Jazz Pharmaceuticals Announces U.S. FDA Approval of Modeyso™ (dordaviprone) as the First and Only Treatment for Recurrent H3 K27M-mutant Diffuse Midline Glioma

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Modeyso is the first treatment option for this ultra-rare and aggressive brain tumor, which primarily affects children and young adults

Accelerated approval based on an overall response rate in patients with progressive disease following prior therapy

Company to host investor webcast on August 27, 2025

For U.S. media and investors only

DUBLIN, Aug. 6, 2025 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for Modeyso ™ (dordaviprone) for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in the Phase 3 ACTION confirmatory trial.[1]

Modeyso is the first and only treatment option approved by the FDA for this ultra-rare and aggressive brain tumor that affects an estimated 2,000 people in the U.S. each year, many of whom are children and young adults.[2] The disease is characterized by rapid progression and historically has had no effective systemic treatment options.[3] To address this urgent unmet patient need, *Modeyso* is expected to be commercially available in the coming weeks.

"This is a major turning point in neuro-oncology," said Patrick Wen, M.D., Director, Center for Neuro-Oncology, Dana-Farber Cancer Institute and Professor of Neurology, Harvard Medical School. "For the first time, we have an FDA-approved therapy for patients with recurrent H3 K27M-mutant diffuse midline glioma. While outcomes remain challenging for many patients, the objective responses observed with dordaviprone, including durable benefit in some patients, represent a meaningful advancement. This therapy was developed with the underlying biology of the tumor in mind and introduces a new treatment option for a population with historically limited choices."

Modeyso is administered as an oral capsule once weekly. The FDA's decision was based on an integrated efficacy analysis of 50 patients with recurrent H3 K27M-mutant diffuse midline glioma, selected from five open-label clinical studies based on prespecified eligibility criteria. The overall response rate (ORR), as assessed by blinded independent central review (BICR) using Response Assessment in Neuro-Oncology (RANO) 2.0 criteria, was 22% (95% CI: 12 to 36), with an additional responder identified by integrated RANO 2.0. Among responders, the median duration of response was 10.3 months (95% CI: 7.3 to 15.2), with 73% maintaining their response for at least six months and 27% for at least 12 months.[1]

"The FDA approval of *Modeyso* is a milestone moment for the patients and families who have long needed new options, the clinicians who have tirelessly searched for solutions, and the researchers and advocates who never gave up," said Joshua E. Allen, Ph.D., Chief Scientific Officer, Chimerix, a Jazz Pharmaceuticals Company. "We're proud to deliver precisely the kind of transformative innovation we strive for, and we congratulate our combined Chimerix and Jazz team, and the community who worked together tirelessly to bring this treatment forward. This approval not only equips clinicians with the first targeted option for this disease but also signals a meaningful shift in what patients and families can expect after diagnosis. We would like to extend our thanks to the patients, advocates, clinicians, principal investigators, scientists, regulators and partner institutions who made this possible."

"This approval represents a long-awaited treatment option for families affected by H3 K27M-mutant diffuse midline glioma," said David F. Arons, President and Chief Executive Officer of the National Brain Tumor Society. "This is a fast-moving, devastating disease that turns families' lives upside down. For years, this diagnosis has lacked an approved treatment and today, that changes. Families finally have a treatment option, and a reason to believe in more time together to make memories that might not have otherwise been possible."

The safety of *Modeyso* was evaluated in 376 adult and pediatric patients with glioma across four open-label clinical studies. Serious adverse reactions occurred in 33% of patients. Serious adverse reactions reported in more than 2% of patients included hydrocephalus (5%), vomiting (4.3%), headache (3.2%), seizure (2.4%) and muscular weakness (2.1%). The most common adverse reactions in patients who received *Modeyso* (≥20%) were fatigue, headache, vomiting, nausea and musculoskeletal pain.[1] See additional safety information below and full prescribing information: https://pp.jazzpharma.com/pi/modeyso.en.USPI.pdf

About the Phase 2 Clinical Trial Program
The efficacy and safety of *Modeyso* were evaluated in adult and pediatric patients with glioma across five open-label, non-randomized clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018). A pre-specified integrated efficacy analysis included 50 patients with recurrent H3 K27M-mutant diffuse midline glioma who had measurable disease per Response Assessment in Neuro-Oncology (RANO) criteria. Tumor response was assessed every eight weeks by blinded independent central review (BICR). The primary efficacy endpoint was objective response rate (ORR). Safety was evaluated across four of the clinical studies.[1]

More information about *Modeyso*, the Full Prescribing Information, and Patient Information, is available **here**.

Investor Webcast on August 27, 2025
The company will host a webcast on August 27, 2025, at 4:30 p.m. ET / 9:30 p.m. IST to provide investors an overview of clinical data, patient need and commercialization strategy for Modeyso. The webcast will include commentary from a leading neuro-oncology expert and the company's senior management.

A live webcast of the presentation may be accessed from the Investors section of the Jazz Pharmaceuticals website at www.jazzpharmaceuticals.com. Please connect to the website prior to the start of the presentation to ensure adequate time for any software downloads that may be necessary to listen to the webcast. An archive of the webcast will be available for at least one week following the presentation on the Investors section of the company's website at www.jazzpharmaceuticals.com.

About H3 K27M-Mutant Diffuse Midline Glioma

H3 K27M-mutant diffuse midline glioma is a rare and highly aggressive brain tumor that primarily affects the midline structures of the brain and spinal cord.[4,5] It is characterized by a specific genetic mutation (H3 K27M) that disrupts epigenetic regulation and drives tumor growth.[6] Most commonly diagnosed in children and young adults, patients with this type of glioma often face an extremely poor prognosis, with limited therapeutic options and very low survival rates following recurrence.[7] Median survival is approximately one year from diagnosis and less than six months after progressing following frontline therapy.[7]

About Modeyso ™ (dordaviprone)

Modeyso (dordaviprone) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy.[1] *Modeyso* is an orally administered small molecule given once weekly. *Modeyso* is a protease activator of the mitochondrial caseinolytic protease P (ClpP) and also inhibits dopamine D2 receptor (DRD2). In vitro, dordaviprone activates the integrated stress response, induces apoptosis, and alters mitochondrial metabolism, leading to restored histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma.[1]

Modeyso received accelerated approval based on a pre-specified integrated efficacy analysis of 50 adult and pediatric patients with recurrent H3 K27M-mutant diffuse midline glioma enrolled across five open-label clinical studies (ONC006, ONC013, ONC014, ONC016, and ONC018). Continued approval may be contingent upon verification and description of clinical benefit in the ongoing Phase 3 ACTION trial (NCT05580562), which is evaluating the safety and clinical benefit of *Modeyso* in newly diagnosed patients with H3 K27M-mutant diffuse glioma following radiotherapy.[6] *Modeyso* was developed by Chimerix prior to its acquisition by Jazz Pharmaceuticals in April 2025.

Modeyso (dordaviprone) is not approved anywhere else in the world.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity

MODEYSO can cause severe hypersensitivity reactions.

In the pooled safety population, Grade 3 hypersensitivity reactions occurred in 0.3% of patients receiving MODEYSO. Signs and symptoms of hypersensitivity may include rash, hives, fever, low blood pressure, wheezing, or swelling of the face or throat.

Inform patients about the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical attention if symptoms occur.

If clinically significant hypersensitivity or anaphylaxis occur, immediately interrupt MODEYSO and initiate appropriate medical treatment and supportive care. Based on the severity of the adverse reaction, temporarily interrupt or permanently discontinue MODEYSO.

QTc Interval Prolongation

MODEYSO causes concentration-dependent QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g. torsades de pointes) or sudden death.

In patients who received MODEYSO and underwent at least one post baseline ECG, QTcF increase of >60 msec compared to baseline and QTcF >500 msec occurred in 6% and 1.2% of patients, respectively.

Monitor ECGs and electrolytes prior to initiation and periodically during treatment, as clinically indicated. Increase the frequency of monitoring in patients with congenital long QT syndrome, existing QTc prolongation, a history of ventricular arrhythmias, electrolyte abnormalities, heart failure, or who are taking strong or moderate CYP3A4 inhibitors.

Avoid concomitant use with other agents known to prolong the QT interval. If concomitant use cannot be avoided, increase the frequency of monitoring and separate administration of MODEYSO and QT-prolonging product.

Interrupt or reduce the dose of MODEYSO in patients who develop QT prolongation; permanently discontinue in patients with signs of life-threatening arrhythmias.

Embryo-Fetal Toxicity

MODEYSO can cause fetal harm when administered to a pregnant woman.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MODEYSO and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with MODEYSO and for 1 month after the last dose.

ADVERSE REACTIONS

Serious adverse reactions occurred in 33% of the 376 patients who received MODEYSO. Serious adverse reactions in >2% of patients included hydrocephalus (5%), vomiting (4.3%), headache (3.2%), seizure (2.4%), and muscular weakness (2.1%). Fatal adverse reactions occurred in 1% of patients who received MODEYSO, including cardiac arrest (0.5%), intracranial hemorrhage (0.3%), and encephalopathy (0.3%).

The most common adverse reactions (≥20%) reported in clinical trials with MODEYSO were fatigue (34%), headache (32%), vomiting (24%), nausea (24%), and musculoskeletal pain (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (7%), decreased calcium (2.7%), and increased alanine aminotransferase (2.4%).

DRUG INTERACTIONS

Strong and Moderate CYP3A4 Inhibitors

Avoid concomitant use of MODEYSO with strong and moderate CYP3A4 inhibitors. If concomitant use cannot be avoided, reduce the MODEYSO dose as recommended and monitor for toxicity.

Strong and Moderate CYP3A4 Inducers
Avoid concomitant use of strong and moderate CYP3A4 inducers with MODEYSO.

USE IN SPECIFIC POPULATIONS
Lactation
There are no data on the presence of MODEYSO in human milk because of the potential for serious adverse reactions from MODEYSO in breastfed children, advise women not to breastfeed during treatment with MODEYSO and for 1 week after the last dose.

Pediatric Use
The safety and effectiveness of MODEYSO have not been established in patients less than 1 year of age. Dosing has not been established for patients weighing less than 22 pounds (10 kg).

Please refer to the full Prescribing Information, including both Patient Information and Instructions for Use, for complete safety and administration information.

About Jazz Pharmaceuticals
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharma company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing potentially life-changing medicines for people with serious diseases – often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience. Jazz is headquartered in Dublin, Ireland with research and development laboratories, manufacturing facilities and employees in multiple countries committed to serving patients worldwide. Please visit www.jazzpharmaceuticals.com for more information.

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[1] MODEYSO (dordaviprone) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

[2] Jazz Pharmaceuticals. *ZS Epidemiology Analysis*. Data on File. Durham, NC; 2025.

[3] Arrillaga-Romany, I., Lassman, A., et al. A randomized phase 3 study of ONC201 (dordaviprone) in patients with newly diagnosed H3 K27M-mutant diffuse glioma. *Neuro-oncology*. 2024; 26(Supplement_2), S173-S181.

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[5] National Cancer Institute. Diffuse Midline Glioma: Diagnosis and Treatment. Updated August 20, 2024. Accessed July 23, 2025. https://www.cancer.gov/rare-brain-spine-tumor/tumors/diffuse-midline-gliomas

[6] ClinicalTrials.gov. ONC201 in H3 K27M-mutant Diffuse Glioma Following Radiotherapy (the ACTION Study) (ACTION). Updated June 6, 2025. Accessed July 23, 2025. Study Details | ONC201 in H3 K27M-mutant Diffuse Glioma Following Radiotherapy (the ACTION Study) | ClinicalTrials.gov

[7] Bagley, S. J., Umemura, et al. Prognostic Features of Recurrent Midline and H3 K27M-Mutant Glioma. *Cancers*. 2025; 17(13):2107. https://doi.org/10.3390/cancers17132107

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