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HEALTH TECHNOLOGY BRIEFING
May 2021

Conbercept for neovascular age-related macular degeneration

NIHRIO ID	12167	**NICE ID**	10469
Developer/Company	Chengdu Kanghong Pharmaceuticals Group Co Ltd	**UKPS ID**	

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

SUMMARY

Conbercept is currently in clinical development for treatment of adults (≥ 50 years old) with Neovascular age-related macular degeneration (AMD), also known as wet AMD, a chronic eye disease. This disease is characterised by the formation of immature blood vessels that grow between the retina (macula; a layer of tissue in the back of the eye that senses light and sends images to the brain). Such blood vessels easily haemorrhage and cause scarring, which leads to vision impairment and is a leading cause of central sight loss and blindness.

Conbercept is a novel protein that is administered via injection into the eye (intravitreal injection). Its main function is to inhibit the vascular endothelial growth factor (VEGF), a protein that promotes he growth of new blood vessels. As conbercept blocks VEGF it leads

to reduced growth of the abnormal blood vessels to treat neovascular AMD. If licensed, Conbercept may offer an additional treatment option for patients with neovascular AMD.

PROPOSED INDICATION

Treatment of patients with neovascular age-related macular degeneration (AMD).[1,2]

TECHNOLOGY

DESCRIPTION

Conbercept (KH-902) is a recombinant fusion protein.[3] It is a novel vascular endothelial growth factor (VEGF) inhibitor.[4] Specifically, it binds to the human VEGFR-1 and -2 combined with the Fc portion of the human immunoglobulin G-1.[5] As the drug blocks VEGF it leads to regression of the abnormal blood vessels to treat neovascular AMD.[3]

Conbercept is currently in phase III clinical development for treatment of adults (≥ 50 years old) with neovascular AMD (NCT03577899; PANDA-1 and NCT03630952; PANDA-2). During the trials the patients are provided with either a 0.5mg or 1.0mg intravitreal injection on day 1, week 4 and week 8. The 0.5mg group then receives a dose every 8 weeks thereafter, while the 1.0mg group receives a dose every 12 weeks. For a total of 92 weeks.[1,2]

INNOVATION AND/OR ADVANTAGES

If licenced conbercept will offer an additional treatment option for patients with neovascular AMD. Conbercept could be advantageous due to its high affinity, lower VEGF dissociation (compared to other treatments such as aflibercept), decreased adhesion to extracellular matrix and a lower isoelectric point that results in a longer clearance time.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Conbercept does not currently have marketing authorisation in the EU/UK for any indication.

Conbercept is currently in phase II and III clinical development for uveitis, macular oedema and VEGF. Additionally, conbercept is currently in phase II clinical development for diabetic macular edema.[6]

PATIENT GROUP

DISEASE BACKGROUND

Age-related macular degeneration (AMD) is a progressive, degenerative disease of the central retina (macula) that leads to irreversible blindness, primarily in central vision.[3-5] There are two main types of AMD, neovascular (wet) and non-neovascular (dry) AMD.[4]

Neovascular AMD is characterised by the formation of immature blood vessels that grow between the retinal pigment epithelial cells and photoreceptor cells in the centre of the retina (known as choroidal neovascularisation; CNV). Such blood vessels easily haemorrhage and cause scarring in the macula, which leads to vision impairment. The protein VEGF, which induces new blood vessel formation (angiogenesis), vascular permeability and inflammation, has been implicated in the development and progression of CNV. CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography.[7] Classic lesions appear early, are well-defined and leak intensely, whereas occult lesions appear early to mid-phase, leak less intensely and are ill-defined.[8] A mixture of classic and occult CNV can occur in the same lesion. CNV can also be described in terms of its location: the fovea is the central part of the macula, and CNV that develops below the foveal area is termed "subfoveal CNV".[7]

The condition usually affects people who are over 50 years old, and the risk increases significantly with age. The most cited risk factor for AMD is cigarette smoking; the risk of developing AMD is 3.6 times greater for current and former smokers than for people who have never smoked.[7] Hypertension, obesity, lack of exercise, a diet high in fat, a diet low in omega 3 and 6 and a family history of neovascular AMD are also common risk factors.[9]

Neovascular AMD accounts for 10% of all cases of AMD, but about 60% of those are considered advanced at presentation. Progression of neovascular AMD varies from a few months to three years. If left untreated, the diagnosis is poor with a significant visual loss (6/60 or worse) occurring within two to three years.[10] People with macular degeneration retain their peripheral vision but lose central vision. Loss of central vision, particularly when affecting both eyes, is associated with a loss of quality of life, affecting the ability to read, recognise faces and drive, and with an increased risk of falls and potentially significant loss of independence.[7]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of late AMD in the UK among people aged 50 years or over is 2.4% (from a meta-analysis applied to UK 2007–09 population data). This increases to 4.8% in people aged 65 years or over, and 12.2% in people aged 80 years or over.[11]

The prevalence of neovascular AMD in the UK among people aged 50 years and over is between 1.2% and 6.3%. Estimates indicate that around 39,800 people develop neovascular AMD in the UK each year.[9]

There has been a significant increase in hospital activity in England for episodes with a primary diagnosis of AMD, from less than 10,000 episodes in the years 2005/06 to over 75,000 episodes in the years 2013/14.[9] Due to the aging population, the number of people with neovascular AMD will increase during the next decades.[12]

In England, between 2019-20, there were 55,681 finished consultant episodes (FCE) of degeneration of macular and posterior pole (ICD-10 code H35.3), which includes those with neovascular AMD and active subfoveal CNV.[13-15] Of those FCE there were 54,155 day cases and 1,084 FCE bed days.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment is dependent upon the type of AMD. For neovascular (wet) AMD regular eye injection may be required and, very occasionally, photodynamic therapy (a light treatment) to aid in vision worsening prevention.[16]

CURRENT TREATMENT OPTIONS

According to NICE guidelines for treating neovascular age-related macular degeneration the following antiangiogenic therapies:[17]

- Brolucizumab is recommended as an option in adults, only if the eye been treated is has the best corrected visual acuity between 6/12 and 9/69; there is no permanent structural damage to the central fovea; the lesion size is less than or equal to 12-disc areas in greatest linear dimension; and there is recent presumed disease progression.
- Aflibercept is recommended only if it is used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155 and the manufacturer provides the discount agreed in the patient access scheme.
- Ranibizumab and pegaptanib is recommended when the best corrected visual acuity between 6/12 and 9/69; there is no permanent structural damage to the central fovea; the lesion size is less than or equal to 12 disc areas in greatest linear dimension; there is recent presumed disease progression; and the manufacturer provides it with the agreed discount in the patient access scheme.

PLACE OF TECHNOLOGY

If licenced, conbercept will offer an additional treatment option for patients with neovascular AMD.

CLINICAL TRIAL INFORMATION

Trial	**PANDA-1; NCT03577899; A multicentre, double-masked, randomized, dose-ranging trial to evaluate the efficacy and safety trial of conbercept intravitreal injection for neovascular age-related macular degeneration (PANDA-1)** **Phase III –** Active, not recruiting **Locations –** Europe (not incl. UK), USA, Canada and other countries **Primary completion date** – October, 2020
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N = 1140 (estimated); men and women (1 year post menopausal or surgically sterilised, or a negative pregnancy test and take highly effective contraception) ≥50 years old at the screening visit; no previous treatment for neovascular AMD; have active subfoveal choroidal neovascularization lesions secondary to AMD (incl. polypoidal choroidal

	vasculopathy); an ETDRS BCVA letter score of 78 to 25 in study screening.
Intervention(s)	- Participants receive a 0.5mg conbercept intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every eight weeks thereafter (0.5mg, q8w) for a total of 92 weeks treatment in the study eye. - Participant receive a 1.0mg conbercept intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every twelve weeks thereafter (1.0mg, q12w) for a total of 92 weeks treatment in the study eye.
Comparator(s)	Participants receive a 2.0mg aflibercept (Eylea®) intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every eight weeks thereafter (2.0mg, q8w) for a total of 92 weeks treatment in the study eye.
Outcome(s)	Mean change from baseline in best corrected visual acuity (BCVA) at week 36 in the study eye, as assessed by early treatment of diabetic retinopathy study (ETDRS). See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**PANDA-2; NCT03630952; A multicentre, double-masked, randomized, dose-ranging trial to evaluate the efficacy and safety trial of conbercept intravitreal injection for neovascular age-related macular degeneration (PANDA-2).** **Phase III –** Active, not recruiting. **Locations –** Europe (incl. UK), USA, and other countries **Primary completion date** – December, 2020
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N = 1140 (estimated); men and women (1 year post menopausal or surgically sterilised, or a negative pregnancy test and take highly effective contraception) ≥50 years old at the screening visit; no previous treatment for neovascular AMD; have active subfoveal choroidal neovascularization lesions secondary to AMD (incl. polypoidal choroidal vasculopathy); an ETDRS BCVA letter score of 78 to 25 in study screening.
Intervention(s)	- Participants receive a 0.5mg conbercept intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every eight weeks thereafter (0.5mg, q8w) through week 36. At week 40 visit, the criteria based pro re nata approach will begin

	through the end of the treatment at wee 92, for a total of 92 weeks treatment in the study eye. - Participant receive a 1.0mg conbercept intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every twelve weeks thereafter (1.0mg, q12w) through week 36. At week 40 visit, the criteria based pro re nata approach will begin through the end of the treatment at wee 92, for a total of 92 weeks treatment in the study eye.
Comparator(s)	Participants receive a 2.0mg aflibercept (Eylea®) intravitreal injection at day 1, week 4 and week 8 (three injection loading dose), and treated every eight weeks thereafter (2.0mg, q8w) through week 36. At week 40 visit, the criteria based pro re nata approach will begin through the end of the treatment at wee 92, for a total of 92 weeks treatment in the study eye.
Outcome(s)	Mean change from baseline in best corrected visual acuity (BCVA) at week 36 in the study eye, as assessed by early treatment of diabetic retinopathy study (ETDRS). See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of conbercept is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Brolucizumab for treating wet age-related macular degeneration. (TA672). February 2021
- NICE clinical guidance. Age-related macular degeneration (NG82). January 2018
- NICE interventional procedures guidance. Miniature lens system implantation for advanced age-related macular degeneration (IPG565). September 2016
- NICE technology appraisal. Aflibercept solution for injection for treating wet age-related macular degeneration (TA 294). July 2013
- NICE technology appraisal. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (TA155). May 2012
- NICE interventional procedures guidance. Macular translocation with 360° retinotomy for wet age-related macular degeneration (IPG340). May 2010
- NICE interventional procedures guidance. Limited macular translocation for wet age-related macular degeneration (IPG339). May 2010

- NICE interventional procedures guidance. Transpupillary thermotherapy for age-related macular degeneration (IPG58). May 2004
- NICE interventional procedures guidance. Radiotherapy for age-related macular degeneration (IPG49). March 2004

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (Adult). D12/S/a

OTHER GUIDANCE

- European Society of Retina Specialists (EURETINA). Guidelines for the Management of Neovascular Age-Related Macular Degeneration. September 2014.[18]
- The College of Optometrists and The Royal College of Ophthalmologists. Commissioning better eye care: Age-related macular degeneration. November 2013.[19]

ADDITIONAL INFORMATION

Chengdu Kanghong Pharmaceuticals Group Co Ltd 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.

No information was received from Chengdu Kanghong Pharmaceuticals Group Co Ltd in the preparation of this technology briefing.

REFERENCES

1 ClinicalTrials.gov. *Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular Age-related Macular Degeneration (PANDA-2).Trial ID: NCT03630952. 2018. Active, not recruiting.* Available from: https://clinicaltrials.gov/ct2/show/NCT03630952?term=NCT03630952&draw=2&rank=1 [Accessed 30 April 2021]

2 ClinicalTrials.gov. *Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular Age-related Macular Degeneration (PANDA-1). Trial ID: NCT03577899. 2018. Active, not recruiting.* Available from: https://clinicaltrials.gov/ct2/show/NCT03577899?term=NCT03577899&draw=2&rank=1 [Accessed 30 April 2021]

3 Nguyen TT, Guymer R. Conbercept (KH-902) for the treatment of neovascular age-related macular degeneration. *Expert Review of Clinical Pharmacology*. 2015 2015/09/03;8(5):541-8. Available from: https://doi.org/10.1586/17512433.2015.1075879.

4 Zhang J, Liang Y, Xie J, Li D, Hu Q, Li X, et al. Conbercept for patients with age-related macular degeneration: a systematic review. *BMC Ophthalmology*. 2018 2018/06/15;18(1):142. Available from: https://doi.org/10.1186/s12886-018-0807-1.

5 Li X, Xu G, Wang Y, Xu X, Liu X, Tang S, et al. Safety and Efficacy of Conbercept in Neovascular Age-Related Macular Degeneration: Results from a 12-Month Randomized Phase 2 Study: AURORA Study. *Ophthalmology*. 2014 2014/09/01/;121(9):1740-7. Available from: https://doi.org/10.1016/j.ophtha.2014.03.026.

6 ClinicalTrials.gov. *Search: Conbercept, Phase 3, Pase 2*. 2021. Available from: https://clinicaltrials.gov/ct2/results?term=conbercept&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 30 April 2021]

7 National Institute for Health and Care Excellence. *Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (guidance TA155).* Last update: May 2012. Available from: https://www.nice.org.uk/guidance/ta155/resources/ranibizumab-and-pegaptanib-for-the-treatment-of-agerelated-macular-degeneration-pdf-82598316423109 [Accessed 30 April 2021]

8 Domalpally A, Danis RP. *Fluorescein Angiography in Neovascular AMD*. 2008. Available from: https://www.reviewofophthalmology.com/article/fluorescein-angiography-in-neovascular-amd [Accessed 30 April 2021]

9 National Institute for Health and Care Excellence. *Age-related macular degeneration (NG82).* 2018. Available from: https://www.nice.org.uk/guidance/ng82/resources/agerelated-macular-degeneration-pdf-1837691334853 [Accessed 30 April 2021]

10 Greater Manchester Medicines Management Group (GMMMG). *Macular drugs pathway (Version 1.2).* Last update: Nov 2017. Available from: http://gmmmg.nhs.uk/docs/guidance/GMMMG-Macular-Drugs-Pathways-v-1-2-FINAL.pdf [Accessed 30 April 2021]

11 Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *British Journal of Ophthalmology*. 2012;96(5):752. Available from: https://doi.org/10.1136/bjophthalmol-2011-301109.

12 Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, et al. Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. (1549-4713 (Electronic)). Available from: https://doi.org/10.1016/j.ophtha.2017.05.035.

13 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20.* 2019-20. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 30 April 2021]

14 American Academy of Ophthalmology- EyeNet. *How to use the ICD-10 codes for age-related macular degeneration.* 2017. Available from: https://www.aao.org/eyenet/article/how-to-use-the-icd-10-codes-for-amd [Accessed 30 April 2021]

15 McCune DiRoO. *ICD-1- Updates.* 2016. Available from: https://www.reviewofophthalmology.com/article/icd10-updates [Accessed 30 April 2021]

16 National Health Service UK. *Treatments: age-related macular degenration (AMD).* 2018. Available from: https://www.nhs.uk/conditions/age-related-macular-degeneration-amd/treatment/ [Accessed 30 April 2021]
17 National Institute for Health and Care Excellence. *Treating late age-related macular degeneration (wet active).* Available from: https://pathways.nice.org.uk/pathways/age-related-macular-degeneration#path=view%3A/pathways/age-related-macular-degeneration/treating-late-age-related-macular-degeneration-wet-active.xml&content=view-node%3Anodes-antiangiogenic-therapies [Accessed 30 April 2021]
18 Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *British Journal of Ophthalmology*. 2014;98(9):1144. Available from: https://doi.org/10.1136/bjophthalmol-2014-305702.
19 The College of Optometrists and The Royal College of Ophthalmologists. *Commission better eye care.* 2013. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/AMD-guidance-25-11-13-2013_PROF_262.pdf [Accessed 30 April 2021]

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.