NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Ondansetron for treating alcohol use disorder

Company/Developer	Adial Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28420	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Completed phase III trial

Summary

Ondansetron is currently in clinical development for the treatment of alcohol use disorder (AUD). AUD consist of disorders characterised by compulsive heavy alcohol use and loss of control over alcohol intake. AUD are some of the most prevalent mental disorders globally, especially in high-income and upper-middle-income countries; and are associated with high mortality and burden of disease, mainly due to medical consequences, such as liver cirrhosis or injury. Despite their high prevalence, AUD are undertreated partly because of the high stigma associated with them. The relapse rate of people with AUD is high with few effective treatment options available. Factors such as family circumstances, age, and social norms are said to influence alcohol misuse.

Ondansetron is in a class of medications called serotonin 5-HT3 receptor antagonists. It works by blocking the action of serotonin, a natural substance that may contribute to alcohol dependence. Several studies have shown that ondansetron helps reduce alcohol cravings for people with AUD. Ondansetron has an oral route of administration, and if licenced, will offer additional treatment option for people with AUD.

Proposed Indication

Treatment of alcohol use disorder (AUD) in adults.[1]

Technology

Description

Ondansetron (Zofran, ADO4) is a potent, highly selective 5-hydroxytryptamine receptor-antagonist.[2] Serotonin-3 receptors, also called 5-Hydroxytryptamine (5-HT_3) receptors, are classes of proteins expressed in the central nervous system in regions involved in the reward system, processing of pains and other controls.[3] Molecular studies show that alcohol potentiates selective 5-HT3 receptor-mediated ion currents, an effect blocked by selective 5-HT3 receptor antagonists.[4-6] Mesocorticolimbic dopamine pathways mediate alcohol's rewarding effects and that of other abused substances.[6-11] Densely distributed 5-HT3 receptors in mesocorticolimbic neuronal terminals regulate dopamine release.[6,12,13] Selective 5-HT3 receptor blockade, by attenuating dopamine release, reduces alcohol consumption in several animal models and across species.[6,14-22]

Ondansetron is currently in clinical development for the treatment of adult patients with AUD. In phase III clinical trial (NCT04101227; ONWARD), participants received an oral dose (0.33 mg) of ondansetron twice a day.[1]

Key Innovation

Effective treatment for AUD and alcohol-associated diseases remains challenging, and cognitive and behavioural treatment, with or without pharmaceutical interventions, remains the most commonly used method; however, their efficacy is limited.[23] People who develop early-onset AUD historically are not helped by counselling, exhibit anti-social behaviour, and have a high relapse rate when they attempt to stop drinking.[24] Ondansetron has been shown to reduce alcohol use in animal models and has the potential to reduce alcohol consumption in humans.[25] Studies have reported that ondansetron reduces alcohol-induced positive subjective effects and alcohol preference.[26-28] If licenced, ondansetron will offer an additional treatment option for people with AUD.

Regulatory & Development Status

Ondansetron is licensed in the UK for the following indications:[2]

- For the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults
- For the management of chemotherapy-induced nausea and vomiting in children aged ⩾ 6 months, and for the prevention and treatment of PONV in children aged ⩾ 1 month

Ondansetron is in phase II/III development for a number of indications, some of which include:[29]

- Gastroenteritis
- Sleep syncope
- Indigestion
- Sepsis

Patient Group

Disease Area and Clinical Need

AUD, which is also called alcohol misuse, occurs when one drinks in a way that is harmful, or when one is dependent on alcohol.[30-32] AUD is marked by uncontrolled drinking behaviour, and some of the risk factors for AUD include; family history of AUD, drinking at an early age, and other socio-economic factors arising from the loss of a job, housing, or a loved one.[33-36] AUD presents several risks that can be short- or long-term risks. The short-term risks include accidents and injuries, violent behaviours and being victims of such violence, loss of personal possessions, alcohol intoxication and the infection with sexually transmitted diseases through engaging in unprotected sex. Long-term risks of AUD include stroke, liver cancer, bowel cancer, breast cancer, pancreatitis, mouth cancer, heart disease, liver disease and brain damage.[30]

AUD accounts for approximately 5.3% and 5.1%, of global mortality and morbidity respectively.[7] In England, 4% of those aged between 16 and 65 are dependent on alcohol (6% of men and 2% of women), with more than 24% of the English population consuming alcohol in a way that is harmful to their health or well-being.[37] There were 17,040, (equating 10.8 deaths per 100,000) alcohol-specific deaths in England between 2016 and 2018 while in 2018 alone, an estimated 24,720 alcohol-related deaths (equating 46.5 deaths per 100,000) were reported in England.[38] In England (2021-22), there were 68,236 finished consultant episodes (FCEs) and 38,753 admissions for mental and behavioural disorders due to use of alcohol (ICD-10 code F10). This resulted in 60 day cases and 182,864 FCE bed days.[39]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following pharmacological treatment options for AUD (assisted withdrawal):[37] Benzodiazepine (chlordiazepoxide or diazepam), except in cases of liver impairment.

NICE also recommends the following pharmacological treatment options for moderate and severe alcohol dependence following successful withdrawal:[37]

- Acamprosate or oral naltrexone in combination with a psychological intervention
- Disulfiram in combination with a psychological intervention

Clinical Trial Information

Trial	**ONWARD**; NCT04101227, EudraCT 2019-000737-39; Study to Evaluate the Efficacy, Safety and Tolerability of AD04 (Ondansetron) in Adults With Alcohol Use Disorder (AUD) and Selected Polymorphisms in the Serotonin Transporter and Receptor Genes. **Phase III** – Completed **Location(s):** Seven EU countries **Study completion date:** March 2022
Trial Design	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled
Population	N= 302 (actual); adults of age 18 years and above who have moderate to severe diagnosis of AUD as measured by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria
Intervention(s)	• Oral ondansetron 0.33 mg twice a day • Companion diagnostic for genetic testing • Brief psychological counselling
Comparator(s)	• Matching placebo orally administered twice a day • Companion diagnostic for genetic testing

	• Brief psychological counselling
Outcome(s)	**Primary outcome measure:** Change from baseline in the percentage of monthly heavy drinking days [Time frame: weeks 16 to 24] See trial record for a full list of other outcomes.
Results (efficacy)	• Ondansetron demonstrated statistically significant difference in AUD severity, as compared to placebo, with an 84% decrease in the number of heavy drinking patients meeting the criteria for AUD diagnosis.[40] • Ondansetron achieved a statistically significant mean reduction in heavy drinking days among pre-specified group of heavy drinkers, compared to placebo, with an approximately 79% reduction from baseline drinking.[40]
Results (safety)	• No serious adverse events (SAEs) were determined to be related to ondansetron treatment.[40] • More SAEs were reported in the placebo group compared with the ondansetron group (7 on placebo vs. 3 on ondansetron).[40]

Estimated Cost

Ondansetron is already marketed in the UK; 10 tablets of 4 mg ondansetron cost £9.00 according to the National Health Service (NHS) indicative price.[41]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Nalmefene for reducing alcohol consumption in people with alcohol dependence (TA325). November 2014.
- NICE clinical guideline. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence (CG115). February 2011.
- NICE clinical guideline. Alcohol-use disorders: diagnosis and management of physical complications (CG100). April 2017.
- NICE quality standard in development. Alcohol-use disorders update (GID-QS10164). Expected July 2023.
- NICE quality standard. Alcohol-use disorders: diagnosis and management (QS11). August 2011.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- University Hospital Sussex NHS Foundation Trust. Alcohol Withdrawal Syndrome: Management guidelines for adults. 2021.[42]

Additional Information

Adial Pharmaceuticals are yet to enter information about this technology onto the UK PharmaScan database, which serves as the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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