Aganirsen for pathological corneal neovascularisation

August 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Aganirsen for pathological corneal neovascularisation

Target group
- Pathological corneal neovascularisation (CoNV).

Technology description
Aganirsen is an antisense oligonucleotide against the insulin receptor substrate-1 (IRS-1). Antisense oligonucleotides are short, synthetic oligonucleotides which are complementary in sequence and function by specific hybridisation to their cognate gene product (mRNA), inducing inhibition of gene expression. IRS-1 is known to be over-expressed in pro-angiogenic conditions, and by reducing the over-expression of IRS-1 associated with pathological neovascularisation, aganirsen regulates both the expression of angiogenic growth factors and inflammatory cytokines. Aganirsen is administered via twice daily eye drops at a total dose of 86µg daily for 2-6 months depending on the spread and degree of pathological neovascularisation.

Aganirsen is in phase II trials for psoriasis and rosacea.

Innovation and/or advantages
If licensed, aganirsen may offer a new pharmacological treatment option with the potential to improve outcomes in patients who currently have limited therapeutic options, and it may also reduce the risk of rejection in patients who subsequently undergo corneal grafts.

Developer
Gene Signal International SA.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The National Service Framework for Long-term Conditions (2005).

Relevant guidance

Clinical need and burden of disease
The cornea is normally avascular which is important in maintaining its clarity. CoNV is a sight-threatening condition usually associated with disorders of the ocular surface, and is one of the most common manifestations associated with a range of eye diseases, including inflammatory and infectious disorders, bacterial pathogens and extended use of contact lenses. CoNV results from the growth of new vessels into the cornea which change the ocular surface microenvironment leading to corneal opacity. Neovascularisation leads to tissue scarring, lipid deposition, stromal haemorrhage and oedema of the cornea, severely altering visual acuity (VA). In addition, vascularisation also introduces circulating immune cells, reducing the immune privilege of the cornea and the graft survival of a subsequent penetrating keratoplasty (PKP).
Neovascularisation occurs in many eye diseases, and its impact is thought to be significant. However, information on the prevalence and incidence of CoNV in the UK is sparse. In the United States, CoNV has been reported in 4.14% of patients presenting for general ophthalmic care. In 2009-10, there were 69 hospital admissions for CoNV in England, accounting for 12 bed days. Graft rejection is a leading cause of failure of PKP – whilst the success rate for this type of graft is close to 90%, where considerable CoNV exists, rejection frequency is reduced to between 3.5% and 65%. In 2009-10, there were 3,061 corneal grafts in the UK, equating to 4.96 per 100,000 population.

**Existing comparators and treatments**

There are currently no drugs licensed for the treatment of pathological CoNV alone, or in association with a planned graft. Unlicensed options include photodynamic therapy, VEGF inhibitors and restoration of the ocular surface. Conventional therapies such as corticosteroids and immunosuppressants are only partly effective and are associated with severe side effects.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>2008-005388-33, GS101-P3-CG, The I-GRAFT Study; adults; aganirsen vs placebo; phase III.</th>
<th>2004-005015-29, GS101-P2-CG, CN-00745524; adults; aganirsen vs placebo; phase II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Les Laboratoires CTRS.</td>
<td>Les Laboratoires CTRS.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Abstract, publication, trial registry.</td>
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<tr>
<td>Location</td>
<td>EU.</td>
<td>EU.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=64 (planned); adults; keratitis or keratouveitis of bacterial, viral or traumatic origin with stromal neovascularisation. Randomised to aganirsen, 50µl, or placebo, as 2 eye drops, 1 in the morning and 1 in the evening.</td>
<td>n=40; adults, keratitis or keratouveitis of infectious, inflammatory or traumatic origin with stromal neovascularisation. Randomised to aganirsen, 43, 86 or 172µg, or placebo, as 2 eye drops, 1 in the morning and 1 in the evening.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period 3 months; 6 months follow-up.</td>
<td>Active treatment period 6 months.</td>
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<td>Primary outcome</td>
<td>VA.</td>
<td>Corneal (epithelial or stromal) neovascularisation.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Corneal angiogenesis; quality of life; need for transplantation; risk of graft rejection.</td>
<td>VA.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>At 3 months, for aganirsen 43, 86, 172µg, and placebo respectively (p-value vs placebo): change in neovascularised area (% of total corneal area), mean±SD, 0.07±2.94, -2.04±1.57, 1.60±7.63, 0.89±2.15; progression/regression of neovascularisation (%), 66.7/33.3 (p=0.454), 14.3/85.7 (p=0.004), 62.5/37.5 (p=0.208), 100/0/0.0.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Not reported.</td>
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</tr>
</tbody>
</table>
### Adverse effects (AEs)

| 57 reported AEs, including mild (68%), moderate (25%), severe (7%). |

### Estimated cost and cost impact

The cost of aganirsen is not yet known.

### Claimed or potential impact – speculative

#### Patients

- Reduced mortality or increased length of survival
- Other:
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

#### Services

- Increased use
- Service organisation
- Staff requirements
- Decreased use: potential for reduced transplant rejection
- Other: new outpatient treatment option
- None identified

#### Costs

- Increased unit cost compared to alternative
- New costs: additional treatment
- Increased costs: more patients coming for treatment
- Savings: potential for reduced transplant rejection
- Increased costs: capital investment needed
- Other:
- None identified

#### Other issues

- Clinical uncertainty or other research question identified:
- None identified

### References

