Jazz Pharmaceuticals to Present Advancements in Neuroscience at American Academy of Neurology Annual Meeting

April 19, 2023

Eleven abstracts emphasize Jazz's leadership in neuroscience and commitment to advance understanding of sleep disorders, epilepsy and movement disorders

Three oral presentations share meaningful data results in idiopathic hypersomnia and essential tremor

DUBLIN, April 19, 2023 */PRNewswire/* -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that eleven abstracts from across its neuroscience portfolio and pipeline, including three oral presentations, will be featured at the 75th Annual American Academy of Neurology Meeting (AAN) being held April 22-27, 2023 in Boston.

"Our presence at the 2023 AAN Annual Meeting further reflects Jazz's scientific leadership in developing therapies for debilitating sleep disorders and rare epilepsy syndromes that advance treatment for people living with these conditions," said Kelvin Tan, MB BCh, MRCPCH, senior vice president and chief medical officer of Jazz Pharmaceuticals. "Jazz has long been at the forefront of providing novel therapies and support for patients living with serious neurologic conditions. We look forward to presenting these findings, as they provide another opportunity to highlight the impact of our medicines and educate about the unmet needs our pipeline is dedicated to addressing."

Highlights at the 2023 AAN Annual Meeting include:

- Three posters demonstrating the impact of Xywav® (calcium, magnesium, potassium, and sodium oxybates), the first and only low-sodium oxybate, on narcolepsy patients. Presentations include interim results from the SEGUE study of adults with narcolepsy transitioning from Xyrem®, a high-sodium oxybate, to *Xywav*, a study that explored the increased incidents and risk of hypertension onset among patients with narcolepsy newly treated with *Xyrem*, and long-term safety results from a clinical trial of *Xywav* in patients with narcolepsy type 1.
- An oral presentation of a post hoc analysis evaluating treatment response to *Xywav* on Epworth Sleepiness Scale (ESS) and Idiopathic Hypersomnia Severity Scale (IHSS) scores within a Phase 3 clinical trial. Results demonstrate that the strong majority (80%) of participants achieved a clinically meaningful response on the ESS and IHSS, with response rates increasing over the course of the study. The safety profile of *Xywav* was consistent with that observed in narcolepsy.
- Subgroup analyses of the BECOME survey of caregivers of adult and pediatric patients with Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) prescribed Epidiolex® (cannabidiol) oral solution, which reported on patients' seizure- and non-seizure related outcomes, including seizure frequency, seizure-free days, alertness, cognition and executive function, and emotional and social function.
- Two oral presentations of retrospective analyses of U.S. healthcare claims that estimate the prevalence of diagnosed and drug-treated essential tremor (ET) in adult and pediatric patients. These analyses found ET affects over 525,000 adults and that most of these patients (over 70%) received regimens not indicated as first-line for ET, suggesting the need for novel therapies for this disorder.

The 2023 AAN Annual Meeting abstracts are available online at https://index.mirasmart.com/aan2023/index.php.

A full list of Jazz-sponsored presentations follows:

Presentation Title	**Lead Author**	**Date / Time (CT) / Session Title / Presentation Number**
Idiopathic Hypersomnia Data		
Efficacy of Lower-Sodium Oxybate in the Treatment of Idiopathic Hypersomnia: Evaluation of Treatment Response Based on the Epworth Sleepiness Scale and Idiopathic Hypersomnia Severity Scale Scores	R Rosenberg	Type: Oral Session Name: S6: Sleep Medicine Highlights Code: S6.009 Session Date/Time: Sunday, April 23, 5:06 PM
Characteristics and Disease Burden of Patients With Idiopathic Hypersomnia With and Without Long Sleep Time: The Real-World Idiopathic Hypersomnia Outcomes Study (ARISE)	L Schneider	Type: Poster Session Name: P2: Sleep and Neurology 2 Code: P2.13-006 Session Date/Time: Sunday, April 23, 11:45 AM – 12:45 PM
Effects of Lower-Sodium Oxybate on 24-Hour Total Sleep Time: Data From a Phase 3 Clinical Study in Adults With Idiopathic Hypersomnia	AM Morse	Type: Poster Session Name: P5: Sleep Therapeutics 2 Code: P5.13-001

		Session Date/Time: Monday, April 24, 11:45 AM – 12:45 PM
Narcolepsy Data		
Increased Risk of Hypertension Onset Among Patients With Narcolepsy Newly Treated With High-Sodium Oxybate	RH Ben-Joseph	Type: Poster Session Name: P5: Sleep Therapeutics 2 Code: P5.13-002 Session Date/Time: Monday, April 24 11:45 AM – 12:45 PM
Effectiveness and Optimization of Lower-Sodium Oxybate in Participants With Narcolepsy Switching From Sodium Oxybate: Interim Data from the Substitution of Equal Grams of Uninterrupted Xyrem to Xywav (SEGUE) Study	EB Leary	Type: Poster Session Name: P5: Sleep Therapeutics 2 Code: P5.13-003 Session Date/Time: Monday, April 24, 11:45 AM – 12:45 PM
Long-term Safety During a Clinical Trial of Lower-Sodium Oxybate in Participants With Narcolepsy With Cataplexy	RK Bogan	Type: Poster Session Name: P5: Sleep Therapeutics 2 Code: P5.13-006 Session Date/Time: Monday, April 24, 11:45 AM – 12:45 PM
Epilepsy Data		
Long-term Safety and Efficacy of Add-on Cannabidiol (CBD) for Seizures Associated With Tuberous Sclerosis Complex (TSC): 3-Year Results From GWPCARE6 Open-Label Extension (OLE)	E Thiele	Type: Poster Session Name: P14: Epilepsy/Clinical Neurophysiology (EEG): ASMs Clinical Trial 2 Code: P14.1-004 Session Date/Time: Thursday, April 27 11:45 AM – 12:45 PM
Seizure Outcomes With Cannabidiol (CBD) in Pediatric Versus Adult Patients With Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS): Subgroup Analysis of BECOME, a Caregiver Survey	T Saurer	Type: Poster Session Name: P14: Epilepsy/Clinical Neurophysiology (EEG): ASMs Clinical Trial 2 Code: P14.1-006 Session Date/Time: Thursday, April 27 11:45 AM – 12:45 PM
Nonseizure Outcomes With Cannabidiol (CBD) in Pediatric Versus Adult Patients With Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS): Subgroup Analysis of BECOME, a Caregiver Survey	T Dixon-Salazar	Type: Poster Session Name: P14: Epilepsy/Clinical Neurophysiology (EEG): ASMs Clinical Trial 2 Code: P14.1-008 Session Date/Time: Thursday, April 27 11:45 AM – 12:45 PM
Essential Tremor Data		
Diagnosed and Drug-Treated Prevalence of Essential Tremor in Pediatric Patients: Retrospective Analyses of Two US Healthcare Claims Databases	R Saad	Type: Oral Session Name: S51: Movement Disorders: Tremor, Parkinsonism, and Non-motor Symptoms Code: S51.003 Session Date/Time: Thursday, April 27, 3:54 PM
Diagnosed and Drug-Treated Prevalence of Essential Tremor in Adult Patients: Retrospective Analyses of Two US Healthcare Claims Databases	R Saad	Type: Oral Session Name: S51: Movement Disorders: Tremor, Parkinsonism, and Non-motor Symptoms Code: S51.004 Session Date/Time: Thursday, April 27, 4:06 PM

About Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution

Xywav is a low-sodium oxybate approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy and for the treatment of idiopathic hypersomnia in adults. FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* in June 2021 for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and in December 2021 for the treatment of idiopathic hypersomnia in adults. The Office of Orphan Product Development (OOPD) at FDA also published its summary of clinical superiority findings for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7

years of age and older with narcolepsy by means of greater cardiovascular safety compared to Xyrem® (sodium oxybate) oral solution. The decision of the OOPD is based on FDA findings that *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem*. *Xywav* is comprised of a unique composition of cations resulting in 92% less sodium, or a reduction of approximately 1,000 to 1,500 mg/night, than sodium oxybate at the recommended adult dosage range of 6 to 9 grams. While the exact mechanism of action of *Xywav* is unknown, it is hypothesized that the therapeutic effects of *Xywav* on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.[1] The U.S. Drug Enforcement Agency (DEA) has designated *Xywav* as a Schedule III medicine. The DEA defines Schedule III drugs, substances, or chemicals as drugs with a moderate to low potential for physical and psychological dependence.[1,2] Because of the risks of CNS depression and abuse and misuse, *Xywav* is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

Important Safety Information for Xywav

WARNING: Taking XYWAV with other central nervous system (CNS) depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), fainting (syncope), and death.

The active ingredient of XYWAV is a form of gamma hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death. Call your doctor right away if you or your child has any of these serious side effects.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYWAV filled.

Do not take XYWAV if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drinks alcohol, or has a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.

XYWAV can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYWAV.
- **Mental health problems, including** confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, thoughts of killing yourself or trying to kill yourself, increased tiredness, feelings of guilt or worthlessness, or difficulty concentrating. Tell your doctor if you or your child have or had depression or have tried to harm yourself or themselves. **Call your doctor right away if you have or your child has symptoms of mental health problems or a change in weight or appetite.**
- **Sleepwalking**. Sleepwalking can cause injuries. Call your doctor if this occurs.

The most common side effects of XYWAV in adults include nausea, headache, dizziness, anxiety, insomnia, decreased appetite, excessive sweating (hyperhidrosis), vomiting, diarrhea, dry mouth, parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleep walking, and other abnormal sleep-related events), somnolence, fatigue, and tremor.

The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include nausea, bedwetting, vomiting, headache, weight decrease, decreased appetite, dizziness, and sleepwalking.

XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYWAV.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full Prescribing Information, including Boxed Warning, here: https://pp.jazzpharma.com/pi/xywav.en.USPI.pdf

About Xyrem® (sodium oxybate)
Xyrem oral solution, CIII, is a product approved by the U.S. Food and Drug Administration (FDA) for both cataplexy and excessive daytime sleepiness in narcolepsy in adult and pediatric patients ages 7 and older.[3] *Xyrem* may only be dispensed to patients enrolled in the XYWAV and XYREM REMS. *Xyrem* was first approved in the U.S. in 2002, based on clinical trial data in adults.

Important Safety Information for Xyrem

WARNING: Taking XYREM with other CNS depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), dizziness (syncope), and death.

XYREM is a form of gamma hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYREM filled.

Do not take XYREM if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drink alcohol, or have a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYREM in a safe place to prevent abuse and misuse. Selling or giving away XYREM may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYREM should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYREM. Those activities should not be done until you know how XYREM affects you or your child.

XYREM can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYREM.
- **Mental health problems, including confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, or thoughts of killing yourself or trying to kill yourself. Tell your doctor if you or your child have or had depression or have tried to harm yourself. Call your doctor right away if you have or your child has symptoms of mental health problems.**
- **Sleepwalking. Sleepwalking can cause injuries. Call your doctor if you or your child starts sleepwalking.** Your doctor should check you or your child.

Tell your doctor if you are or your child is on a salt-restricted diet or if you have or your child has high blood pressure, heart failure, or kidney problems. XYREM contains a lot of sodium (salt) and may not be right for you or your child.

The most common side effects of XYREM include nausea, sleepiness, dizziness, vomiting, bedwetting, and tremor (in adults). In pediatric patients, headache, decreased appetite, and weight decrease were also common. Your side effects may increase when you take higher doses of XYREM. XYREM can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYREM.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please find full prescribing information here: http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf

About Epidiolex®/Epidyolex® (cannabidiol)
Epidiolex/Epidyolex is a prescription, plant-derived cannabis-based medicine administered as an oral solution which contains highly purified cannabidiol (CBD). Cannabidiol, the active ingredient in *Epidiolex*, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant. The precise mechanisms by which *Epidiolex* exerts its anticonvulsant effect in humans are unknown. *Epidiolex* was approved by the U.S. Food and Drug Administration (FDA) for use in the U.S., the European Commission (EC) for use in Europe, the Medicines and Healthcare products Regulatory Agency (MHRA) for use in Great Britain, the Therapeutic Goods Administration for use in Australia, Swissmedic for use in Switzerland, the Food & Nutrition Services of the Israel Ministry of Health for use in Israel, and the New Zealand Medicines and Medical Devices Safety Authority for use in New Zealand, is an oral solution which contains highly purified cannabidiol (CBD). In the U.S., *Epidiolex* is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) or tuberous sclerosis complex (TSC) in patients one year of age and older. *Epidiolex* has received approval in the European Union under the tradename *Epidyolex* for adjunctive use in conjunction with clobazam to treat seizures associated with LGS and DS in patients two years and older, and for adjunctive use to treat seizures associated with TSC, in patients two years of age and older. *Epidiolex* has received Orphan Drug Designation (ODD) from the U.S. FDA for the treatment of seizures associated with LGS, DS, and TSC. Similarly, *Epidyolex* received ODD from the European Medicines Agency (EMA) for the same indications.

Important Safety Information & Indications

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

WARNINGS & PRECAUTIONS

Hepatocellular Injury:
EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury.

Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more

commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

ADVERSE REACTIONS:
The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

PREGNANCY:
EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

DRUG INTERACTIONS:
Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates (see full Prescribing Information). Consider dose reduction of orally administered everolimus, with appropriate therapeutic drug monitoring, when everolimus is combined with EPIDIOLEX. A lower starting dose of everolimus is recommended when added to EPIDIOLEX therapy. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

INDICATIONS:
EPIDIOLEX (cannabidiol) oral solution is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

Please refer to the EPIDIOLEX full Prescribing Information for additional important information here.

About Jazz Pharmaceuticals plc Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. Please visit www.jazzpharmaceuticals.com for more information.

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References:

1. Xywav (calcium, magnesium, potassium and sodium oxybates) oral solution. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2021.
2. United States Drug Enforcement Agency. Drug Scheduling. https://www.dea.gov/drug-scheduling. Accessed September 2022.
3. Xyrem (sodium oxybate) oral solution. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2022.

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