National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: June 2018

ISV-305 for ocular inflammation and pain following cataract surgery

NIHRIO (HSRIC) ID: 21694 NICE ID: 9858

LAY SUMMARY

A cataract is any opacity of the lens, whether it is a small local opacity or a diffuse general loss of transparency. Sometimes, it can cause a significant reduction in visual acuity or a functional impairment. Cataract is the leading cause of blindness in the world. Cataract surgery is currently the only effective treatment to improve or maintain vision. Inflammation and pain are the most common difficulties associated with cataract surgery. These difficulties often cause significant patient discomfort, delayed recovery and reduced visual outcome. Treatment of inflammation and pain following cataract surgery are commonly managed with anti-inflammatory eye drops that contain steroids and painkillers.

ISV-305 is an eye drop medication being developed to administer the steroid drug, dexamethasone, to treat inflammation and pain following cataract surgery. ISV-305 uses an innovative vehicle that stabilizes the dexamethasone on the surface of the eye for up to 4-6 hours, during which time the active drug is gradually released. The increased time that ISV-305 remains in the eye allows lower concentrations of a drug to be administered over a longer period of time. If licensed, ISV-305 has the potential to improve safety concerns and treatment adherence through reduced dosing regimen in the treatment of inflammation and pain that occurs after a cataract surgery.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Ocular inflammation and pain following cataract surgery

TECHNOLOGY

DESCRIPTION

ISV-305 (DexaSite™; 0.1% Dexamethasone) is a DuraSite formulation of 0.1% dexamethasone.[1] DuraSite is a nontoxic and biocompatible polymer that can maintain therapeutic doses of a drug on the eye surface for up to 6 hours. The DuraSite polymer forms a matrix in which drug particles are suspended. In the aqueous environment of the eye, these drugs are released from the polymer matrix and diffuse into the tear film where they wash over the cornea and the conjunctiva. When the eye lids blink, a layer of DuraSite formulation and suspended drug is exposed to the cornea and conjunctiva. With each blink, the DuraSite layer and suspended drug are refreshed, maintaining the drug concentration and solution. The unused polymer and drug particles are removed via the tear-film into the lacrimal sac, without impeding normal tear drainage. Due to their high molecular weight, the insoluble DuraSite polymer particles do not penetrate the eye or other mucous membranes. They pass safely from the eye and out of the body without changing chemically.[2]

Dexamethasone and its derivatives are synthetic glucocorticoids (a group of corticosteroid). Dexamethasone is used for its anti-inflammatory or immunosuppressive properties and ability to penetrate the CNS. It is a glucocorticoid agonist. Unbound dexamethasone crosses cell membranes and binds with high affinity to specific cytoplasmic glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements) which results in a modification of transcription and, hence, protein synthesis in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in oedema or scar tissue. The anti-inflammatory actions of dexamethasone are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.[3]

In the phase III clinical trials to evaluate ISV-305 for the treatment of inflammation and pain associated with cataract surgery (NCT03192137; NCT03192150), ISV-305 was given as 2 eye drops twice daily for 16 days. [4,5]

ISV-305 is not currently licensed in the UK for any indication.[6,7] There are dexamethasone 0.1% eye drops solution available in the UK which are indicated for non-infected, steroid responsive, inflammatory conditions of the eye.[8]

ISV-305 is in phase III stage of development for the treatment of ocular inflammation (e.g., blepharitis).[2]

INNOVATION and/or ADVANTAGES

ISV-305 uses the DuraSite drug delivery vehicle to deliver dexamethasone into the eye. DuraSite is a drug delivery vehicle that stabilizes small molecules in a polymeric mucoadhesive matrix. The topical ophthalmic solution can be described as a gel forming drop, which extends the residence time of the drug relative to conventional eye drops.[9] Safety studies have shown DuraSite drug delivery to be non-toxic and biocompatible. The increased time that DuraSite remains in the eye allows lower concentrations of a drug to be administered over a longer period of time.[10]

If licensed, ISV-305 has the potential to improve safety concerns and treatment adherence through reduced dosing regimen in the treatment of ocular inflammation and pain associated with cataract surgery.

DEVELOPER

InSite Vision (a Sun Pharma Company).

PATIENT GROUP

BACKGROUND

A cataract is any opacity of the lens, whether it is a small local opacity or a diffuse general loss of transparency. To be clinically significant, however, the cataract must cause a significant reduction in visual acuity or a functional impairment.[11] Cataract is the leading cause of blindness in the world. Cataract surgery is currently the only effective treatment to improve or maintain vision.[12]

Although cataract surgery is generally safe, the risk of operative complications and a poor visual outcome can vary by 10-fold or more depending on the presence of a range of common ocular and systemic risk factors.[12] Among the most common difficulties arising after surgery are persistent inflammation.[13] Patienta with diabetes, macular disease, glaucoma, ocular vein occlusion, retinitis pigmentosa, or uveitis are at higher risk of developing post-cataract surgery.

The physical trauma associated with cataract surgery can induce an inflammatory response and the release of inflammatory mediators. Post-cataract surgery is still a common cause of patient discomfort, delayed recovery and reduced visual outcome. Persistent inflammation leads to higher rates of post-operative cystoid macular oedema, patient discomfort and compromised visual outcomes consequent to the breakdown of the blood–retinal barrier. Multiple potential complications of untreated post-operative inflammation include pain, photophobia, posterior synechiae, pseudophakic cellular precipitates, uveitis, elevated intraocular pressure and glaucoma.[14]

CLINICAL NEED and BURDEN OF DISEASE

Around 330,000 cataract operations performed per year in England in recent years. Overall crude estimates from Hospital Episode Statistics data suggests surgery incidence rates of approximately 530 per 100,000 population or 3200 per 100,000 for those over 65 years old per year in recent years (2011 data). Incidence rates of post-cataract surgery inflammation range from 1.5% and 2% but does not take into account people with diabetes. [15] This would equivalent to 4590 to 6600 cases of post-cataract surgery inflammation in England per year.

There is noticeable variation in the rates of cataract surgery taking place across England and these include both first and second eye procedures. Over 50% of commissioners have introduced arbitrary thresholds to restrict access to cataract surgery and cannot be sure that they are providing optimum care.[16] In 2016-17, hospital admissions in England for prosthesis of lens procedure (OPCS-4: C75) were 393,360.[17] Hospital admissions in England in 2016/17 for senile cataract (ICD10: H25) were 190,909 and for other cataract (ICD10: H26) were 236,737 resulting in 192,914 and 238,462 finished consultant episodes (FCE) and 3,536 and 4,154 FCE bed days respectively.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Dexamethasone intracanalicular insert for treating inflammation and pain after cataract surgery ID1154 (GID-TA10198). Expected date of issue to be confirmed.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for specialised ophthalmology (Adult). D12/Sa.
- NHS England. 2013/14 NHS Standard Contract for ophthalmology pathology services (All Ages). D12/S (HSS)/b.

OTHER GUIDANCE

- Royal College of Ophthalmologists Cataract Surgery Commissioning Guidance Development Group. The Royal College of Ophthalmologists' Cataract Surgery Commissioning Guidance: executive summary.2016.[12]
- The Royal College of Ophthalmologists. Cataract Surgery Guidelines. 2010.[19]
- Guidelines for managing post-cataract surgery inflammation Can we reach a consensus? November 2008[15]
- American Optometric Association. Optometric clinical practice guideline: Care of the adult patient with cataract. 1995 (Reviewed 2004).[11]
- American Optometric Association. Optometric clinical practice guideline: care for patients with anterior uveitis. 1994 (Reviewed 2004).[20]
- American Optometric Association. Optometric clinical practice guideline: care for patients with conjunctivitis. 1995 (Reviewed 2002).[21]

CURRENT TREATMENT OPTIONS

There are no established treatment guidelines to prevent or reduce inflammation following ocular surgery. Therefore, treatment includes pre- and post-operative anti-inflammatory therapies such as corticosteroids and NSAIDs. Since it is impossible to predict which patients will develop clinically significant post-operative inflammation, anti-inflammatory agents are routinely used post-operatively. In some institutions, especially those in the UK, corticosteroids are the preferred option.[14]

The Royal College of Ophthalmologists indicates that for pain and discomfort after surgery, patients may take pain reliever such as paracetamol (but not aspirin - this can cause bleeding).[19] NICE indicates that inflammation should be treated immediately with postoperative subconjunctival steroids with or without orbital floor steroids. Post operatively, intensive treatment with topical steroids and cycloplegic agents should be given.[22]

EFFICACY and SAFETY

Trial	**NCT03192150, C-16-305-003; ISV-305 vs placebo; phase III**
Sponsor	InSite Vision
Status	Ongoing
Source of Information	Trial registry[4]
Location	USA
Design	Randomised, placebo-controlled, parallel assignment
Participants	n= 240 (planned); aged 17 years and older; males and females; scheduled for uncomplicated unilateral cataract surgery
Schedule	Randomised to Dexamethasone in DuraSite® 2 drops twice daily for 16 days or placebo twice daily for 16 days.
Follow-up	Active treatment period: 16 days Follow up period: 15 days
Primary Outcomes	Anterior Chamber Cell Grade 0 (Primary efficacy endpoint for the comparison of ISV-305 and Vehicle) [Time frame: Day 15]
Secondary Outcomes	
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as February 2019.

Trial	**NCT03192137, C-13-305-002; ISV-305 vs placebo; phase III**
Sponsor	InSite Vision
Status	Ongoing,
Source of Information	Trial registry[5]
Location	USA
Design	Randomised, placebo-controlled, parallel assignment
Participants	n= 240 (planned); aged 17 years and older; males and females; scheduled for uncomplicated unilateral cataract surgery
Schedule	Randomised to Dexamethasone in DuraSite® 2 drops twice daily for 16 days or placebo twice daily for 16 days.
Follow-up	Active treatment period: 16 days Follow up period: 15 days
Primary Outcomes	Anterior Chamber Cell Grade 0 (Primary efficacy endpoint for the comparison of ISV-305 and Vehicle) [Time frame: Day 15]
Secondary Outcomes	
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as February 2019.

ESTIMATED COST and IMPACT

COST

The cost of ISV-305 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *Improved patient convenience*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☒ Reduced drug treatment costs

☐ Other

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] InSite Vision Incorporated. Product candidates. 2016. Available from: http://www.insitevision.com/Pipeline_Products.html [Accessed 13th Mar 2018].

[2] InSite Vision Incorporated. *DuraSite mechanism of action*. 2016. Available from: http://www.insitevision.com/durasite_moa.html [Accessed 13th Mar 2018].

[3] DrugBank. *Dexamethasone.* 13th Jun 2005 (Reviewed 12th Mar 2018). Available from: https://www.drugbank.ca/drugs/DB01234 [Accessed 13th Mar 2018].

[4] ClinicalTrials.gov. *Independent Comparative Study to Evaluate ISV-305 Compared to Vehicle for the Treatment of Inflammation and Pain Associated With Cataract Surgery (ISV-305): NCT03192150*. Available from: https://clinicaltrials.gov/ct2/show/NCT03192150 [Accessed 13th Mar 2018].

[5] ClinicalTrials.gov. *Comparative Study to Evaluate ISV-305 Compared to Vehicle for the Treatment of Inflammation and Pain Associated With Cataract Surgery (ISV-305): NCT03192137.* Available from: https://clinicaltrials.gov/ct2/show/NCT03192137 [Accessed 13th Mar 2018].

[6] National Institute for Health and Care Excellence. *BNF: ISV-305.* Available from: https://bnf.nice.org.uk/#Search?q=ISV-305 [Accessed 12th Jun 2018].

[7] National Institute for Health and Care Excellence. *BNF: dexamethasone.* Available from: https://bnf.nice.org.uk/drug/dexamethasone.html#indicationsAndDoses [Accessed 12th Jun 2018].

[8] The electronic Medicines Compendium (eMC). Minims Dexamethasone sodium phosphate 0.1% w/v, eye drops solution. Available from: https://www.medicines.org.uk/emc/product/3742/smpc%20-#INDICATIONS [Accessed 25th Jun 2018].

[9] InSite Vision Incorporated. *DuraSite compound advantage*. Available from: http://www.insitevision.com/durasite.html [Accessed 4th Jun 2018].

[10] InSite Vision Incorporated. *Staying power.* Available from: http://www.insitevision.com/core_technology.html [Accessed 4th Jun 2018].

[11] American Optometric Association. *Optometric clinical practice guideline: Care of the adult patient with cataract.*1995 (Reviewed 2004). Available from: https://www.aoa.org/documents/optometrists/cpg-8.pdf [Accessed 13th Mar 2018].

[12] Day AC, Wormald R, Coronini-Cronberg S, Smith R, Royal College of Ophthalmologists Cataract Surgery Commissioning Guidance Development Group. The Royal College of Ophthalmologists' Cataract Surgery Commissioning Guidance: executive summary. *Eye (Lond).* 2016 Mar;30(3):498-502. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791709/pdf/eye2015271a.pdf [Accessed 16th Mar 2018]

[13] MedicineNet, Inc. *Cataract Surgery.* Available from: https://www.medicinenet.com/cataract_surgery/article.htm#what_should_one_expect_prior_to_and_on_the_day_of_cataract_surgery [Accessed 4th Jun 2018].

[14] Dua HS, Attre R. Treatment of post-operative inflammation following cataract surgery: a review. *European Ophthalmic Review*. 2012; 6 (2):98-103. Available from: http://www.touchophthalmology.com/sites/www.touchophthalmology.com/files/dua.pdf [Accessed 25th Jun 2018].

[15] Guidelines for managing post-cataract surgery inflammation Can we reach a consensus? Ophthalmology Times Europe November. 2008. Available from:http://ophthalmologytimes.modernmedicine.com/sites/default/files/images/OphthalmologyTimesEurope/PDF/Guidelines-for-managing-post-cataract-surgery-inflammation.pdf [Accessed 4th Jun 2018].

[16] Royal National Institute of Blind People. *Cataract campaign report.* Available from: http://www.rnib.org.uk/cataract-campaign-report [Accessed 16th Mar 2018]

[17] NHS Digital, Hospital Episode Statistics for England. *Admitted Patient Care statistics, 2016 - 2017.* Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 16th Mar 2018]

[18] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17.* Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 23rd Oct 2017]

[19] The Royal College of Ophthalmologists. *Cataract surgery guidelines: September 2010*. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2010-SCI-069-Cataract-Surgery-Guidelines-2010-SEPTEMBER-2010-1.pdf [Accessed 4th Jun 2018].

[20] American Optometric Association. *Optometric clinical practice guideline: care for patients with anterior uveitis.* 1994 (Reviewed 2004). Available from: https://www.aoa.org/documents/optometrists/CPG-7.pdf [Accessed 15th Mar 2018].

[21] *American Optometric Association. Optometric clinical practice guideline: care for patients with conjuctivitis. 1995 (Reviewed 2002).* Available from: https://www.aoa.org/documents/optometrists/CPG-11.pdf [Accessed 15th Mar 2018].

[22] National Institute for Health And Care Excellence. Draft scope for the proposed appraisal of dexamethasone intracanalicular insert for treating inflammation and pain after cataract surgery. July 2017. https://www.nice.org.uk/guidance/gid-ta10198/documents/draft-scope-pre-referral [Accessed 25th Jun 2018].