**Why was this clinical trial needed?**

Leber Congenital Amaurosis (LCA) is a genetic condition of the eye causing impaired night vision and variable impairment of daylight vision. LCA affects approximately 1 in 80,000 people worldwide. It often begins in early childhood and leads to progressive degeneration of the retina (the light sensitive part of the eye) and in many cases severe sight impairment. Unfortunately, there is currently no treatment for LCA.

At least 13 different types of LCA have now been identified, each caused by defects in different genes required for normal sight. LCA Type 2 (LCA2), which is caused by defects in the gene RPE65, is one of the most common forms of the condition.

The RPE65 gene encodes an important molecule (also called a protein) that is found in a special layer of cells in the retina called the retinal pigment epithelium (RPE) and is required to help the layers of photoreceptor cells (the light sensing cells of the eye) detect light entering the eye.

**What is gene therapy?**

Gene therapy is when we use DNA, rather than a drug or surgery, to treat a condition. In the case of LCA2, a harmless virus is used to deliver a new, normal copy of the RPE65 gene to those cells which need it (i.e. the RPE cells) with the aim of helping the cells to gain more normal function.
Summary of Results from RPE65 Gene Therapy Clinical Trial (NCT00643747)

What was the design of the trial?

The RPE65 gene therapy trial was a phase I/II trial. For this trial this means that:
• this was the first time the therapy had even been tested in people
• the purpose of the trial was to determine what dose of gene therapy would give the best results with the least side effects.

The RPE65 gene therapy trial was a controlled open-label trial. For this trial this means that:
• all the participants and doctors knew what therapy was being administered (open-label)
• all participants received the therapy in one eye whilst the other eye remained untreated (controlled).

By only treating one eye, doctors could better assess the effect of the gene therapy. Changes seen in the treated eyes, but not in the untreated eyes, were most likely the result of the eye having received an injection of gene therapy.

Why has the trial only recently concluded?

Begun in 2007, this trial was completed to schedule in 2014 after treating 12 people with the RPE65 gene therapy and following their progress over 3 years. It is perfectly normal for a clinical trial to take several years from start to finish. Not everyone is enrolled onto a trial at the same time. So as you were coming to the end of your time on the trial, others may have only recently been enrolled.

How was the gene therapy administered?

Participants underwent a short surgical procedure under anaesthetic. During the procedure the retina was detached and the gene therapy injected into the space underneath. This helps the virus to reach the layer of the retina where the RPE cells are. Following surgery, participants had a short stay in hospital and received a standard drug regimen to ensure the retina healed in place properly and that their immune system didn’t reject the gene therapy.
What was assessed during the three year monitoring period?

Following treatment, participants returned to the hospital at intervals over the course of 3 years to assess:

- any changes in retinal sensitivity (light perception)
- any changes in ability to navigate in low light levels (night vision)
- any changes in visual acuity (the clarity of vision)

Participants were also assessed for any associated side effects or adverse events and for the overall health of the retina.

What were the results of the trial?

What was the effect of RPE65 gene therapy on vision?

In this trial half of the participants experienced an improvement in retinal sensitivity; five of which also experienced an improved ability to navigate in dim light (i.e. improved night vision). These improvements appear to be unrelated to a participants age, gender or the dose of gene therapy given. The greatest improvement in retinal sensitivity were seen in the first 6 to 12 months after treatment but declined over the 3 year monitoring period.

In the majority of participants visual acuity remained unchanged demonstrating that for the majority, the injection of gene therapy did not negatively affect existing vision.

What were the side effects or adverse events experienced by participants?

Receiving any medical intervention carries with it a risk of side effects or adverse events. The results of this clinical trial provide confirmation that the RPE65 gene therapy does not cause any significant long-term side effects in the majority of people.

Whilst some people receiving the higher dose of gene therapy experienced either inflammation or an immune response in the treated eye, this resolved itself over time with no lasting ill-effect. This suggests that the higher dose of gene therapy used in this trial was the maximum dose the eye could tolerate.

Two participants did experience a decline in their visual acuity and 10 participants experienced a thinning of the retina following the use of standard, surgical procedure to administer the gene therapy in the eye.
Summary of Results from RPE65 Gene Therapy Clinical Trial (NCT00643747)

**How do these results compare with other RPE65 gene therapy research?**

This trial was the world’s first clinical trial of gene therapy for inherited blindness. Since this trial began in 2007, a number of other research groups have published findings and interim reports of RPE65 gene therapy. The results from this trial are consistent with those reported by these other groups.

From these results, along with those from other research, we have concluded that humans may require a higher level of RPE65 protein in the eye than can be generated with currently available gene therapies. We believe that treating patients earlier, with a more efficient gene therapy delivery system may provide greater benefit including the protection of daytime vision and reduction of progressive retinal degeneration in people with LCA2.

**What are the next steps for developing the gene therapy?**

In light of these results, we have now designed and are currently producing a new optimised gene therapy which we believe has the potential to offer greater improvements in visual function than other therapies currently in development.

We are delighted to announce that the potential for this next phase of clinical development has been recognised by the UK Medical Research Council who have awarded us with a major grant to begin a new clinical trial into RPE65 gene therapy for LCA2 in the near future.

**Where can I find the full results from the trial?**

There are two scientific publications resulting from this trial:
