Phase III clinical trials of brolucizumab in patients with neovascular age-related macular degeneration

What is brolucizumab (also known as RTH258)?

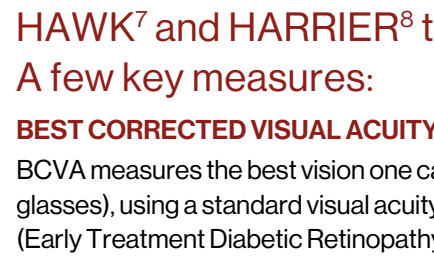
- A unique, small (26 kDa), humanized, investigational single-chain antibody fragment, which is a potent inhibitor of vascular endothelial growth factor (VEGF)[1,2,3]
- Abnormally high levels of VEGF are key in the development of neovascular age-related macular degeneration (nAMD), resulting in the formation of abnormal blood vessels in the retina and increased retinal thickness, due to fluid accumulation within or beneath the retinal layers[4]
- nAMD is the leading cause of severe vision loss and legal blindness in people over the age of 65 in North America, Europe, Australia and Asia, impacting an estimated 20 to 25 million people worldwide[5,6]
- The efficacy and safety of brolucizumab in patients with nAMD is being tested in two pivotal Phase III studies called HAWK and HARRIER[7,8]

HAWK and HARRIER

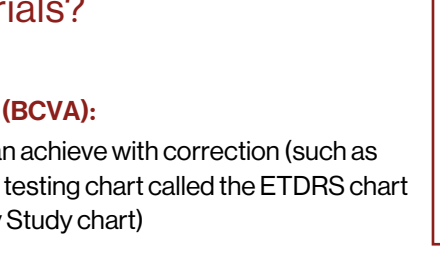
Study Overview

HAWK and HARRIER are prospective, randomized, double-masked, 2-year ongoing studies to evaluate the efficacy and safety of brolucizumab for the treatment of nAMD:

HAWK
(NCT02307682)
Began in December 2014
in study sites in North, Central, and South America, Israel, Australia, New Zealand and Japan.[7]



HARRIER
(NCT02434328)
Began in July 2015
across Europe and Asia.[8]



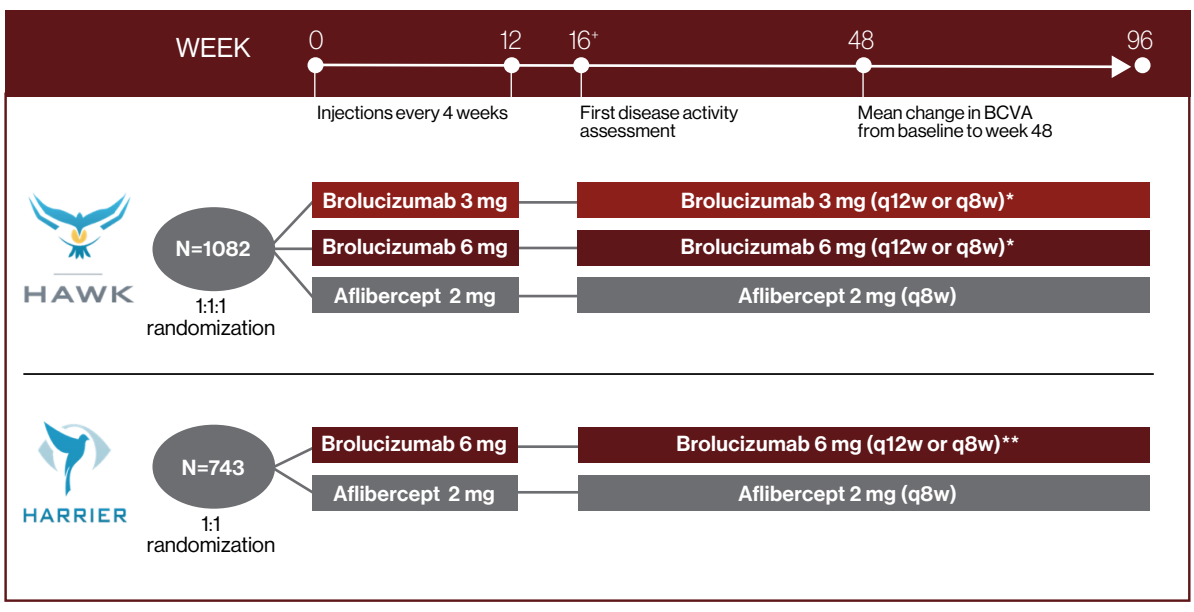
BOTH STUDIES
have completed patient recruitment, enrolling
>1800 PATIENTS
over
400 STUDY SITES
in total[2]

Study Design

What?

Two pivotal trials to test the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and brolucizumab 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD

How?



\+ Matched regimen head-to-head assessment

* Disease activity assessments were conducted at prespecified visits by the masked investigator supported by protocol guidance based on dynamic functional and anatomical characteristics. at weeks 20, 32, 44, 56, 68, 80 and 92

** Additional assessments and potential dosing interval adjustments occurred at weeks 28, 40, 52, 64, 76 and 88 in HARRIER only.

What is the disease activity assessment?

Disease activity assessment (DAA) is the step in which physicians determine which brolucizumab patients are suitable for a 12-week dosing interval and which should be adjusted to an 8-week interval.

In all patients, regardless of treatment arm, disease activity was assessed by the masked investigator. Among patients who received brolucizumab, if the masked investigator determined disease activity to be present, patients were interval adjusted to q8w dosing and they remained at q8w for the remainder of the study.

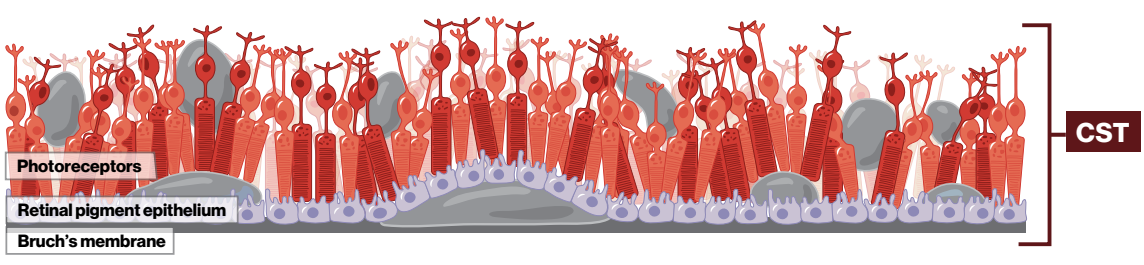
How is the severity of nAMD measured in the HAWK[7] and HARRIER[8] trials? A few key measures:

BEST CORRECTED VISUAL ACUITY (BCVA):

BCVA measures the best vision one can achieve with correction (such as glasses), using a standard visual acuity testing chart called the ETDRS chart (Early Treatment Diabetic Retinopathy Study chart)

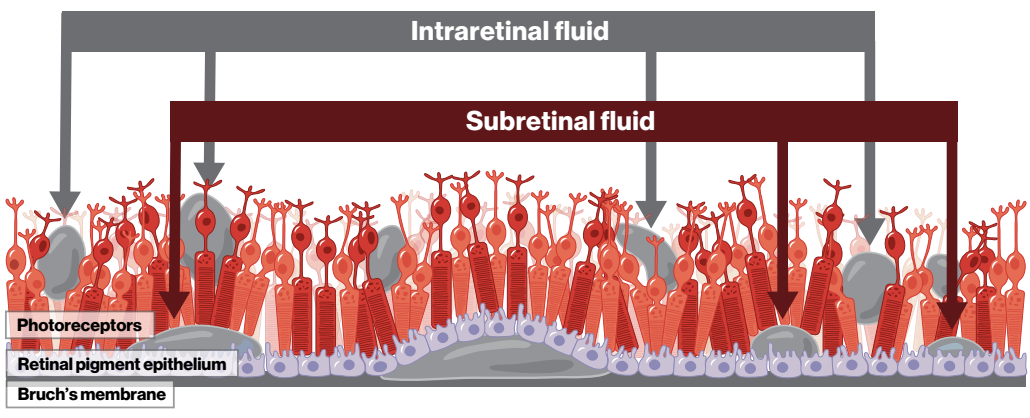
CENTRAL SUBFIELD THICKNESS (CST):

Increases in CST may indicate abnormal fluid accumulation (known as macular edema) in the fovea – the part of the retina responsible for sharp, central vision.



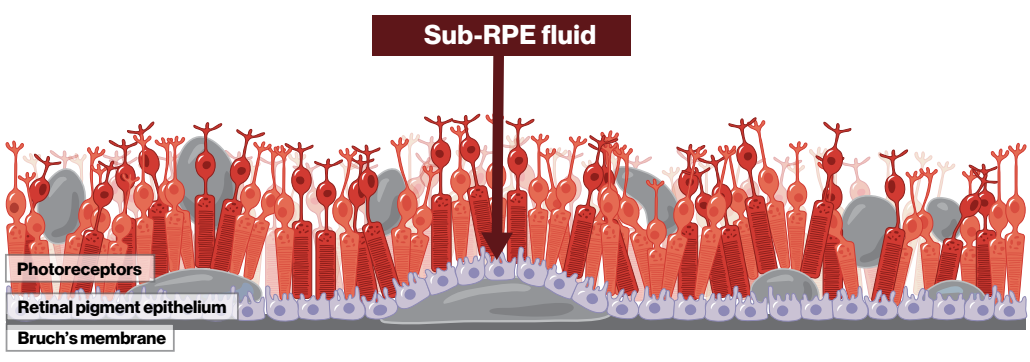
SUB-RETINAL FLUID (SRF) AND INTRA-RETINAL FLUID (IRF):

SRF/IRF is an accumulation of abnormal fluid pockets that may damage cells and surrounding tissue.



SUB-RETINAL PIGMENT EPITHELIUM (RPE) FLUID:

Accumulation of fluid under the RPE may cause a reduction in visual acuity.



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1. Gaudreault J, Gunde T, Floyd HS, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. ARVO Annual meeting abstract. Invest Ophthalmol Vis Sci 2012; 53:3025. Available at: http://iovs.arvojournals.org/article.aspx?articleid=2354604. **2.** Escher D, Schmidt A, STeiner P, Maurer P, Weissgerber G. Single-chain antibody fragments in ophthalmology. Oral presentation at EURETINA congress. 2015. Abstract. Available at: http://www.euretina.org/nice2015/programme/free-papers-details.asp?id=4072&day=0 (accessed 10 May 2017). **3.** Tietz J, Spohn G, Schmid G, et al. Affinity and Potency of RTH258 (ESBA1008), a Novel Inhibitor of Vascular Endothelial Growth Factor A for the Treatment of Retinal Disorders. IOVS. 2015; 56(7): 1501. **4.** A.N. Witmer, G.F.J.M. Vrensenb, C.J.F. Van Noordenc, R.O. Schlingemann, Vascular endothelial growth factors and angiogenesis in eye disease. Prog. Retina Eye Res., 22, (2003), 1– 29. **5.** Schmidt-Erfurth U, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol. 2014; 98:1144-1167. **6.** Chopdar A et al. Age related macular degeneration. BMJ. 2003; 26(7387):485-488. **7.** NCT02307682. Efficacy and Safety of RTH258 Versus Aflibercept. Clinicaltrials.gov. Last updated 24 Feb2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02307682 [HAWK]. **8.** NCT02434328. Efficacy and Safety of RTH258 Versus Aflibercept - Study 2. Clinicaltrials.gov. Last updated 24 Feb2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02434328 [HARRIER]. **9.** Novartis Data on File.

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