This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Oxabact for primary hyperoxaluria

Target group
- Primary hyperoxaluria (PH): type 1 and 2.

Background
There are four main types of hyperoxaluria: primary hyperoxaluria (types 1 and 2), enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic or mild hyperoxaluria\(^1\). Primary hyperoxaluria type 1 (PH1) is a rare metabolic disorder transmitted as an autosomal recessive disease, caused by a defect of the peroxysomal hepatic enzyme L-alanine, glyoxylate aminotransferase (AGT). The defect in AGT, which normally converts glyoxylate to glycin, results in an increase of the glyoxylate pool, which is converted to oxalate\(^2\). Hyperoxaluria type 2 (PH2) is caused by a deficiency in glyoxylate reductase (formerly known as D-glycerate dehydrogenase).

Haematuria, dysuria, uraemia, recurrent urolithiasis and nephrocalcinosis are the earliest clinical manifestations of PH. The first symptoms occur before one year of age in 15% of patients and before 5 years of age in 50%\(^2\). The infantile form is characterised by chronic renal failure due to massive oxalate deposition. In other patients, urolithiasis develops with infections, haematuria, renal colics or acute renal failure due to complete obstruction. End-stage renal failure occurs before 15 years of age in half the cases and the resulting increase of circulating oxalate leads to its deposition in tissues causing cardiac conduction defects, distal gangrene, and reduced joint mobility and pain\(^7\). As both PH1 and PH2 are inherited as autosomal recessive disorders, although rare, one family may have several affected children requiring active management.

Technology description
Oxabact is an oral product consisting of lyophilised live *Oxalobacter formigenes*, an oxalate-degrading bacterium isolated from the human gastrointestinal tract. *Oxalobacter formigenes* promotes the removal of endogenously produced oxalate and facilitates the transport of oxalate from the plasma into the intestines, thereby decreasing the amount of oxalate eliminated through the kidneys. Lowering of urinary oxalate levels is expected to reduce urinary calcium oxalate super saturation, thus preventing the formation of kidney stones, obstructive uropathy, nephrocalcinosis and renal failure.

Oxabact is supplied as an enteric-coated hard capsule, designed for delivery of live organisms beyond the stomach to the intestinal tract. Each capsule contains \(\geq10^7\) to \(\leq10^{10}\) colony forming units (CFU) of freeze dried live *Oxalobacter formigenes* and is administered twice daily for chronic use.

Innovation and/or advantages
If licensed, Oxabact will be the first specific treatment for PH.

Developer
OxThera.

Availability, launch or marketing dates, and licensing plans:
Oxabact has orphan drug designation in the EU and USA and is in phase II/III clinical trials.
NHS or Government priority area:

This topic relates to:


Relevant guidance

- The Renal Association Clinical Practice Guidelines for Haemodialysis (2007)\(^4\).

Clinical need and burden of disease

The incidence of PH1 can be underestimated because diagnosis is often delayed or overlooked. PH1 has been shown to occur in Europe at a rate of approximately 1 per 10\(^7\) of population per year\(^5\). Data from UK, Switzerland and France suggest that 1 in 60,000 to 120,000 children has PH1\(^6\). The prevalence of PH1 has been estimated to be between 1-3 per million of the population\(^5,7,8,9\). The incidence of PH2 has not been accurately defined, and may also be under-diagnosed. The prevalence of PH2 is estimated to be 0.1 times that of PH1, thus the prevalence of PH (both PH1 and PH2) is about 3 per million\(^a\) (equating to around 150 patients in England and Wales).

Existing comparators and treatments

Currently there are no approved therapies to manage the underlying cause of PH. Renal transplantation alone does not correct the metabolic disorder, which will recur in the graft\(^2\). Current interventions include\(^1\):

- Combined liver/kidney transplant.
- Dialysis for renal failure.
- Vitamin B-6 (pyridoxine).
- Diet/high fluid intake/compounds to increase calcium oxalate solubility in urine.
- Compounds such as orthophosphate or a mixture of sodium, potassium or magnesium citrate can be used to increase the urinary solubility of calcium oxalate.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code or name</th>
<th>NCT00638703 (PHOENIX)(^10); OC3-DB-01: PH1 and PH2; phase II/III.</th>
<th>Extension study (OC3-OL-01)(^b): PH1 and PH2; phase II/III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>OxThera.</td>
<td>OxThera.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing but not recruiting.</td>
<td>Ongoing but not recruiting.</td>
</tr>
<tr>
<td>Location</td>
<td>UK, Netherlands, France, Germany and USA.</td>
<td>UK, Netherlands, France, Germany and USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Double-blind, randomised, placebo-controlled.</td>
<td>Open-label extension.</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=42; patients aged ≥5 years; PH1 and PH2. Randomised to Oxabact or placebo.</td>
<td>n=42; patients aged ≥5 years; PH1 and PH2. All patients received Oxabact.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>24 weeks.</td>
<td>24 weeks.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Reduction in urinary oxalate and safety.</td>
<td>Safety and efficacy.</td>
</tr>
<tr>
<td>Expected reporting</td>
<td>Results expected Q4 of 2008. Expected date of final analysis or publication: Q1/2</td>
<td>Expected date of final analysis or publication: Q2/3 2009.</td>
</tr>
</tbody>
</table>

\(^a\) Information from expert.

\(^b\) Information from the company.
Trial code or name | IxOC-2, IxOC-3; PH1; normal renal function, renal failure or kidney-liver transplant.
---|---
Sponsor | OxThera.
Status | Published\(^\text{1}\)\(^\text{1}\).
Location | Germany, USA.
Design | Uncontrolled.
Participants in trial | n=16; PH1. *Oxalobacter* for 4 weeks, administered either as frozen paste equivalent to >10\(^{10}\) CFUs (IxOC-2 study) or 2 enteric-coated capsules each equivalent to ~10\(^{7}\) CFUs (IxOC-3 study).
Follow-up | 2 weeks.
Primary outcome | >20% reduction in urinary oxalate (expressed as mmole/mole creatinine), plasma oxalate in end stage renal failure (ESRF) patients and safety.
Key results | IxOC-2: 3/5 participants with normal renal function responded with 22-48% reduction in urinary oxalate. 2 participants with renal failure experienced reduction in plasma oxalate and amelioration of clinical symptoms. IxOC-3: 4/6 participants with normal renal function responded with 38.5-92% reduction in urinary oxalate. Faecal recovery generally dropped directly at follow up, indicating only transient gastro-intestinal tract colonisation.
Adverse effects | No major side effects reported; flatulence was infrequently reported in both study groups.

**Estimated cost and cost impact**

The cost of Oxabact has not been determined.

**Potential or intended impact – speculative**

If Oxabact is proven to be successful in significantly reducing urinary oxalate, live-kidney transplantation with its attendant problems of life-long immunosuppression and lack of donor organs, may not be required\(^\text{1}\).

<table>
<thead>
<tr>
<th>Patients</th>
<th>☑ Reduced morbidity</th>
<th>☐ Reduced mortality or increased survival</th>
<th>☐ Improved quality of life for patients and/or carers</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Quicker, earlier or more accurate diagnosis or identification of disease</td>
<td>☐ Other:</td>
<td>☐ None identified</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Services</th>
<th>☐ Increased use</th>
<th>☐ Service reorganisation required</th>
<th>☐ Staff or training required</th>
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</thead>
<tbody>
<tr>
<td>☑ Decreased use e.g. reduced length of stay in hospital.</td>
<td>☐ Other:</td>
<td>☐ None identified</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs</th>
<th>☐ Increased unit cost compared to alternative</th>
<th>☐ Increased costs: more patients coming for treatment</th>
<th>☐ Increased costs: capital investment needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ New costs:</td>
<td>☑ Savings: may reduce future renal and other major complications.</td>
<td>☐ Other:</td>
<td></td>
</tr>
</tbody>
</table>

**References**


\(^{1}\) Expert opinion.


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The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.