Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

http://www.novartis.com

Two-year data for Novartis brolucizumab reaffirm superiority versus aflibercept in reducing retinal fluid in patients with nAMD

- *Year two results consistent with previously announced key secondary endpoint data on retinal fluid (IRF and/or SRF) showing superior reductions versus aflibercept*
- *Superior reductions in central subfield thickness demonstrated at year one were reaffirmed at year two with brolucizumab 6 mg versus aflibercept*
- *Robust visual gains shown in year one with brolucizumab were maintained in year two*

Basel, 27 October, 2018 – Novartis announced additional brolucizumab Phase III results from year two that reaffirmed its positive year one findings. Brolucizumab met its primary endpoint of non-inferiority versus aflibercept in best corrected visual acuity (BCVA) and exhibited superiority in key retinal outcomes at year one (48 weeks)[1,2]. Secondary endpoints at year two (96 weeks) reaffirmed superiority of brolucizumab 6 mg in reduction of retinal fluid, an important marker of disease activity in patients with neovascular age-related macular degeneration (nAMD)[1,3]. Approximately 20 to 25 million people are affected by nAMD, also known as wet AMD, a leading cause of blindness worldwide[4,5].

The year two HAWK and HARRIER findings demonstrated that fewer patients with nAMD had intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) — key markers used by physicians to determine injection frequency in clinical practice — with brolucizumab 6 mg versus aflibercept at week 96 [24% for brolucizumab 6 mg vs. 37% for aflibercept in HAWK (P=0.0001); 24% vs. 39%, respectively, in HARRIER (P<0.0001)][1*].

Additionally, brolucizumab 6 mg patients continued to demonstrate reductions in central subfield thickness (CST) at week 96[1]. An increase in CST in nAMD is an important measure of abnormal fluid accumulation and edema and may result in reduced vision. Absolute reductions in CST from baseline were -175 µm for brolucizumab 6 mg versus -149 µm for aflibercept in HAWK (P=0.0057) and -198 µm versus -155 µm, respectively, in HARRIER (P<0.0001)[1*].

Also at week 96, fewer brolucizumab 6 mg patients had sub-retinal pigment epithelium (sub-RPE) fluid (11% for brolucizumab 6 mg vs. 15% for aflibercept in HAWK; 17% vs. 22%, respectively, in HARRIER)[1]. Additionally, of the patients on brolucizumab 6 mg who successfully completed year one on a 12-week dosing interval, 82% in HAWK and 75% in HARRIER were maintained on a 12-week dosing interval in year two[1].

“These findings at year two reaffirm the excellent year one brolucizumab data regarding retinal fluid reduction, a key goal for physicians treating patients with nAMD,” said Dr. Pravin U. Dugel, Managing Partner, Retinal Consultants of Arizona; Clinical Professor, Roski Eye Institute, Keck School of Medicine, University of Southern California; and principal investigator of both trials. “These consistent results continue to support brolucizumab as a potential new treatment for patients with nAMD.”

As previously announced, HAWK and HARRIER met their primary endpoint of non-inferiority in mean change in BCVA at week 48 with brolucizumab versus aflibercept[2]. Brolucizumab maintained robust visual gains in year two, with mean change in BCVA of 5.9 letters for

brolucizumab 6 mg versus 5.3 letters for aflibercept in HAWK, and 6.1 letters versus 6.6 letters, respectively, in HARRIER[1].

“Over two years, brolucizumab consistently dried retinal fluid better than aflibercept while keeping many patients on a quarterly dosing schedule. Additionally, the robust visual gains shown in year one with brolucizumab were maintained in year two,” said Shreeram Aradhye, Global Head Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals. “With sustained improvements in key anatomical outcomes that denote disease activity, brolucizumab is an important scientific advance and underscores our commitment to reimagining medicine.”

No new, previously unreported types of safety events were identified at week 96, and brolucizumab continued to be comparable to aflibercept with the overall incidence of adverse events balanced across all treatment groups in both studies[1]. The most frequent ocular adverse events (≥5% of patients in any treatment arm) were reduced visual acuity, conjunctival hemorrhage, vitreous floaters, eye pain, dry eye, retinal hemorrhage, cataract and vitreous detachment[1]. The most frequent non-ocular adverse events were typical of those reported in a nAMD population; there were no notable differences between arms[1].

These new 96-week data, based on pre-specified secondary endpoints from the HAWK and HARRIER trials, were presented at the American Academy of Ophthalmology (AAO) 2018 Annual Meeting as a follow-up to the year one data presented in November 2017[1,2].

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[6,7,8].

The proprietary innovative structure results in a small molecule (26 kDa) with potent inhibition of, and high affinity to, all VEGF-A isoforms[6,9]. In preclinical studies, brolucizumab inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction[6,8,9]. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema[10]. 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[11].

About HAWK and HARRIER study design
With more than 1,800 patients across 400 centers 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[2,12,13]. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of brolucizumab[12,13].

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[12,13]. In both trials, patients were randomized to either brolucizumab or aflibercept. 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. Aflibercept was dosed bi-monthly according to its label at the time of study initiation[2,12,13].

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[2]. 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[2].

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%)[1]. 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%)[1].

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[4,5]. 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[14,15,16].

Early symptoms of nAMD include distorted vision or metamorphopsia and difficulties seeing objects clearly[17]. 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[18].

About Novartis in ophthalmology
For more than 70 years, patients, caregivers and healthcare providers worldwide have looked to Novartis for state-of-the-art treatments in eye diseases. We continue to invest in science as well as in strategic alliances to help ensure patients have access to screening, diagnosis, and our eye medicines. Our commitment to vision extends globally across ages, from premature infants to seniors, from rare diseases to those affecting millions, from eye drops to gene therapies. Our aspiration: reimagining eye care to help *everyone* see possibilities.

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About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 125,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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Novartis Media Relations
Central media line: +41 61 324 2200
E-mail: media.relations@novartis.com

Eric Althoff
Novartis Global Media Relations
+41 61 324 7999 (direct)
+41 79 593 4202 (mobile)
eric.althoff@novartis.com

Amy Wolf
Global Head, Ophthalmology Communications
+41 61 696 5894 (direct)
+41 79 576 0723 (mobile)
amy.wolf@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Richard Pulik	+1 212 830 2448
Pierre-Michel Bringer	+41 61 324 1065	Cory Twining	+1 212 830 2417
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		

*Descriptive P-values related to pre-specified secondary endpoints assessed at weeks 16 and 48