory Committee meeting at acceptance of the Priority Review; however, a few months later the FDA informed Biohaven that an Advisory Committee was being planned but then cancelled it weeks before the anticipated meeting, preventing qualified clinical experts the opportunity to publicly weigh in on their opinion of what is a large and robust treatment effect and after the Company spent significant resources preparing for the Advisory Committee.*

- *In the CRL, the FDA recommended that Biohaven meet with the Division to discuss the evidence that will be needed to support a future NDA for the treatment of SCA with troriluzole. Following receipt of the CRL today, Biohaven is in the process of formally requesting a meeting as soon as possible given the large number of patients who are currently being treated in the expanded access program.*
- Biohaven remains committed to working with the FDA to find a path forward for its NDA for VYGLXIA and plans to meet with the FDA to discuss potential next steps.
- *Given the CRL, Biohaven is initiating strategic portfolio and cost-optimization measures to prioritize 3 key, late-stage, clinical programs with the greatest potential for value generation:*

    - *Key areas of focus over the near term include: 1) Clinical-stage, lead extracellular degraders for IgA nephropathy (BHV-1400) and Graves' disease (BHV-1300); 2) Opakalim, Kv7 ion channel activator, pivotal trials in adult focal epilepsy and depression; and 3) Taldefgrobep alfa, myostatin-activin pathway inhibitor for obesity and SMA.*
    - *Restructuring of business priorities underway to achieve an approximately 60% reduction in annual direct R&D*

spend (which excludes personnel and SBC), will result in delay of non-priority programs.

- *New data will be presented from several of Biohaven's priority programs at an annual healthcare conference in January 2026.*

NEW HAVEN, Conn., Nov. 4, 2025 /PRNewswire/ -- Biohaven Ltd. (NYSE: BHVN) ("Biohaven"), a global clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of life-changing therapies to treat a broad range of rare and common diseases, today announced that it has received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) for the New Drug Application (NDA) seeking approval of VYGLXIA (troriluzole) for the treatment of spinocerebellar ataxia (SCA).

biohaven®

Committed to Advancing Innovative Treatments for Patients with Unmet Medical Needs

There Is No FDA-Approved Therapy for Spinocerebellar Ataxia (SCA), a Rare and Life-Threatening Neurodegenerative Disease

REGULATORY TIMELINE SUMMARY OF TRORILUZOLE NDA

2017

Biohaven develops and validates f-SARA scale for use as primary outcome measure in clinical trials, working closely with SCA experts and FDA

2022

SCA3 genotype analysis from 1 year double-blind placebo controlled trial shows signal for efficacy of troriluzole in SCA3, the most common form of SCA affecting over 40% of patients

2023

MAY 26 — Biohaven submits troriluzole NDA for the treatment of SCA3, but FDA Office of Neuroscience refuses to review the NDA

2024

Type A and then Type C meetings are held between FDA and Biohaven, along with the National Ataxia Foundation, people living with SCA, and SCA clinicians to discuss path forward for the SCA development program

At FDA Type C meeting, discussion focuses on Real-World Evidence (RWE) analyses of 3 years of troriluzole data to assess efficacy across all SCA genotypes

FEB 8 — *In official FDA Meeting Minutes, March 8, 2024, FDA notes,* ***"a large and robust treatment effect would be needed to overcome the biases of an externally controlled trial, in order for it to be used as the primary basis for substantial evidence for effectiveness"***

MAR 7 — Per FDA request, Biohaven submits initial statistical analysis plan (SAP) for proposed

ATAXIA COMMUNITY CALLS FOR FDA TO USE AVAILABLE REGULATORY FLEXIBILITY

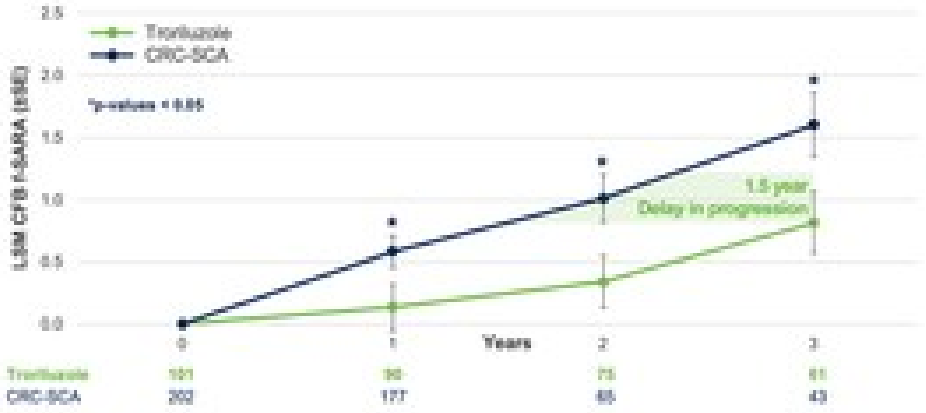
FDA regulations and guidance have established procedures for FDA to appropriately exercise the broadest flexibility in applying the statutory standards of safety and effectiveness for rare, life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists (21CFR312.80).

Moreover, regulations emphasize "... it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses..."

SCA clearly falls within these FDA regulations and guidance.

TRORILUZOLE DATA

Figure 2. Positive Prespecified Primary and Secondary Endpoints: Troriluzole vs US Natural History External Control



f-SARA
LS Mean
Difference (SE)
−0.79 (0.36)

CRC-SCA, Clinical Research Consortium for SCA; EUROSCA, European registry of SCA; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; LSM, least squares mean; PSM, Propensity Score Matching; CFB, Change from baseline

KEY POINT Troriluzole reduced SCA disease progression by 50%

Positive Prespecified Primary and Secondary Endpoints

Figure 3. Study 206-RWE Met 9 Prespecified Consecutive Hierarchical Endpoints Demonstrating Robust and Durable Treatment Benefit Over 3 Years

	f-SARA at Year	p-Value
US External Control (CRC-SCA)	3	<0.05
	2	<0.05
	1	<0.05
Europe External Control (EUROSCA)	3	<0.0001
	2	<0.0001
	1	<0.0001
Global External Control (CRC+EURO)	3	<0.0001
	2	<0.0001
	1	<0.003

CRC-SCA, Clinical Research Consortium for SCA; EUROSCA, European registry of SCA; f-SARA, Functional Scale for the Assessment and Rating of Ataxia; Global, CRC-SCA & EUROSCA

Study 206-RWE Met 9 Prespecified Consecutive Hierarchical Endpoints

Figure 4. Prespecified Sensitivity Analysis: Untreated SCA Patients at Greater Risk of Significant Disease Worsening

	Odds Ratio of f-SARA ≥2-Point Worsening in Untreated	P-Value
US External Control vs. Troriluzole*	2.4	<0.05
EU External Control vs. Troriluzole	6.1	<0.0001
Global External Control vs. Troriluzole	4.1	<0.0001

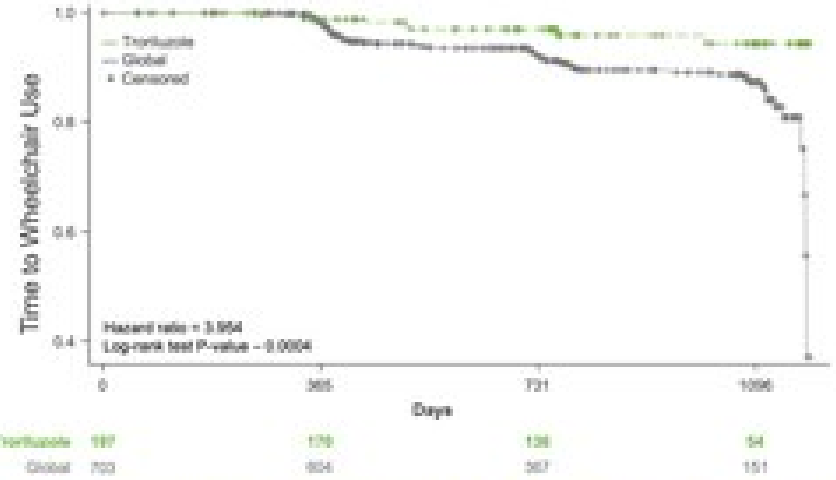
*prespecified

KEY POINT

f-SARA ≥2-point change represents high, clearly clinically important threshold based on SCA disease progression expected over 3 years

Untreated SCA Patients at Greater Risk of Significant Disease Worsening

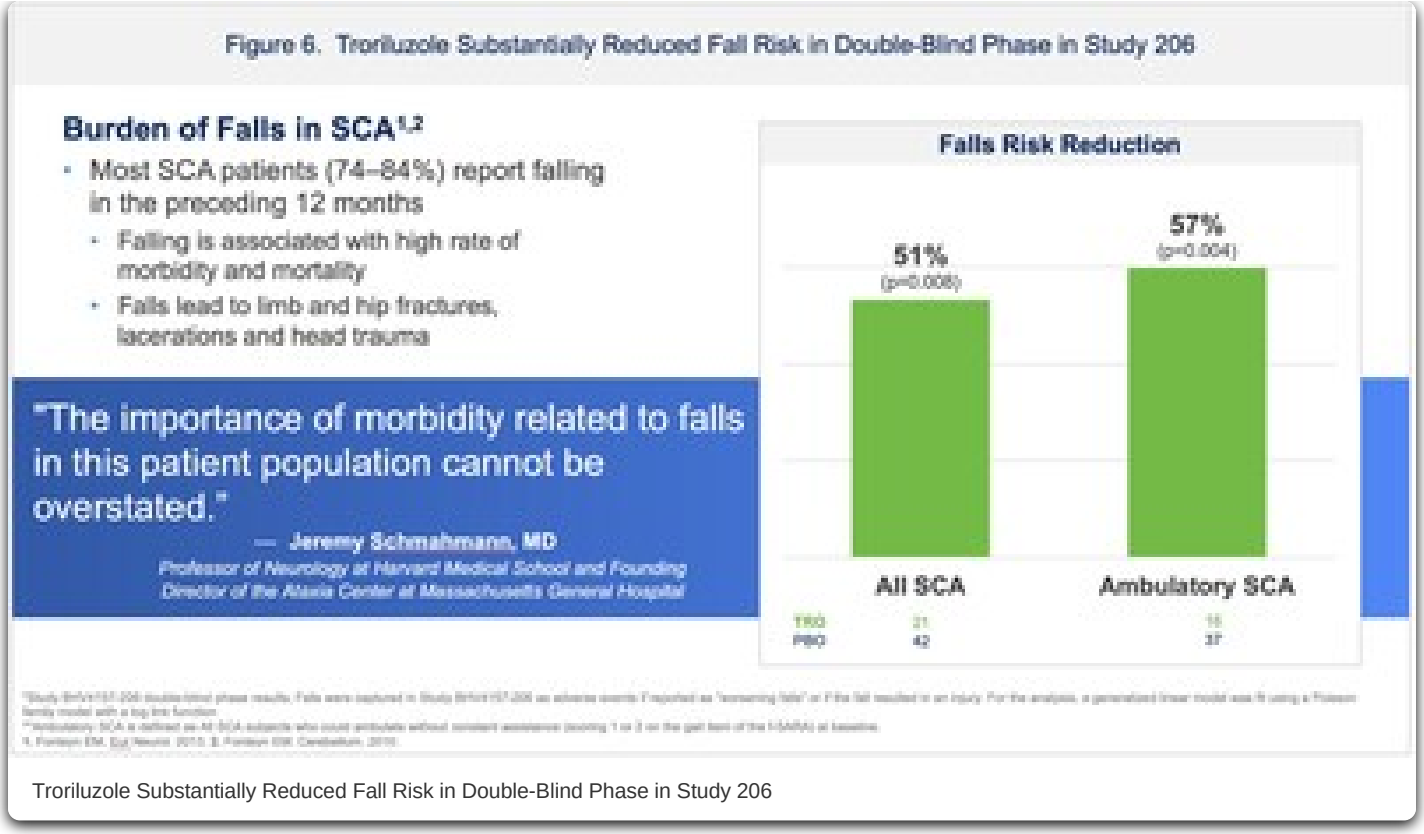
Figure 5. Kaplan-Meier Analysis Shows Delay in Time to Wheelchair Progression in Troriluzole-treated and Untreated Natural History SCA Patients



KEY POINT

Risk of progression to wheelchair use was 4x greater in untreated group as compared to troriluzole-treated patients

Kaplan-Meier Analysis Shows Delay in Time to Wheelchair Progression



Troriluzole Substantially Reduced Fall Risk in Double-Blind Phase in Study 206

Vlad Coric, M.D., Chairman and Chief Executive Officer of Biohaven said, "We are extremely disappointed on behalf of patients by this action from the Office of Neuroscience at FDA. Beyond substantial evidence of safety and efficacy, patients with rare diseases also deserve an efficient, fair and flexible regulatory process that aligns with the urgency of their high unmet medical needs. Such an approach has been mandated by Congress to empower the FDA with maximum regulatory flexibility for rare disease. As a company, we are committed to advancing innovative treatments and remain dedicated to SCA patients despite all the challenges associated with pursuing therapies for rare diseases. Real-world evidence is an important research approach to assessing and delivering new therapies for complex rare diseases but, despite FDA policy initiatives supporting such tools, the front-line review divisions are not yet embracing FDA policy for the use of real-world evidence or the application of regulatory flexibility for rare disease."

Jeremy Schmahmann, M.D., Professor of Neurology at Harvard Medical School and Founding Director of the Ataxia Unit at Massachusetts General Hospital (MGH), added, "Patients with SCA and clinicians who treat them deserve to be heard on this important NDA filing. There is too much at stake for patients. The FDA decision not to listen to disease experts and respect the patient perspective before taking action represents a misstep in the due process, and a failure to deploy regulatory flexibility to evaluate benefit:risk of a medication that has proven to be safe and effective for this rare, debilitating neurodegenerative disease that has no current treatment."

Dr. Coric added, "The development of VYGLXIA® (troriluzole) by Biohaven embodies a strong scientific process and deep commitment that is critical to bringing safe and effective treatments to patients with rare diseases like SCA. Our efforts over eight years, included developing the f-SARA scale in collaboration with the FDA and a real-world evidence study in SCA that showed VYGLXIA achieved highly consistent, sustained, robust and clinically meaningful treatment effects with a safe, once-daily oral pill that slowed disease progression by 50-70%. The NDA also included data showing VYGLXIA reduced the risk of falls and delayed time to becoming wheelchair bound. The leading SCA experts in the United States directly communicated their support of the troriluzole data to the FDA but unfortunately the Office of Neuroscience's inability to collaboratively engage with Biohaven, the patient community and leading experts leave us with concerns about the lack of regulatory flexibility that is being applied for rare, life-threatening conditions. There are a number of common sense solutions and regulatory tools that the Office of Neuroscience could have applied including a fair hearing of the drug's efficacy and safety risks at an Advisory Committee of experts and patients, post-marketing studies, labelling limitations or an accelerated approval pathway. Patients are waiting and the certainty of disease progression for SCA patients far outweighs any residual uncertainty regarding potential design bias or interpretation of study data, especially when the primary outcome measure was achieved in a study protocol and statistical analysis plan that was reviewed by the FDA prior to data analysis. SCA patients deserved approval of VYGLXIA and certainly a more balanced interpretation of benefit:risks."

Biohaven remains committed to working with the FDA to find a path forward for its NDA for VYGLXIA and plans to meet with the FDA to discuss potential next steps.

Prioritizing Clinical-Stage, Innovative Assets

Biohaven will prioritize resources to focus all its R&D resources on other key programs from its diversified portfolio. Consistent with Biohaven's enduring commitment as a patient-first drug developer, the company's pipeline is focused on a range of disease indications which have limited or no treatment options and are long overdue for therapeutic innovation.

Bruce Car Ph.D., Chief Scientific Officer at Biohaven, commented, "As drug developers we expect setbacks and our diversified portfolio affords us the opportunity to pivot to other key programs. We remain as resilient as ever in following science in order to make a difference in the lives of people with

debilitating diseases. Much important work remains, and we are energized and focused on achieving the critical milestones that lie ahead, mindful that days matter and patients are waiting."

Biohaven is initiating strategic portfolio and cost optimization across multiple programs and will focus forward-looking spend on restructuring of business priorities to achieve an approximately 60% reduction in annual direct R&D spend (which excludes personnel and SBC). This may include pausing or delaying non-priority programs to maintain its cash runway to focus on the priority clinical-stage programs over the next year.

Key areas of focus over the next year will include:

1) Clinical-stage, lead extracellular degraders for IgA nephropathy (BHV-1400) and Graves' disease (BHV-1300);
2) Opakalim, Kv7 ion channel activator, pivotal trials in adult focal epilepsy and depression; and
3) Taldefgrobep alfa, myostatin-activin pathway inhibitor, for SMA and obesity.

About Spinocerebellar Ataxia (SCA)
Spinocerebellar ataxia is a group of dominantly inherited neurodegenerative disorders characterized by progressive loss of voluntary motor control and atrophy of the cerebellum and brainstem. SCA affects approximately 15,000 people in the United States and 24,000 in Europe and the United Kingdom. Patients experience significant morbidity, including impaired gait leading to falls, loss of ambulation and progression to a wheelchair, inability to communicate due to speech impairment, difficulty swallowing, and premature death. While signs and symptoms can appear anytime from childhood to late adulthood, SCA typically presents in early adulthood and progresses over a number of years. Currently, there are no FDA-approved treatments and no cure for SCA.

About Troriluzole
Troriluzole is a new chemical entity (NCE) and third-generation novel prodrug that modulates glutamate, the most abundant excitatory neurotransmitter in the human body. The primary mode of action of troriluzole is reducing synaptic levels of glutamate. Troriluzole increases glutamate uptake from the synapse, by augmenting the expression and function of excitatory amino acid transporters located on glial cells that play a key role in clearing glutamate from the synapse. The glutamate modulating activity of troriluzole addresses the widely documented glutamate deregulation that underlies neurodegeneration and Purkinje cell dysfunction in patients with SCA. Troriluzole also has the potential to be developed in a number of other diseases associated with excessive glutamate. More information about troriluzole can be found at the Biohaven's website: https://www.biohaven.com/pipeline/glutamate/

About Biohaven
Biohaven is a biopharmaceutical company focused on the discovery, development and commercialization of life-changing treatments in key therapeutic areas, including immunology, neuroscience and oncology. Biohaven is advancing its innovative portfolio of therapeutics, leveraging its proven drug development experience and multiple proprietary drug development platforms. Biohaven's key clinical and preclinical programs include Kv7 ion channel modulation for epilepsy and mood disorders; MoDE™ and TRAP™ extracellular protein degradation for immunological diseases; and myostatin-activin pathway targeting agent for neuromuscular and metabolic diseases, including SMA and obesity. For more information, visit www.biohaven.com.

Forward-looking Statements
This news release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the expected timing and amounts of funding under the NPA. The use of certain words, including "continue", "plan", "will", "believe", "may", "expect", "anticipate", "potential first-in-class" and similar expressions, is intended to identify forward-looking statements. Investors are cautioned that any forward-looking statements, including statements regarding the future development, timing and potential marketing approval and commercialization of development candidates and regarding reduction in annual direct R&D spend, are not guarantees of future performance or results and involve substantial risks and uncertainties. Actual results, developments and events may differ materially from those in the forward-looking statements as a result of various factors including: the expected timing, commencement and outcomes of Biohaven's planned and ongoing clinical trials; the timing of planned interactions and filings with the FDA; the timing and outcome of expected regulatory filings; complying with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates and the expected timing thereof; the potential for Biohaven's product candidates to be successful therapies; the effectiveness of restructuring of business priorities; and the effectiveness and safety of Biohaven's product candidates. Additional important factors to be considered in connection with forward-looking statements are described in Biohaven's filings with the Securities and Exchange Commission, including within the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations". The forward-looking statements are made as of the date of this news release, and Biohaven does not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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