Novartis RTH258 (brolucizumab) demonstrates robust visual gains in nAMD patients with a majority on a 12-week injection interval

- **RTH258 achieved the primary efficacy endpoint of non-inferiority to aflibercept in mean change in BCVA from baseline to week 48**\(^1,4\) in two head-to-head pivotal Phase III studies\(^1,4\).

- **57% and 52% of patients receiving RTH258 6 mg in the respective trials were maintained exclusively on a q12w interval immediately following the loading phase and continuing through week 48**\(^1,2\).

- **In both studies overall ocular and non-ocular adverse event rates for RTH258 were comparable to aflibercept**\(^1,2\).

**Base, June 20, 2017** – Novartis, the global leader in Ophthalmology, today reported that RTH258 (brolucizumab) 6 mg met the primary and key secondary endpoints in two Phase III studies, HAWK and HARRIER. RTH258 3 mg, evaluated in HAWK, also met these endpoints. These pivotal studies enrolled more than 1,800 patients with neovascular age-related macular degeneration (nAMD) across 400 centers worldwide. The primary and key secondary efficacy endpoints were non-inferiority of RTH258 to aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to week 48, and average mean change over the period of week 36-48, respectively.\(^1,4\) Both were met with highly significant p values. RTH258 was generally well tolerated with overall ocular and non-ocular (systemic) adverse event rates comparable to aflibercept.\(^1,2\)

RTH258 demonstrated long-lasting efficacy versus aflibercept dosed every eight weeks. A majority of patients, 57% (HAWK) and 52% (HARRIER), were maintained exclusively on a q12w (every 12 week) interval immediately following the loading phase through week 48.\(^1,2\)

“These results clearly and convincingly demonstrate RTH258 has the potential to reduce injection burden while providing excellent visual outcomes. Given our legacy in developing medicines to preserve vision, we are pleased that RTH258 carries the promise of being the next major advancement for patients with nAMD” said Vas Narasimhan, Global Head, Drug Development and Chief Medical Officer, Novartis. “Based on these robust data, we are looking forward to working with regulatory agencies to bring this pioneering treatment to patients.”

Detailed analysis of the data is ongoing and will be presented at an upcoming medical congress. RTH258 is a highly innovative single chain antibody that enables much higher concentrations of antibody in the eye than approved therapies. Given the complexity of the formulation, Novartis has invested to ensure a competitive, low cost of goods formulation over the past 18 months to maximize the long term value of RTH258. Novartis expects to complete the pharmacokinetic study with the final manufacturing process to enable filing in 2018.

RTH258 has the potential to address the needs of patients with nAMD who would benefit from a long-lasting, efficacious treatment with a less frequent dosing regimen.\(^5\)
About RTH258 (brolucizumab)
Designed specifically for the eye, RTH258 is the most clinically advanced, humanized single chain anti-body fragment in development. The proprietary innovative architecture results in a small molecule (26 kDa) with potent inhibition of, and high affinity to all VEGF-A isoforms. Potential benefits of the small size include better tissue penetration and rapid clearance from the systemic circulation.

In preclinical studies, RTH258 inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction. Increased signalling 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 choroiretinal vascular diseases.

About HAWK and HARRIER
With more than 1,800 patients across 400 centers worldwide, HAWK and HARRIER are the first and only global head-to-head trials in patients with nAMD that prospectively demonstrate efficacy with a pre-specified injection interval of 12 weeks. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of RTH258.

The studies were designed to compare the efficacy and safety of intravitreal injections of RTH258 6 mg and 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD. The primary efficacy objective of HAWK and HARRIER trials was to confirm that RTH258 is non-inferior to aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to Week 48. Secondary endpoints include average mean change in BCVA from baseline over the period week 36-48, the proportion of patients on a q12w interval at week 48 and anatomical parameters.

In both protocols, patients were randomized to either RTH258 or aflibercept. Immediately following the 3-month loading phase, patients in the RTH258 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.

RTH258 6 mg met the primary and key secondary endpoints in two Phase III studies, HAWK AND HARRIER. RTH258 3 mg, evaluated in HAWK, also met these endpoints. In both studies, these endpoints were met with highly significant p.

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. nAMD occurs when abnormal blood vessels form and grow underneath the macula, the area of the retina responsible for sharp, central vision. These blood vessels are fragile and leak fluid and blood, disrupting the normal retinal architecture and ultimately causing damage to the light sensitive cells.

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

About Novartis in Ophthalmology
Novartis is a leading ophthalmology company, with therapies that treat both front and back of the eye disorders, including retina diseases, glaucoma, dry eye and other external eye diseases. In 2016, 200 million patients worldwide were treated with Novartis ophthalmic products.
Disclaimer
The foregoing release contains forward-looking statements that can be identified by words such as “prospective,” “commitment,” “potential,” “looking forward,” “above expectations,” “ongoing,” “will,” “upcoming,” “on track,” “end of 2018,” “can,” “would,” “in development,” or similar terms, or by express or implied discussions regarding potential marketing approvals for RTH258, or regarding potential future revenues from RTH258. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that RTH258 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that RTH258 will be commercially successful in the future. In particular, management’s expectations regarding RTH258 could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the company’s ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing and reimbursement pressures; safety, quality or manufacturing issues, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 118,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

References

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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

Friedrich von Heyl
Novartis Pharma Communications
+41 61 324 8984 (direct)
+41 79 749 0286 (mobile)
friedrich.vonheyl@novartis.com

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

Central
Samir Shah +41 61 324 7944
Pierre-Michel Bringer +41 61 324 1065
Thomas Hungerbuehler +41 61 324 8425
Isabella Zinck +41 61 324 7188

North America
Richard Pulik +1 212 830 2448
Cory Twining +1 212 830 2417

Central
Samir Shah +41 61 324 7944
Pierre-Michel Bringer +41 61 324 1065
Thomas Hungerbuehler +41 61 324 8425
Isabella Zinck +41 61 324 7188

North America
Richard Pulik +1 212 830 2448
Cory Twining +1 212 830 2417