

**HEALTH TECHNOLOGY BRIEFING  
NOVEMBER 2020**

**Timrepigene emparvovec for choroideremia**

<b>NIHRIO ID</b>	10333	<b>NICE ID</b>	9727
<b>Developer/Company</b>	Biogen	<b>UKPS ID</b>	653537

<b>Licensing and market availability plans</b>	Currently in phase III clinical development.
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**SUMMARY**

Timrepigene emparvovec is in clinical development for the treatment of choroideremia. Choroideremia is a rare inherited eye disorder that causes progressive loss of sight, eventually leading to complete blindness. Choroideremia is caused by certain genetic mutations that prevent the eye from producing an important protein, REP-1. Without this protein, cells in the light-sensitive part of the eye (the retina) and the surrounding network of blood vessels (the choroid) begin to die. The disease largely affects males while females can be carriers with less severe symptoms. Currently, there are no treatments for choroideremia.

Timrepigene emparvovec is a gene therapy that, when injected into the eye, allows cells to produce the missing REP-1 protein. With REP-1 present, the early stages of cell death can be slowed down or reversed, preventing the progressive loss of vision seen in choroideremia. If licenced, Timrepigene emparvovec will offer a gene therapy option for patients with choroideremia who currently have no effective treatments available.

## PROPOSED INDICATION

Indicated for the bi-lateral treatment of choroideremia (CHM) in adult patients who have a confirmed mutation in the CHM gene and viable retinal cells.<sup>a</sup>

## TECHNOLOGY

### DESCRIPTION

Timrepigene emparvovec (AAV2-REP1, NSR-REP1, BIIB-111) is a gene therapy comprised of an Adeno-Associated Viral Vector (AAV2) containing recombinant complement DNA that is designed to produce human Rab Escort Protein 1 (REP-1) in the retinal cells.<sup>1,2</sup> Choroideremia (CHM) is a rare, inherited, X-linked recessive retinal disease caused by mutations in the CHM gene. The CHM gene encodes REP1, a protein involved in intracellular protein trafficking and the elimination of waste products from retinal cells. Timrepigene emparvovec delivers the CHM gene to cells, allowing the expression of the functional REP-1 protein. This potentially reduces the accumulation of waste products in the retinal cells, slowing or reversing the early stages of cell death in already damaged retinal cells.<sup>2</sup>

Timrepigene emparvovec is currently in clinical development for the treatment of choroideremia. In the phase III clinical trial (NCT03496012, STAR), participants receive a single sub-retinal injection of timrepigene emparvovec following vitrectomy.<sup>3</sup>

### INNOVATION AND/OR ADVANTAGES

There is currently no cure for CHM and no treatment to slow it down, which represents a significant unmet medical need.<sup>2</sup> The mutations in the CHM gene that cause choroideremia are predominantly functionally null mutations so gene therapy is an appropriate treatment strategy.<sup>4</sup>

In phase I/II trials, results suggest that retinal gene therapy can sustain and improve visual acuity in choroideremia patients (adult males with BCVA > 34 ETDRS letter score in at least 1 eye) in whom rapid visual acuity loss would ordinarily be predicted.<sup>4,5</sup> Long term effectiveness demonstrating sustained efficacy and safety from these studies is available out to 3.5 years.<sup>5,6</sup>

Timrepigene emparvovec may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).<sup>7</sup> Timrepigene emparvovec is considered a highly specialised technology (HST) by NICE.

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Timrepigene emparvovec does not currently have Marketing Authorisation in the EU/UK for any indication.

Timrepigene emparvovec has been granted PIP (EMA-002430-PIP01-18) as of July 2020.<sup>8</sup>

Timrepigene emparvovec has an orphan drug designation in the EU awarded in June 2014 for the treatment of choroideremia.<sup>1</sup>

Timrepigene emparvovec received Regenerative Medicine Advanced Therapy (RMAT) Designation from the US FDA for Choroideremia in June 2018.<sup>9</sup>

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<sup>a</sup> Information provided by Biogen

## PATIENT GROUP

### DISEASE BACKGROUND

Choroideremia (CHM) is a recessive, X-linked chorioretinal dystrophy characterised by progressive degeneration of the vascular layer of the eye (the choroid), the retinal pigment epithelium and the retina. It is caused by inherited mutations in the X-linked CHM gene which encodes REP-1. REP-1 is involved in the targeting of vesicles for trafficking in and out of the cell.<sup>10,11</sup> There are around 280 known mutations in the CHM gene that can cause choroideremia.<sup>12</sup> These mutations impair the production of the REP-1 protein. The lack of functional REP-1 prevents Rab proteins from reaching and attaching to the organelle membranes. Without the aid of Rab proteins in intracellular trafficking, cells die prematurely.<sup>11,13</sup> While most tissues have REP-2 that can compensate for the loss of REP-1, the retina do not, causing progressive cell loss.<sup>14</sup>

The condition is recessive and X-linked so largely affects males who inherit a CHM mutation as they do not have a second X-chromosome with a functional CHM gene to compensate. Female carriers tend to be asymptomatic but some experience limited damage that may affect vision later in life.<sup>14</sup>

Symptoms of the condition begin with night blindness in early childhood, then progressive tunnel vision and decreasing visual acuity, all caused by the ongoing loss of cells in the retina and vascular layer of the eye. While the speed of vision loss varies between patients, all will eventually develop blindness, usually in the fifth decade.<sup>2,14</sup> It is thought that choroideremia accounts for 4% of all blindness.<sup>14</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

The most recent published epidemiology study in 2014, the prevalence of generalised retinal dystrophy in Denmark, indicated the prevalence rate for choroideremia to be 0.45 per 100,000 population.<sup>15</sup> As no UK/England based epidemiological study has been identified, applying the prevalence from this study to the UK midyear population estimate for 2019, the number of patients diagnosed with choroideremia in the UK would be 235 people.<sup>16</sup> However, it is likely that this condition is underdiagnosed because of its similarities to other eye disorders.<sup>14</sup> The company estimates a UK patient population range of less than 1 per 50,000.<sup>b</sup>

The Hospital Episode Statistics for England 2019/20 recorded a total of 15 admissions, 15 finished consultant episodes (FCE) and 3 FCE bed days for primary diagnosis hereditary choroidal dystrophy for which choroideremia is a sub condition (ICD-10 code H31.2).<sup>17</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Currently, there is no cure for choroideremia. Management involves periodic ophthalmologic examination to monitor the progression of the disease. UV-blocking sunglasses may be used to prevent further damage to the retina.<sup>11</sup> Vitamins, supplements and a healthy diet are also used to manage the disease.<sup>1</sup> Patients with choroideremia will usually receive genetic counselling on the risks of passing the condition on to their children.<sup>1</sup>

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<sup>b</sup> Information provided by Biogen on UK PharmaScan

## CURRENT TREATMENT OPTIONS

There are currently no medications for the treatment of choroideremia.<sup>1,18</sup>

## PLACE OF TECHNOLOGY

If licensed, timrepigene emparvovec will offer a gene therapy option for patients with choroideremia who currently have no effective therapies available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>STAR, NSR-REP-01, <a href="#">NCT03496012</a>, <a href="#">EudraCT2015-003958-41</a></b> ; A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial Of Retinal Gene Therapy For Choroideremia Using An Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1) <b>Phase III</b> - Active, not recruiting <b>Location(s)</b> : EU (incl UK), USA and Canada. <b>Estimated completion date</b> : November 2020.
<b>Trial design</b>	Randomised, Open Label, Outcomes-Assessor Masked
<b>Population</b>	N = 169, aged 18 years and older; males; genetically confirmed CHM; have active disease clinically visible within the macular region in the study eye; fulfil pre-defined visual acuity criteria of 34-72 ETDRS letters.
<b>Intervention(s)</b>	Randomised to: <ul style="list-style-type: none"> <li>a single sub-retinal injection of high-dose timrepigene emparvovec in one eye after vitrectomy;</li> <li>a single sub-retinal injection of low-dose timrepigene emparvovec in one eye after vitrectomy.</li> </ul>
<b>Comparator(s)</b>	Untreated control group
<b>Outcome(s)</b>	Primary outcome(s); <ul style="list-style-type: none"> <li>Best Corrected Visual Acuity (BCVA) [Time Frame: 12 Months]</li> </ul> See trial record for full list of other outcomes
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<b>REGENERATE, <a href="#">NCT02407678</a>, <a href="#">EudraCT2015-001383-18</a></b> ; An Open Label Phase 2 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-associated Viral Vector (AAV2) Encoding Rab-escort Protein 1 (REP1) <b>Phase II</b> - Active, not recruiting <b>Location(s)</b> : United Kingdom <b>Estimated completion date</b> : August 2021
<b>Trial Design</b>	Randomised, controlled, parallel assignment, open label
<b>Population</b>	N=30 (planned); 18 years and older; males; confirmed diagnosis of choroideremia, active disease visible clinically within the macula region, Best corrected visual acuity better than or equal to of $\geq 34$ ETDRS letters in the study eye.
<b>Intervention(s)</b>	Clinically or randomly assigned eye received timrepigene emparvovec, administered by subretinal injection
<b>Comparator(s)</b>	Untreated eye as control

<b>Outcome(s)</b>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> <li>Change from baseline in best corrected visual acuity in the treated eye [Time Frame: 2 years]</li> </ul> <p>See trial record for full list of other outcomes</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<p><b>GEMINI, NSR-REP-02</b>, <a href="#">NCT03507686</a>, <a href="#">EudraCT2017-002395-75</a>; An Open-Label Safety Study of Retinal Gene Therapy for Choroideremia With Bilateral, Sequential Administration of Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)  <b>Phase II</b> - Active, not recruiting  <b>Location(s)</b>: Germany and United States  <b>Primary completion date</b>: February 2022</p>
<b>Trial Design</b>	Single Group Assignment, Open Label
<b>Population</b>	N=60 (planned); adults; males; confirmed diagnosis of choroideremia, active disease visible clinically within the macula region, Best corrected visual acuity of $\geq 34$ ETDRS letters in both eyes, or in the untreated eye, if the other eye was previously treated with timrepigene emparvovec.
<b>Intervention(s)</b>	Bilateral sub-retinal administration of timrepigene emparvovec post vitrectomy.
<b>Comparator(s)</b>	None
<b>Outcome(s)</b>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> <li>Adverse events as a measure of safety and tolerability [Time Frame: up to 2 years]</li> </ul> <p>See trial record for full list of other outcomes</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<p><b>SOLSTICE, NSR-CHM-OS2</b>, <a href="#">NCT03584165</a>; A Long-term Follow-up Study to Evaluate the Safety and Efficacy of Retinal Gene Therapy in Subjects With Choroideremia Treated Previously With Adeno-Associated Viral Vector Encoding Rab Escort Protein-1 (AAV2-REP1) in an Antecedent Study  <b>Extension</b> - Enrolling by invitation  <b>Location(s)</b>: EU (incl UK), USA and Canada.  <b>Estimated completion date</b>: April 2024</p>
<b>Trial design</b>	Observational
<b>Population</b>	N = 100 (planned), aged 18 years and older; males; CHM; treated previously with timrepigene emparvovec in an antecedent study.
<b>Intervention(s)</b>	Sub-retinal injection of timrepigene emparvovec after vitrectomy.
<b>Comparator(s)</b>	None
<b>Outcome(s)</b>	<p>Primary outcome(s);</p> <ul style="list-style-type: none"> <li>Adverse events as a measure of safety and tolerability [Time Frame: up to 5 years]</li> </ul>
<b>Results (efficacy)</b>	-

## Results (safety)

-

## ESTIMATED COST

The cost of timrepigene emparvovec is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

No relevant guidance identified.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

### OTHER GUIDANCE

No relevant guidance identified.

## ADDITIONAL INFORMATION

## REFERENCES

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