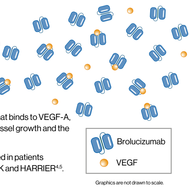
Phase III brolucizumab clinical trials in wet AMD

What is wet AMD?

- Wet age-related macular degeneration (wet AMD) includes activating the vascular endothelial growth factor A (VEGF-A) pathway which signals blood vessels to grow abnormally in the eye's retina, which may cause fluid leakage and vision loss[1,2].



Graphics are not drawn to scale.

What is brolucizumab?

- Brolucizumab is a specially engineered molecule that binds to VEGF-A, potentially reducing or stopping abnormal blood vessel growth and the leaking fluid[3].
- The efficacy and safety of brolucizumab were tested in patients with wet AMD in two pivotal Phase III studies, HAWK and HARRIER[4,5].

HAWK and HARRIER

Study overview

HAWK and HARRIER were global, randomized, double-masked, Phase III studies of 1817 adults with wet AMD carried out over two years. Patients ranged in age from 50 to 97 (average, 76)[4,5].

The trials compared the efficacy and safety of brolucizumab and aflibercept for the treatment of wet AMD[4,5].

HAWK
(NCT02307682)[4]
Study sites in The Americas, Israel, Australia, New Zealand and Japan

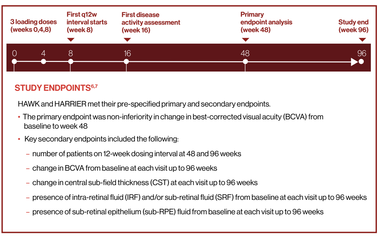
HARRIER
(NCT02434328)[5]
Study sites cross Europe and Asia.

>1800 PATIENTS
1088 brolucizumab
729 aflibercept
over
400 STUDY SITES

Following a loading phase*, wet AMD disease activity was assessed at scheduled visits over 96 weeks[4,5]. A vision test was given and anatomical parameters measured, including retinal fluid and central sub-field thickness *(see additional details below)*[6,7].

Patients in the brolucizumab arm were treated quarterly (q12w) following a loading phase* unless disease activity was noted[6,7]. These brolucizumab patients showing disease activity were adjusted to treatment every other month (q8w) for the remainder of the study[6,7]. Once on q8w, brolucizumab patients could not go back to q12w, even if there was no disease activity[4,5]. All aflibercept patients were treated every other month (q8w) following the loading phase, according to its label at the time of the study[4].

* Treatment with an anti-VEGF therapy for wet AMD begins with three doses given at weeks 0, 4 and 8.



STUDY ENDPOINTS[6,7]

HAWK and HARRIER met their pre-specified primary and secondary endpoints.

- The primary endpoint was non-inferiority in change in best-corrected visual acuity (BCVA) from baseline to week 48.
- Key secondary endpoints included the following:
  - number of patients on 12-week dosing interval at 48 and 96 weeks
  - change in BCVA from baseline at each visit up to 96 weeks
  - change in central sub-field thickness (CST) at each visit up to 96 weeks
  - presence of intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) from baseline at each visit up to 96 weeks
  - presence of sub-retinal epithelium (sub-RPE) fluid from baseline at each visit up to 96 weeks

How disease activity was measured: anatomical and functional outcomes

BEST CORRECTED VISUAL ACUITY (BCVA):

Brolucizumab met its primary endpoint of non-inferiority versus aflibercept at week 48[6]. The robust visual gains shown in year one were maintained in year two[6,7].

BCVA was used to compare a patient's vision at the trial's start with their vision at later visits[6,7]. BCVA was obtained using the standard and validated ETDRS eye chart[8].

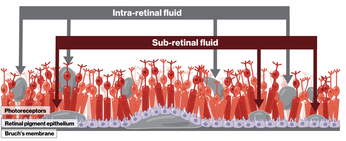
	MEAN CHANGE (± STANDARD ERROR) IN BCVA (IN LETTERS)[6,7]*			
	HAWK		HARRIER	
	Brolucizumab 6 mg	Aflibercept	Brolucizumab 6 mg	Aflibercept
WEEK 48	6.6 (0.71)	6.8 (0.71)	6.9 (0.61)	7.6 (0.61)
WEEK 96	5.9 (0.78)	5.3 (0.78)	6.1 (0.73)	6.6 (0.73)

* Brolucizumab met the primary efficacy endpoint of non-inferiority in mean change in BCVA from baseline at week 48.

IRF AND/OR SRF:

Brolucizumab demonstrated superiority in reducing retinal fluid, an important marker of disease activity, at week 48[1,6]. Reduction of retinal fluid was maintained at week 96[7].

Optical coherence tomography (OCT), an eye imaging method, was used to detect the presence of clear or lipid-rich fluid[1]. Fluid may be an indication of active blood vessel leakage, which may lead to damage to the retina[1]. Fluid within the retina, known as IRF, and fluid under the retina, known as SRF, may contribute to worsening vision[1].



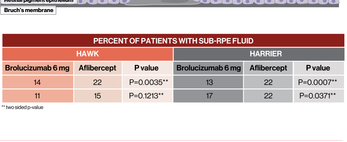
	PERCENT OF PATIENTS WITH IRF AND/OR SRF[6,7]					
	HAWK			HARRIER		
	Brolucizumab 6 mg	Aflibercept	P value	Brolucizumab 6 mg	Aflibercept	P value
WEEK 48	31	45	P<0.0001*	26	44	P<0.0001*
WEEK 96	24	37	P=0.0002**	24	39	P<0.0001**

* one sided p-value
** two sided p-value

SUB-RPE:

Fewer patients had sub-RPE fluid at weeks 48 and 96 versus aflibercept[6,7].

The accumulation of fluid under the RPE, which may cause a reduction in visual acuity, was also examined using OCT[9].



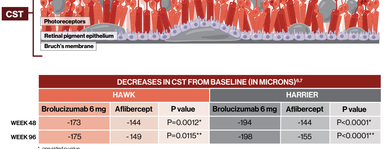
	PERCENT OF PATIENTS WITH SUB-RPE FLUID					
	HAWK			HARRIER		
	Brolucizumab 6 mg	Aflibercept	P value	Brolucizumab 6 mg	Aflibercept	P value
WEEK 48	14	22	P=0.0035**	13	22	P=0.0007**
WEEK 96	11	15	P=0.1213**	17	22	P=0.0371**

** two sided p-value

CST:

Superior reductions in CST were seen at week 48 with brolucizumab[6]. Reductions in CST were reaffirmed at week 96[7].

OCT was also used to measure the thickness of the central subfield of the retina[1]. An increase in CST may indicate abnormal fluid accumulation[9,10].



	DECREASES IN CST FROM BASELINE (IN MICRONS)[6,7]					
	HAWK			HARRIER		
	Brolucizumab 6 mg	Aflibercept	P value	Brolucizumab 6 mg	Aflibercept	P value
WEEK 48	-173	-144	P<0.0012*	-194	-144	P<0.0001*
WEEK 96	-175	-149	P=0.0115**	-198	-155	P<0.0001**

* one sided p-value
** two sided p-value

References

1. Arnold J et al. The role of sub-retinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration—a phase IV randomised clinical trial with ranibizumab: the FLUID study. *BMC Ophthalmol.* 2016;14(34):679-690 **2.** Kim R. Introduction, mechanism of action and rationale for anti-vascular endothelial growth factor drugs in age-related macular degeneration. *Indian J Ophthalmol.* 2007;55(6):413-415. **3.** Data on file. RTH258 Core Data Sheet. Novartis, 2019. **4.** ClinicalTrials.gov. Identifier NCT02307682. Available at https://clinicaltrials.gov/ct2/show/NCT02307682 (link is external). Accessed May 2019. **5.** ClinicalTrials.gov. Identifier NCT02434328. Available at https://clinicaltrials.gov/ct2/show/NCT02434328 (link is external). Accessed May 2019. **6.** Dugel P, et al. HAWK & HARRIER: 48-week results of 2 multi-centered, randomized, double-masked trials of brolucizumab versus aflibercept for neovascular AMD. Presented at: The American Academy of Ophthalmology 2017 Annual Meeting on November 10, 2017, New Orleans. **7.** Dugel P, et al. Phase 3, randomized, double-masked, multi-center trials of brolucizumab versus aflibercept for neovascular AMD: 96-week results from the HAWK and HARRIER studies. Presented at: The American Academy of Ophthalmology on October 27, 2018, Chicago. **8.** Eyles [product information] Tarrytown, NY: Regeneron Pharmaceuticals, Inc.2018. **9.** 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. **10.** Kang SW, et al. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. *Am J Ophthalmol* 2004;137(2):313-322.

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