XWPharma Ltd.
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Addressing unmet needs in treating a wide range of neurological disorders

XWPharma is harnessing clinically validated mechanisms of action to develop novel drug candidates with optimized pharmacokinetics, resulting in superior therapies for the treatment of common, debilitating neurological diseases.

XWPharma is a biopharmaceutical company dedicated to the discovery and development of potential first- and best-in-class medicines with unique features to address the medical needs of patients suffering from debilitating neurological diseases. The company, which has offices in the United States, China, and Taiwan, has created novel therapies that leverage mechanisms of action that have been validated as highly effective in clinical studies and medical practice.

The goal of this drug discovery approach is to achieve therapeutic efficacy while avoiding side effects associated with available treatments. Ultimately, this strategy will increase the odds that these internally discovered medicines will succeed in clinical testing and commercialization. The company's two clinical-stage programs focus on the development of XW10172 for sleep dysfunction, and XW10508 for treatment-resistant depression and chronic pain.

"XWPharma has built a highly productive drug discovery platform, capitalizing on its extensive experience with proprietary techniques to improve pharmacology," said president and chief executive officer, Leonard Blum. "The company's current pipeline is evidence of its capability to generate multiple exciting new investigational drugs for patients with severely debilitating neurological disorders."

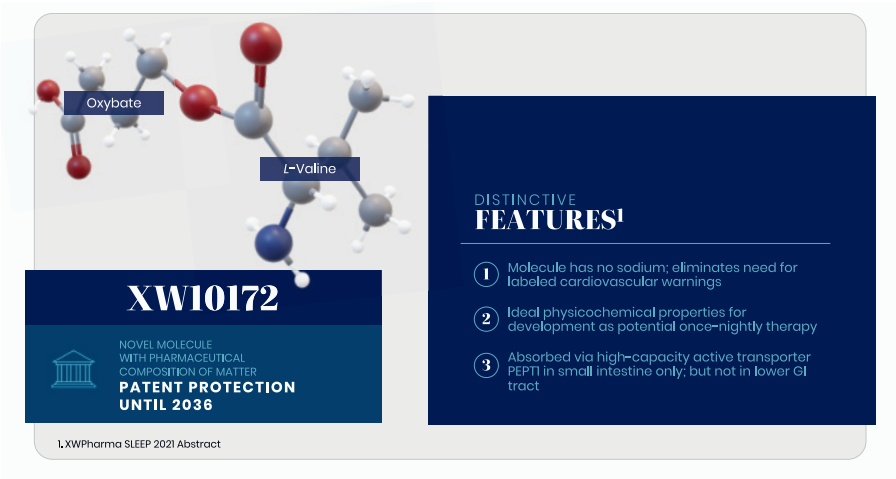

Fig. 1 | Distinctive features of XWPharma's candidate XW10172.

Superior sleep without side effects

Sleep abnormalities are common across neurodegenerative diseases, affecting more than one million people in the United States alone. Typically, patients experience a reduction in slow-wave sleep and frequent episodes of rapid-eye-movement (REM) sleep. This fragmented sleep architecture can result in excessive daytime sleepiness, multiple awakenings, fatigue, insomnia, spontaneous daytime dozing, and hallucinations.

Narcolepsy is a life-long disease characterized by fragmented sleep which manifests primarily as excessive daytime sleepiness and cataplexy—sudden and uncontrollable muscle weakness or paralysis. It is considered an orphan disease in the United States, affecting between 165,000 and 185,000 people. Agonists of gamma-aminobutyric acid ($GABA_B$) receptors, which are indicated for the treatment of narcolepsy, currently represent more than $1.7 billion in annual sales in the United States.

The majority of patients with Parkinson's disease also experience sleep problems. Nearly half a million patients in the United States experience fatigue and excessive daytime sleepiness. These symptoms often manifest at early disease stages, and negatively impact both productivity and quality of life. In the United States, no treatments have been approved by the Food and Drug Administration (FDA) for sleep disorders resulting from Parkinson's disease. Currently available treatment options either have poor efficacy or cause adverse events such as anxiety and a rise in blood pressure.

To address this significant unmet need, XWPharma has developed the $GABA_B$ agonist XW10172 as a superior alternative to sodium oxybate, which is FDA approved for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy. Sodium oxybate has also demonstrated efficacy for normalizing sleep architecture and improving sleep outcomes in patients with Parkinson's disease.

In contrast to sodium oxybate, XW10172 contains no sodium and therefore poses no excess cardiovascular risk. Moreover, XW10172 requires only one dose at night rather than the twice-nightly dosing used for sodium oxybate.

XW10172 is a stabilized form of oxybate consisting of a high concentration of uniformly small and spherical granules, which are ideal for yielding predictable release (Fig. 1). In addition, absorption occurs in the small intestine within four to six hours, avoiding late-stage absorption in the large intestine. Together, these optimized drug design features will lead to fast sleep onset, sustained sleep during the night, and low concentrations at waking hours to prevent any hangover effect.

XW10172 has completed phase 1 clinical trials. XWPharma expects to release this data soon and initiate phase 2 studies in patients with Parkinson's disease. In addition, a single pivotal phase 3 trial is planned for patients with narcolepsy. The orphan drug designation is expected to expedite further development of XW10172 for narcolepsy. The FDA grants orphan status to promising investigational drugs designed to treat, prevent, or diagnose rare medical diseases or conditions that affect fewer than 200,000 individuals in the United States.

"In just over three years, we went from an idea to first-in-human clinical trials," said XWPharma's founder and Chief Scientific Officer Jia-Ning Xiang. "This demonstrates that our platform technology can deliver better compounds into the clinic in a shorter time than traditional Research and Development approaches for neurological disorders."

Safer solution for common conditions

Treatment-resistant depression and chronic pain are both highly prevalent and debilitating conditions. More than 264 million people worldwide suffer from major depressive disorder, and one-third of these patients are considered treatment-resistant, failing two or more antidepressants.

One in five people around the world experience chronic pain. In the United States alone, more than 20 million people have high-impact chronic pain, which frequently limits life or work activities. Despite therapies available, significant needs remain in treating both disorders, and a large number of patients are unable to find relief from existing options.

N-methyl-D-aspartate (NMDA) receptor antagonists such as intravenous ketamine and intranasal esketamine are proven to be effective

Fig. 2 | Distinctive features of XWPharma's candidate XW10508.

for treating patients who have major depressive disorder or chronic pain, and do not respond to other forms of therapy. Spravato is an esketamine therapy that works quickly and has lasting efficacy, but it requires administration under supervision of a healthcare provider, and can lead to adverse events such as dissociation, sedation, and high blood pressure. These side effects peak at 60 minutes, and can last between four and six hours.

To address these limitations, XWPharma developed XW10508 as an esketamine-based therapy with an optimized therapeutic index. XW10508 is a glutamatergic NMDA antagonist and AMPA activator designed for the treatment-resistant depression and chronic pain. Unlike Spravato, XW10508 is an oral therapy that slowly releases esketamine over a longer time period. Due to its improved pharmacokinetics, XW10508 has the potential to avoid adverse events such as dissociation, sedation, and high blood pressure, while providing lasting relief from depression and chronic pain (Box 1).

Compelling evidence suggests that lower concentrations of ketamine or esketamine can be effective for the treatment of depression. Moreover, XW10508 has improved bioavailability, extended absorption throughout the entire gastrointestinal tract for once-daily administration, and is inactive upon ingestion until it is metabolized in the liver. These unique pharmacological properties minimize the risk of abuse (Fig. 2).

XW10508 has completed FDA Investigational New Drug (IND)-enabling studies, and is expected to enter the clinic in the second quarter of 2021 for the assessment of safety and tolerability. By the middle of next year, XWPharma plans to release phase 2a trial data for patients with treatment-resistant depression and chronic pain.

- Good oral bioavailability shown across multiple nonclinical species
- Absorption throughout the gastrointestinal tract to enable once-daily dosing
- Compound inactive until metabolization in liver, preventing rapid onset of effect following alternative means of delivery directly into the blood stream

Box 1 | Favorable characteristics of XW10508.

Talented team

The successful discovery and development of these two lead drug candidates would not have been possible without the efforts of the company's senior leadership team, including Blum, Xiang, and Chief Medical Officer, Daniel Canafax.

Xiang launched XWPharma in 2014. From 2007 to 2013, he was the senior director of Integrated Platform & Sciences and the head of Medicinal Chemistry at the GlaxoSmithKline Neuroscience Center in Shanghai. He was director of Medicinal Chemistry at XenoPort from 2001 to 2007. Prior to that, he spent nine years at SmithKline Beecham, holding various positions, most recently as assistant director of Medicinal Chemistry. Xiang holds 62 issued United States patents and contributed to nine compounds that were studied in clinical trials of central nervous system disorders, including the marketed drug, Horizant, for the treatment of restless legs syndrome and neuropathic pain.

"I am thrilled to work on expanding XWPharma's footprint in the United States and rapidly advancing our transformative therapeutics through development, registration and launch," Xiang said.

Canafax has been XWPharma's chief medical officer since 2018. He has more than 22 years of experience in the pharmaceutical industry, leading clinical drug development from concept, preclinical studies, and clinical studies through marketing approval and post-marketing research. Canafax has significant expertise in designing and monitoring studies for developing new drug therapies for central nervous system disorders, immunosuppression, renal diseases, gastrointestinal diseases, infectious diseases, and other indications.

"I am delighted to lead the clinical development of new drugs with the potential to benefit many patients in the near future," Canafax said. "I look forward to continuing to work closely with Jia-Ning Xiang and the entire XWPharma management team, the medical community, and the patients in need of new therapies. We will work diligently to provide new treatment options for the millions of patients who suffer from neurologic diseases."

Before joining XWPharma in April 2020, Blum founded, built, and led commercial organizations at a series of emerging growth biopharmaceutical companies, including ICOS Corp. (acquired by Eli Lilly), Theravance, Omeros Corp., and Madrigal Pharmaceuticals. From 1987 to 2000, he progressed through marketing, sales, and business leadership roles at Merck and Co. Over the past 33 years, Blum has been responsible for national and global launches, turnarounds, and rapid sales acceleration for more than 20 medicines in a wide variety of therapeutic categories, including specialty products and blockbusters. His work has earned multiple industry accolades, and is the subject of two Harvard Business School case studies.

"Our team brings together decades of drug discovery, development and commercialization expertise with a notable track record of success," Blum said. "We share a commitment to bring forward truly original medicines for treating sleep disorders, treatment-resistant depression, chronic pain and other disease states that continue to present huge and underserved challenges for patients, healthcare systems, and societies around the world."

Evolving opportunities

XWPharma remains focused on advancing its two lead drug candidates through clinical trials. Meanwhile, the company is also developing potential treatments for epilepsy, neuropathic pain, amyotrophic lateral sclerosis, and gastroparesis.

XWPharma pursues efficient development pathways that are designed to de-risk each program at an early stage of clinical development. Each therapy targets high value commercial markets with favorable reimbursement and market access. Moreover, all therapies in clinical development are new chemical entities with distinctive features and composition-of-matter patent protection.

To date, the company has raised more than $63 million from leading healthcare investors in the United States and Asia. Investors include Kleiner Perkins, Johnson & Johnson Innovation, WuXi AppTec, WI Harper Group and others.

Currently, XWPharma is seeking opportunities for partnership and commercialization at all stages of drug development, both in the United States and in China. "These partnerships will be invaluable as we prioritize the multiple high potential opportunities our research unit has identified and navigate the evolving therapeutics landscape of creating first-of-their-kind therapeutics for patients suffering from neurological disorders with compelling unmet needs," Blum said.

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