NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
DECEMBER 2020

Clobetasol propionate for postoperative pain and inflammation associated with cataract surgery

NIHRIO ID	29292	**NICE ID**	10484
Developer/Company	Laboratorios SALVAT SA	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Clobetasol propionate ophthalmic nanoemulsion is in development for the treatment of post-operative pain or inflammation following cataract surgery. A cataract is a cloudy area in the lens, which can develop slowly and progress to general loss of transparency, which may lead to functional impairment and visual deterioration. Cataract surgery is the only effective treatment to improve or maintain vision, however, inflammation and pain are common difficulties following this treatment.

Clobetasol propionate ophthalmic nanoemulsion 0.05% is an oil in water solution that delivers the drug clobetasol propionate directly into the eye to treat inflammation and pain associated with cataract surgery. This technology promotes anti-inflammatory genes by binding to glucocorticoid receptors. If licensed, this treatment will offer an additional option for adults with postoperative pain and inflammation following cataract surgery.

PROPOSED INDICATION

For the treatment of adults with inflammation and pain postoperative associated with cataract surgery.[1,2]

TECHNOLOGY

DESCRIPTION

Clobetasol propionate, a corticosteroid, is a derivative of prednisolone with higher specificity for glucocorticoid receptors and low specificity for mineralocorticoid receptors.[3,4] Topical corticosteroids act as an anti-inflammatory agent to inhibits late phase allergic reactions via multiple mechanisms.[5] Corticosteroids promote anti-inflammatory genes such as interleukin-10, and inhibit pro-inflammatory transcription factors like NF-Kappa B amongst others, by binding to glucocorticoid receptors.[6] The binding of corticosteroids to glucocorticoid receptors can cause a change in gene expression consequently leading to multiple downstream effects that can range from hours to days. Corticosteroids act by decreasing the density of mast cells, decreasing cytokine production lymphocytes, eosinophils, monocytes and mast cells, decreasing chemotaxis and activation of eosinophils and inhibiting the metabolism of arachidonic acid.[5]

Clobetasol propionate ophthalmic nanoemulsion 0.05% is currently in phase III clinical development for the treatment of inflammation and pain in adults who have undergone cataract surgery. In the phase III clinical trial (NCT04246801 and NCT04249076), participants will receive one self-administered drop of Clobetasol propionate ophthalmic nanoemulsion 0.05% four times a day for 14 days.[1,2]

INNOVATION AND/OR ADVANTAGES

Clobetasol propionate ophthalmic nanoemulsion 0.05% (SVT-15473) is an oil-in-water (o/w), clear or slightly yellowish nanoemulsion containing the active ingredient clobetasol propionate at a concentration of 0.05% weight per weight (w/w).[1,2] It is delivered to the ocular surface via direct instillation.[1,2]

An inflammatory response can be induced by mechanical trauma such as tissue injury during ocular surgery. When the inflammation is inadequately controlled there is an increased risk of postoperative pain and various other adverse events. Direct instillation of this technology to the eye will deliver corticosteroids to the desired site with a reduced risk of systematic adverse events.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Clobetasol propionate ophthalmic nanoemulsion 0.05% does not currently have Marketing Authorisation in the EU/UK for any indication.

Clobetasol propionate is currently licensed in the EU/UK as a topical treatment applied on the skin or scalp for the treatment of severe resistant inflammatory skin disorders such as psoriasis, lupus, lichen planus and recalcitrant eczema (including dermatitis) that is unresponsive to less potent corticosteroids. It alleviates symptoms such as itching, swelling and irritation.[5,8,9]

Some common side-effects for all corticosteroids (topical) are skin reactions and telangiectasia.[9]

Clobetasol propionate is currently in phase II and phase III clinical trials for oral lichen planus and colorectal cancer.[10,11]

PATIENT GROUP

DISEASE BACKGROUND

Cataract is defined as the loss of lens transparency due to opacification within the clear natural crystalline lens. It is commonly recognised that oxidative stress is a direct contributor to the genesis of the opacity of the lens which progressively results in vision deterioration.[12,13] Cataracts are the leading cause of blindness globally.[13]

Although cataract surgery is generally safe and is the most common operation conducted in the UK,[14] 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.[15] The mechanical trauma that occurs during cataract surgery illicits an inflammatory response and the release of inflammatory mediators. Postoperative inflammation is a common cause of patient discomfort, delayed recovery and reduced positive visual outcomes.[16]

Postoperative inflammation is one of the most common difficulties that arise after cataract surgery. Inadequate treatment of inflammation can lead to an increased risk of postoperative pain, uveitis, oedema, secondary glaucoma and potentially cystoid macular oedema (CMO).[17,18]

CLINICAL NEED AND BURDEN OF DISEASE

In England and Wales over 400,000 cataract surgeries were performed in 2015-16. The number of cataract surgeries being performed is projected to increase by 25% over the next 10 years.[19]

In the UK, the average expected rates of cataract surgery are approximately 3,200 per 100,000 (3.2%) for those over 65 years old or 530 per 100,000 (0.53%) population per year.[20] While an overall estimate from Eurostat data suggests an incidence rate of approximately 781 per 100,000 per year of cataract surgeries performed in the UK.[21]
There are large variations in the rates of cataract surgery, including both first and second eye procedures, being performed across England. Arbitrary thresholds are being introduced by over 50% of commissioners in order to restrict access to cataract surgery. It is unknown whether optimum care is being provided to individuals with cataracts.[22] The national average

of cataract surgery referrals receiving treatment is 77% with some providers performing less than 60% of cataract surgery procedures.[23]

In 2019-20, hospital admissions in England for senile cataract (ICD10: H25) were 248,759 and for other cataract (ICD10: H26) were 230,464. This resulted in 251,725 and 232,673 finished consultant episodes (FCE); 2,412 and 3,851 FCE bed days respectively. Hospital admissions for prosthesis of lens procedure (OPCS-4:C75) were 439,747 with 444,722 FCE and 5,422 FCE bed days in 2019-20.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently, surgery is the only effective therapy treatment to maintain or improve vision amongst individuals with cataracts.[15] A preferred regimen for the treatment of postoperative pain and inflammation after cataract surgery is yet to be established as there is currently no conclusive evidence from clinical trials or consensus guidelines to date.[25]

The choices made about the best approach for treatment of pain and inflammation associated with cataract surgery should be discussed with a multidisciplinary team as there is no current established guideline to prevent inflammation.[25,26] In addition to cataract surgery, patients may also need additional care. All healthcare professionals directly involved with the patients are trained to help patients with their emotional, psychological, and nutritional needs, as well as pain management.[26] Since clinically significant postoperative inflammation and pain cannot be predicted, anti-inflammatory corticosteroids are usually prescribed postoperatively.[16]

CURRENT TREATMENT OPTIONS

For the treatment of anti-inflammation in the eye, NICE recommendations includes:[27]
Corticosteroids for the management of adults aged 18 and over with treating anterior segment inflammation that can arise postoperatively.

- An intravitreal implant containing dexamethasone is licensed for the treatment of adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.
- An intravitreal implant containing fluocinolone acetonide is licensed for recurrent non-infectious uveitis relapse prevention in the posterior segment of the eye.

Non-steroidal anti-inflammatory drugs (NSAIDs) eye drops are used for the treatment of inflammation of the eye following surgery.[27]

PLACE OF TECHNOLOGY

If licensed, Clobetasol Propionate Ophthalmic Nanoemulsion 0.05% will offer an additional therapy for patients who have undergone cataract surgery and experience postoperative pain and inflammation.

CLINICAL TRIAL INFORMATION

Trial	**CLOSE-1; NCT04246801; CLOSE-2; NCT04249076; A Phase 3, Multicenter, Randomized, Double-Masked Clinical Trial to Assess the Efficacy and Safety of Clobetasol Propionate Ophthalmic Nanoemulsion 0.05% Compared to Placebo in the Treatment of Inflammation and Pain Associated With Cataract Surgery** **Trial phase** – Phase III **Location(s):** USA **Primary completion date:** October 2020
Trial design	Randomised, double-blinded, and parallel assignment
Population	N=210 (planned); aged 18 and over who have undergone unilateral cataract surgery and have at least 5 cells in anterior chamber on the first day after surgery. Women would need to either be post-menopausal, or of child-bearing potential who are not pregnant or lactating and who are either abstinent or sexually active on an acceptable method of birth control.
Intervention(s)	Participants will receive the first dose of clobetasol propionate ophthalmic nanoemulsion 0.05%) at baseline and then at a dosage of one drop four times a day during 14 days after cataract surgery by self-administration via direct instillation.
Comparator(s)	Vehicle is identical in appearance and composition to clobetasol propionate ophthalmic nanoemulsion 0.05% but without the active substance. First dose of the drug will be dispensed at the end of the Baseline visit at the study center. Then, study medication will be dispensed to the participant for self-administration at a dosage of one drop four times a day during 14 days after cataract surgery.
Outcome(s)	Anterior chamber cell grade [Time Frame: Day 8] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of clobetasol propionate ophthalmic nanoemulsion 0.05% is not yet known.

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.
- NICE Guideline. Perioperative care in adults (NG180). August 2020.
- NICE Guideline. Cataracts in adults: management (NG77). October 2017.

NHS ENGLAND (POLICY/COMMISSIONING) 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

- The Royal College of Ophthalmologists. Commissioning Guide: Adult Cataract Surgery. 2018.[28]
- American Academy of Ophthalmology. Cataract in the Adult Eye Preferred Practice Pattern. 2017.[25]
- Royal College of Ophthalmologists Cataract Surgery Commissioning Guidance Development Group. The Royal College of Ophthalmologists' Cataract Surgery Commissioning Guidance: executive summary. 2016.[15]

ADDITIONAL INFORMATION

Laboratorios Salvat SA did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 ClinicalTrials.gov. *Clobetasol Propionate Ophthalmic Nanoemulsion 0.05% for the Treatment of Inflammation and Pain Associated With Cataract Surgery (CLOSE-1) (CLOSE-1). Trial ID*. 2020. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT04246801 [Accessed 13 November 2020].

2 ClinicalTrials.gov. *Clobetasol Propionate Ophthalmic Nanoemulsion 0.05% for the Treatment of Inflammation and Pain Associated With Cataract Surgery (CLOSE-2) (CLOSE-2). Trial ID*. 2020.

Status: Available from: https://clinicaltrials.gov/ct2/show/NCT04249076 [Accessed 13 November 2020].
3 DRUGBANK. *Clobetasol propionate*. 2005. Available from: https://go.drugbank.com/drugs/DB01013 [Accessed 19 November 2020].
4 Human Metabolic Database. *Showing metabocard for Clobetasol (HMDB0015148)*. 2020. Available from: https://hmdb.ca/metabolites/HMDB0015148#identification Accessed 19 November 2020.
5 Electronic medicines compendium. *Dermovate Ointment*. 2020. Available from: https://www.medicines.org.uk/emc/product/940/smpc#PHARMACOLOGICAL_PROPS [Accessed 30 November 2020].
6 Yasir, M., Goyal, A., Bansal, P., Sonthalia, S. *Mechanism of action*. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531462/ 19 November 2020
7 McGhee, C. N., Dean S., Danesh-Meyer H. *Locally administered ocular corticosteroids*. Drug Safety. 2002;25(1):33-55. Available from: https://pubmed.ncbi.nlm.nih.gov/11820911/ 19 November 2020
8 NHS. *Clobetasol*. 2019. Available from: https://www.nhs.uk/medicines/clobetasol/ [Accessed 19 November 2020].
9 BNF. *CLOBETASOL PROPIONATE*. 2020. Available from: https://bnf.nice.org.uk/drug/clobetasol-propionate.html#sideEffects [Accessed 19 November 2020].
10 clinicalTrials.gov. *Lower or Standard Dose Regorafenib in Treating Patients With Refractory Metastatic Colorectal Cancer*. *Trial ID*. 2019. Status: Available from: https://www.clinicaltrials.gov/ct2/show/NCT02368886?term=Clobetasol+propionate&recrs=adf&phase=12&draw=2&rank=4 [Accessed 14 Dcember 2020].
11 ClinicalTrials.gov. *Efficacy of Topical Treatment With Clobetasol in Symptomatic Oral Lichen Planus*. *Trial ID*. 2020. Status: Available from: https://www.clinicaltrials.gov/ct2/show/NCT04364555?term=Clobetasol+propionate&recrs=adf&phase=12&draw=2&rank=3 [Accessed 14 December 2020].
12 Alshamrani, A. Z. *Cataracts pathophysiology and managements*. The Egyptian Journal of Hospital Medicine. 2018;70(1):151-4. Available from: https://journals.ekb.eg/article_11564_87ac1a0de081503978945de5eeca5443.pdf 19 November 2020
13 Nartey, A. *The pathophysiology of cataract and major interventions to retarding its progression: A mini review*. Adv Ophthalmol Vis Syst. 2017;6(3):00178. Available from: https://www.researchgate.net/profile/Andrews_Nartey2/publication/314217183_The_Pathophysiology_of_Cataract_and_Major_Interventions_to_Retarding_Its_Progression_A_Mini_Review/links/5d858550a6fdcc8fd6ffe1db/The-Pathophysiology-of-Cataract-and-Major-Interventions-to-Retarding-Its-Progression-A-Mini-Review.pdf 19 November 2020
14 NHS. *Cataract surgery*. 2017. Available from: https://www.nhs.uk/conditions/cataract-surgery/ [Accessed 19 November 2020].
15 Day, A., Wormald R., Coronini-Cronberg S., Smith R. *The Royal College of Ophthalmologists' Cataract Surgery Commissioning Guidance: executive summary*. Eye. 2016;30(3):498-502. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791709/pdf/eye2015271a.pdf 19 November 2020
16 Dua H. S., A. R. *Treatment of Post-operative Inflammation following Cataract Surgery – A Review*. Touch Ophthalmology. 2012. Available from: http://doi.org/10.17925/EOR.2012.06.02.98 https://www.touchophthalmology.com/anterior-segment/journal-articles/treatment-of-post-operative-inflammation-following-cataract-surgery-a-review/ 30 November 2020
17 Kato, K., Miyake K., Hirano K., Kondo M. *Management of postoperative inflammation and dry eye after cataract surgery*. Cornea. 2019;38:S25-S33. Available from: https://journals.lww.com/corneajrnl/Abstract/2019/11001/Management_of_Postoperative_Inflammation_and_Dry.5.aspx 19 November 2020
18 Salinger, C. L., Gaynes B. I., Rajpal R. K. *Innovations in topical ocular corticosteroid therapy for the management of postoperative ocular inflammation and pain*. Am J Manag Care. 2019;25(12

Suppl):S215-S26. Available from: https://www.ajmc.com/view/corticosteroid-therapy-for-the-management-of-postoperative-ocular-inflammation-and-pain 19 November 2020

19 The Royal College of Ophthalmologists. *Sustainable Ophthalmic Pathways.* 2018. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2018/06/Sustainable-Cataract-Pathways.pdf [Accessed 19 November 2020].

20 Laser Eye Surgery Hub. *Cataract Statistics & Data.* 2014. Available from: https://www.lasereyesurgeryhub.co.uk/cataract-statistics/ [Accessed 30 November 2020].

21 Eurostat. *Surgical operations and procedures statistics*. Statistics Explained. 2020. Available from: https://ec.europa.eu/eurostat/statistics-explained/pdfscache/37391.pdf Accessed: 19 November 2020

22 Royal National Institute of Blind people. *Surgery deferred sight denied Campaign report*. RNIB campaign report. 2016. Available from: https://www.rnib.org.uk/campaigning-policy-and-reports-hub-eye-health/eye-health-reports Accessed: 19 November 2020

23 Carrie MacEwen, A. D., Lydia Chang,. *Ophthalmology GIRFT Programme National Specialty Report*. NHS; 2019. Available from: https://gettingitrightfirsttime.co.uk/wp-content/uploads/2019/12/OphthalmologyReportGIRFT19P-FINAL.pdf Accessed: 19 November 2020

24 NHS. *Hospital Admitted Patient Care Activity 2019-20.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 19 November 2020].

25 Olson, R. J., Braga-Mele R., Chen S. H., Miller K. M., Pineda R., Tweeten J. P., et al. *Cataract in the adult eye preferred practice pattern®*. Ophthalmology. 2017;124(2):P1-P119. Available from: https://www.aaojournal.org/article/S0161-6420(16)31418-X/pdf 19 November 2020

26 National Institute for Health and Care Excellence. *Patient experience in adult NHS services: improving the experience of care for people using adult NHS services.* 2012. Available from: https://www.nice.org.uk/guidance/cg138 [Accessed 20 November 2020].

27 National Institute for Health and Care Excellence. *Eye, allergy and inflammation.* 2020. Available from: https://bnf.nice.org.uk/treatment-summary/eye-allergy-and-inflammation.html [Accessed 20 November 2020].

28 The Royal College of Ophthalmologists. *Commissioning Guide: Adult Cataract Surgery.* 2018. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2018/02/Cataract-Commissioning-Guide-January-2018.pdf [Accessed 19 November 2020].

NB: 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.