New analysis of Novartis Phase III brolucizumab (RTH258) data reinforces superior reduction of retinal fluid, a key marker of disease activity in nAMD

- Pre-specified analysis provides insight into maintenance treatment effectiveness with like-for-like comparison of brolucizumab versus aflibercept over entire week 36 to 48 treatment period

- Retinal fluid was detected less often in patients treated with brolucizumab 6 mg versus aflibercept between weeks 36 to 48

- Regulatory submissions for brolucizumab on track for December 2018

Basel, 22 September 2018 – Novartis announced a new data analysis showing that retinal fluid was detected less often in patients treated with brolucizumab (RTH258) 6 mg versus aflibercept over four visits between weeks 36 to 48. Retinal fluid is a key marker of disease activity in neovascular age-related macular degeneration (nAMD). The data, from pre-specified secondary endpoints of the Phase III HAWK and HARRIER trials, were presented at EURETINA 2018 as a follow-up to data presented in November 2017.

The data show that brolucizumab 6 mg had superior fluid resolution versus aflibercept over four visits during weeks 36 to 48. The 36- to 48-week analysis is noteworthy because it provides insight into the effect of maintenance treatment, an important clinical focus for a chronic disease like nAMD. Additionally, the analysis accounts for dosing interval differences between the two medicines. Due to the unique design of the HAWK and HARRIER trials, brolucizumab patients were dosed at various intervals, namely q12w with some adjusted to q8w based on disease activity. Aflibercept patients were dosed at q8w, per the label at the time of trial initiation.

In the pre-specified secondary analyses for weeks 36 to 48, patients treated with brolucizumab 6 mg in the HAWK and HARRIER trials had significantly fewer visits in which intraretinal fluid (IRF)/subretinal fluid (SRF) was observed. In HAWK, 47.5% of patients treated with brolucizumab 6 mg q12w or adjusted to q8w had no visits in which IRF/SRF was detected, compared to 42.5% of aflibercept patients \((P=0.0012, \text{ reflecting distribution across all visits during weeks 36 through 48})\). In HARRIER, 53% of patients treated with brolucizumab 6 mg had no visits in which IRF/SRF was detected, compared to 45.5% of aflibercept patients \((P=0.0001, \text{ reflecting distribution across all visits during weeks 36 through 48})\). Importantly, more than half of brolucizumab 6 mg patients were maintained on q12w dosing until week 48.

“Retinal fluid is an important marker of disease activity and the need for treatment. These new data give physicians even more insight into the robustness of the 48 week anatomical findings and support the overall impact brolucizumab has on key measures of retinal fluid, including...”
IRF/SRF, sub-retinal pigment epithelial fluid and central subfield thickness,” said Dirk Sauer, Development Unit Head, Novartis Ophthalmology. “These results were noted even while more than half of brolucizumab 6 mg patients were receiving treatment every 12 weeks at week 48, further reinforcing our confidence in brolucizumab’s superior fluid resolution and supporting our goal of reimagining care for people with nAMD.”

As previously announced, HAWK and HARRIER achieved their primary endpoints of non-inferiority in mean change in best corrected visual acuity (BCVA) at week 48 with brolucizumab versus aflibercept. The key pre-specified secondary endpoint of non-inferiority in mean change in BCVA between weeks 36 and 48 was also met.

Brolucizumab safety was comparable to aflibercept with the overall incidence of adverse events balanced across all treatment groups in both studies. The most frequent ocular adverse events (equal to or greater than 5% of patients in any treatment arm) were reduced visual acuity, conjunctival hemorrhage, vitreous floaters and eye pain. The most frequent non-ocular adverse events were typical of those reported in a nAMD population; there were no notable differences between arms.

**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.

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

**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. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of brolucizumab.

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. 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.

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. 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\textsuperscript{3}. These results were achieved while a majority of brolucizumab patients—56\% in HAWK and 51\% in HARRIER—were maintained on a q12w dosing interval immediately following the loading phase through week 48\textsuperscript{3}.

**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\textsuperscript{13,14}. 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\textsuperscript{15,16,17}.

Early symptoms of nAMD include distorted vision or metamorphopsia and difficulties seeing objects clearly\textsuperscript{18}. 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\textsuperscript{16}. Without treatment, vision can rapidly deteriorate\textsuperscript{19}.

**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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*In August 2018, the aflibercept U.S. Prescribing Information was updated to note, “Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy.”*