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Novartis announces FDA filing acceptance and Priority Review of brolucizumab (RTH258) for patients with wet AMD

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- - By 2020, over 1.5 million people in the U.S. are likely to have wet AMD, the leading cause of blindness in industrialized countries
- - Filing is based on Phase III data from the HAWK and HARRIER trials for brolucizumab
- - Novartis used a priority review voucher to expedite review of brolucizumab in the U.S. and, if approved by FDA, anticipates launching by the end of 2019

EAST HANOVER, N.J., April 15, 2019 /PRNewswire/ -- Novartis announced that the U.S. Food and Drug Administration (FDA) accepted the company's Biologics License Application (BLA) for brolucizumab (RTH258) for the treatment of wet age-related macular degeneration (AMD), also known as neovascular AMD, or nAMD. Seeking to make brolucizumab available as quickly as possible, Novartis used a priority review voucher to expedite FDA review. If approved by the FDA, Novartis anticipates launching brolucizumab by the end of 2019.

Estimates suggest that by 2020, 1.5 to 1.75 million people in the U.S. will be living with wet AMD, a leading cause of blindness worldwide and a rapidly growing public health concern[1]. As the disease progresses, patients may experience loss of central vision, resulting in an inability to complete daily tasks. Without treatment, vision can rapidly deteriorate and may lead to blindness[2].

"Reaching this milestone is an important step in our efforts to reimagine the treatment journey for people with wet AMD and their caregivers," said Fabrice Chouraqui, President, Novartis Pharmaceuticals Corporation. "We are looking forward to the potential of a new option for patients with wet AMD, who often have to navigate considerable physical and emotional difficulties caused by deteriorating vision."

The regulatory application is primarily based on Phase III data from the HAWK and HARRIER trials — prospective, randomized, double-masked multi-center studies[3,4]. The primary endpoint of these studies was non-inferiority to aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to week 48 (mean change in BCVA of 6.6 letters for brolucizumab 6 mg versus 6.8 letters for aflibercept in HAWK and 6.9 letters versus 7.6 letters, respectively, in HARRIER). HAWK and HARRIER are the first and only global head-to-head trials in patients with wet AMD that prospectively demonstrated efficacy at week 48 starting with a 12-week dosing regimen.

Additionally, at week 48 in the studies, key secondary endpoint assessments showed significantly fewer brolucizumab patients with disease activity (23.5% of brolucizumab 6 mg patients versus 33.5% of aflibercept patients in HAWK, and 21.9% versus 31.4%, respectively, in HARRIER (P=0.0022 for both) as well as retinal fluid – key markers used by physicians to help guide management of the disease in clinical practice (31% fewer patients on brolucizumab 6 mg had intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) in HAWK, and 26% fewer in HARRIER, versus aflibercept (P<0.0001 for both)[5,6].

"Wet AMD robs people of their precious sight and takes a major toll on the lives of millions of people who face not only vision loss, but also the burden of frequent injections into their eyes," said Dawn Prall George, executive director, The Support Sight Foundation. "We are always excited about potential new treatment options and hopeful they may help people manage this devastating disease."

About brolucizumab (RTH258)
Brolucizumab (RTH258) is a humanized single-chain antibody fragment (scFv) and the most clinically advanced, humanized single-chain antibody fragment to reach this stage of development. Single-chain antibody fragments are highly sought after in drug development due to their small size, enhanced tissue penetration, rapid clearance from systemic circulation and drug delivery characteristics[7-9].

The proprietary innovative structure results in a small molecule (26 kDa) with potent inhibition of, and high affinity to, all VEGF-A isoforms[7,10]. In preclinical studies, brolucizumab inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction[7,9,10]. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema[11]. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions, resolve retinal edema and improve vision in patients with chorioretinal vascular diseases[12].

About HAWK and HARRIER study design
With more than 1,800 patients across nearly 400 sites worldwide, HAWK (NCT02307682) and HARRIER (NCT02434328) are the first and only global head-to-head trials in patients with nAMD that prospectively demonstrated efficacy at week 48 using an innovative q12w/q8w regimen, with a majority of patients on q12w immediately following the loading phase[3-5]. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of brolucizumab[3,4,6].

The studies were designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD[3,4]. In both trials, patients were randomized to either brolucizumab or aflibercept[3,4]. Immediately following the 3-month loading phase, patients in the brolucizumab arms received a q12w dosing interval with an option to adjust to a q8w dosing interval based on masked disease activity assessments at defined visits[3,4]. Aflibercept was dosed bi-monthly according to its label at the time of study initiation[3-6].

Brolucizumab met the primary efficacy objective of non-inferiority versus aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to week 48 with high statistical significance[5]. Additionally, brolucizumab demonstrated superiority in three secondary endpoints considered key parameters of nAMD: central subfield retinal thickness, retinal fluid (intraretinal fluid and/or subretinal fluid) and disease activity[5].

At year two, the most frequent ocular adverse events (≥5% of patients in any treatment arm) for brolucizumab 3 mg, 6 mg and aflibercept, respectively, in HAWK were conjunctival hemorrhage (10.9%, 8.1% and 8.9%), reduced visual acuity (9.5%, 6.1% and 8.1%), vitreous floaters (7.3%, 6.1% and 4.4%), eye pain (7.8%, 5.0% and 5.8%), retinal hemorrhage (3.9%, 5.8% and 5.6%), cataract (5.0%, 5.6% and 3.6%), vitreous detachment (6.7%, 5.3% and 5.3%) and dry eye (5.6%, 5.3% and 7.2%)[5]. The incidences of these events for brolucizumab 6 mg and aflibercept, respectively, in HARRIER were conjunctival hemorrhage (4.6% and 5.1%), reduced visual acuity (8.6% and 7.0%), vitreous floaters (4.1% and 1.4%), eye pain (3.5% and 5.1%), retinal hemorrhage (3.2% and 1.1%), cataract (3.0% and 11.7%), vitreous detachment (2.7% and 2.2%) and dry eye (2.7% and 3.0%)[6].

About neovascular age-related macular degeneration (nAMD or wet AMD)

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[2,13]. nAMD occurs when abnormal blood vessels form underneath the macula, the area of the retina responsible for sharp, central vision. These blood vessels are fragile and leak fluid, disrupting the normal retinal architecture and ultimately causing damage to the macula[1,14,15].

Early symptoms of nAMD include distorted vision or metamorphopsia and difficulties seeing objects clearly[16]. Prompt diagnosis and intervention are essential. As the disease progresses, cell damage increases, further reducing vision quality. This progression can lead to a complete loss of central vision, leaving the patient unable to read, drive or recognize familiar faces[14]. Without treatment, vision can rapidly deteriorate[2].

About Novartis in ophthalmology
Novartis Ophthalmology is reimagining the treatment and prevention of visual impairment and blindness. By pushing the boundaries of medicine and technology we're developing life-changing gene therapies, next-generation pharmaceuticals, and transformative technologies for diseases and conditions spanning every area of eye disease, from the front to the back of the eye.

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