NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Bardoxolone Methyl for the treatment of chronic kidney disease (CKD) caused by Alport Syndrome

Company/Developer	Reata Pharmaceuticals Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23812	NICE ID: 9998	UKPS ID: -

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Bardoxolone methyl is in clinical development for the treatment of patients aged 12 years and older with Alport syndrome. Alport syndrome is a genetic condition characterized by kidney disease, hearing loss, and eye abnormalities. It is caused by a defect (mutation) in a gene for a protein in the connective tissue, called collagen. There are currently no licensed treatments to treat the underlying mechanism of the condition although some of the symptoms can be managed to slow down the progression of the disease. The condition can become life threatening unless patients receive dialysis treatments several times a week (patients are connected to a machine for several hours that removes waste products from their blood) or receive a kidney transplant.

Bardoxolone methyl is a novel treatment that activates pathways in the body to reduce inflammation and the damage that the Alport syndrome causes to the kidneys, helping to protect cells and make them function more normally. Bardoxolone methyl is administered orally once a day and preliminary studies have shown potential benefits in improving kidney function. If licensed, bardoxolone methyl would offer a treatment option to patients with Alport syndrome with mutations in several different genes.

Proposed Indication

The treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and older.[1,2]

Technology

Description

Bardoxolone methyl (Imbarkyd, RTA-402) is an investigational, oral, once-daily activator of Nrf2, a transcription factor that induces molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signalling.[3] Bardoxolone methyl is expected to work by activating a protein called NrF2, which triggers the production of other proteins that reduce inflammation and help protect cells. It is also expected to block the production of a protein called NF-κB, which is involved in causing inflammation. These two actions are expected to help reduce the scarring and kidney damage in patients with Alport syndrome.[4]

Bardoxolone methyl is in clinical development for the treatment of patients aged 12 years and older with histologically or genetically confirmed Alport syndrome and have a gene mutation in COL4A3, COL4A4, or COL4A5. In the phase II/III clinical trial (NCT03019185), bardoxolone methyl was administered orally once-daily for adult patients or once every two days for patients under the age of 18 before they move to daily administration, starting at 5mg and progressively increasing at weeks two, four and six.[1]

Key Innovation

The novel mechanism of bardoxolone methyl has been shown to result in statistically significant improvement in kidney function through increased eGFR (estimated glomerular filtration rate) when compared to a placebo in all groups studied, reducing the risk of kidney failure events by approximately 50% in the paediatric population subgroup, but significant efficacy was demonstrated in all population subgroups tested.[3]

If licensed, bardoxolone methyl will be the first treatment option available to patients with Alport syndrome that treats the underlying mechanisms of the disease and not just the symptoms, helping to improve kidney function and delay or prevent the patient from needing subsequent dialysis treatment or kidney transplant.

Regulatory & Development Status

Bardoxolone methyl does not currently have Marketing Authorisation in the EU/UK for any indication.

Bardoxolone methyl is in phase III/ II clinical development for the following indications:[5]

- Chronic kidney disease
- Autosomal dominant polycystic kidney disease

Bardoxolone methyl was granted an orphan drug designation by the European Medicines Agency (EMA) in 2018 for the treatment of Alport syndrome.[4]

Patient Group

Disease Area and Clinical Need

Alport syndrome is an inherited condition caused by a mutation in a gene responsible for producing type IV collagen, a fibrous protein needed to form the membranes that separate and support cells in organs such as the kidney, ear and eye.[4] There are three genetic types, the X-linked Alport syndrome (XLAS) being the most common and affected males typically have more severe disease than affected females. In autosomal recessive Alport syndrome (ARAS) the severity of disease in affected males and females is similar. There is also an autosomal dominant form (ADAS) that affects males and females with equal severity.[6] In patients with Alport syndrome, these membranes have an abnormal structure, so the organs cannot develop and function properly. Patients experience internal scarring and inflammation of the kidney and gradually worsening kidney function that eventually results in kidney failure. Patients also suffer hearing loss and may develop cataracts and visual impairment. Alport syndrome is a long-term debilitating disease due to the progressive kidney damage and impaired hearing and vision; it is potentially life threatening because of the resulting kidney failure and patients eventually require dialysis or transplantation.[4]

Alport syndrome is a rare disease, affecting around 40 people per million in the UK, including genetic carriers with no symptoms.[7] Symptoms of Alport syndrome progressively escalate in severity, with most severely affected individuals experiencing end-stage renal disease and deafness by the age of 40 and having a reduced life expectancy without regular dialysis treatment or renal transplant.[8] In England (2020-21), there were 232 finished consultant episodes (FCE) for Alport syndrome (ICD-10 code: Q87.8 [other specified congenital malformation syndromes affecting multiple systems, not elsewhere classified]), with 208 hospital admissions of which 115 were day cases and 802 FCE bed days.[9]

Recommended Treatment Options

If Alport syndrome is detected at an early stage it may be possible to slow down the rate of progression of kidney disease by using ACE (angiotensin-converting enzyme) inhibitors to lower blood pressure. Regular blood and urine tests are also carried out to gauge kidney function and symptoms management treatments can also be offered if secondary issues such as anaemia, high blood pressure or bone weakness occur. Diet, weight management, regular exercise and avoiding use of NSAID (non-steroidal anti-inflammatory) drugs can also help preserve kidney health. Some patients with Alport syndrome may need dialysis or a kidney transplant as the disease progresses.[10]

Clinical Trial Information

Trial	**CARDINAL; NCT03019185;** A Phase 2/3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome **Phase II/III –** Complete **Location(s):** UK, USA, Australia, 3 EU countries and others **Study completion date:** October 2020	**EAGLE; NCT03749447;** An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients with Chronic Kidney Disease **Phase III –** Recruiting **Location(s):** 2 EU countries, USA, Australia, Japan, and Puerto Rico **Primary Completion date:** December 2025

Trial Design	Randomised, parallel assignment, triple-masked	Single group assignment, open label
Population	N= 187 (actual); patients diagnosed with Alport syndrome with a documented mutation in a gene associated with Alport syndrome including COL4A3, COL4A4, or COL4A5; aged 12 to 70 years.[a]	N= 480 (estimated); patients who have participated in qualifying studies and who have not been required to discontinue treatment for safety or protocol reasons, diagnosed with Alport syndrome and CKD; aged 12 years and older.
Intervention(s)	Adult patients (≥ 18 years of age) will receive 5mg bardoxolone methyl once-daily with dose escalating to 10mg at week two, 20mg at week four, and to 30mg at week six (only if baseline urine albumin creatine ratio (ACR) >300 mg/g. Patients under the age of 18 receiving bardoxolone methyl will start 5 mg every other day during the first week and begin once-daily dosing with 5 mg during the second week of the study, and then continue with once-daily dosing following the same aforementioned dose titration scheme based on baseline ACR at Weeks 2, 4, and 6.	Bardoxolone methyl capsules for daily oral administration, escalating from 5mg up to no more than 30mg at weeks two, four and six.
Comparator(s)	Matched placebo, administered via oral capsule	No active comparator
Outcome(s)	Primary outcome measure: Increase in eGFR from baseline (time frame: 48 weeks). See trial record for full list of other outcomes.	Primary outcome measure: Long-term safety by incidence of adverse events and serious adverse events (time frame: up to five years)
Results (efficacy)	The Phase 3 CARDINAL study met its primary and key secondary endpoints at the end of Year 2. At Week 100, in the intent-to-treat ("ITT") population, which include eGFR values for patients who either remained on or discontinued study drug, patients treated with bardoxolone had a statistically significant improvement compared to placebo in mean change	Bardoxolone produced a mean increase from baseline (n = 14) in eGFR of 11.5 mL/min/1.73 m2 at Year 1, 13.3 mL/min/1.73 m2 at Year 2, and 11.0 mL/min/1.73 m2 at Year 3.[3]

[a] Information provided by Reata Pharmaceuticals Inc.

	from baseline in eGFR of 7.7 mL/min/1.73 m2 (p=0.0005). In the modified ITT ("mITT") analysis, which assessed the effect of receiving treatment by excluding values after patients discontinued treatment, patients treated with bardoxolone had a statistically significant improvement compared to placebo in mean change from baseline in eGFR at Week 100 of 11.3 mL/min/1.73 m2 (p<0.0001). At Week 104 (four weeks after last dose in second year of treatment), patients in the ITT population treated with bardoxolone had a statistically significant improvement compared to placebo in mean change from baseline in eGFR of 4.3 mL/min/1.73 m2 (p=0.023).[3]	
Results (safety)	Bardoxolone was generally reported to be well tolerated in this study, and the safety profile was like that observed in prior trials. Seventy-five patients (97%) receiving bardoxolone and 77 patients (96%) receiving placebo experienced an adverse event ("AE"). Ten patients (13%) receiving bardoxolone and four patients (5%) receiving placebo discontinued study drug due to an AE, and no individual AE contributed to more than two discontinuations in either group. The reported AEs were generally mild to moderate in intensity, and the most common AEs observed more frequently in patients treated with bardoxolone compared to patients treated with placebo were muscle spasms and increases in aminotransferases. Eight patients (10%) receiving bardoxolone and 15 patients (19%) receiving placebo experienced a treatment-emergent serious adverse event ("SAE"). No SAEs were reported in paediatric patients treated with bardoxolone. No fluid overload or major adverse cardiac events were	Bardoxolone treatment was generally reported to be well-tolerated.[3]

	reported in patients treated with bardoxolone. Blood pressure was not significantly different between the two groups. The ACR was not significantly different between treatment groups at Week 100 or Week 104. Non-kidney symptoms associated with Alport syndrome, including psychiatric, hearing, vestibular, and ocular AEs, occurred less frequently in bardoxolone-treated patients.[3]	

Estimated Cost

The cost of bardoxolone methyl is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline. Chronic kidney disease: assessment and management (NG203). November 2021.
- NICE interventional procedures guidance. Robot-assisted kidney transplant (IPG609). 2018

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Assessment and preparation for renal replacement therapy (including establishing dialysis access. A06/S/a. December 2015.
- NHS England. Clinical Commissioning Policy: Dialysis away from base. A06/p/a. December 2015.
- NHS England. 2013/14 NHS Standard Contract for Adult Kidney Transplant Service. A07/S/a.

Other Guidance

- European Journal of Human Genetics. Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria. 2021.[11]
- Paediatric Nephrology. Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young-adults- an update for 2020. 2020.[12]
- American Society of Nephrology. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. 2013.[13]

Additional Information

Reata Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; 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.

References

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