Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
https://twitter.com/novartisnews

MEDIA UPDATE

Results from real-world data and post-hoc analysis of Novartis Beovu® pivotal trials presented at AAO 2020

- *Initial findings on patient characteristics and event likelihood provide insights related to Beovu use in wet AMD*[1,2]
- *Follows establishment of multi-disciplinary expert coalition and Novartis commitment to sharing data and findings with ophthalmology community*
- *Despite existing therapies, significant unmet need still exists for wet AMD patients; data shows around half of patients have unresolved fluid, with a third requiring monthly injections*[3,4]

Basel, November 13, 2020 — Novartis today reported initial findings from a coalition convened to answer key questions related to treatment with Beovu® (brolucizumab) for adults with wet age-related macular degeneration (AMD). Analyses of US real-world and Phase III data presented at the American Academy of Ophthalmology (AAO) 2020 Annual Meeting identified baseline patient characteristics potentially associated with the incidence of inflammation-related adverse events that may occur following treatment with Beovu[1,2]. Novartis has a comprehensive program of work underway examining the root cause and potential risk factors for these events, as well as identifying mitigation strategies and treatment protocols.

In the analysis of data from the IRIS Registry, including 12,000 patients treated with Beovu, the highest observed risk for experiencing retinal vasculitis (RV) and/or retinal vascular occlusion (RO) in the six months after first treatment with Beovu was prior intraocular inflammation (IOI) and/or prior RO in the 12 months before first Beovu injection[1]. Against an observed overall RV/RO risk rate of 0.46% for all Beovu-treated patients in the registry, this increased to 3.97% in individuals with prior IOI and/or RO[1].

“We are pleased to share these findings that underscore the importance of carefully examining a patient for active ocular inflammation before injecting Beovu and throughout the course of treatment,” said Marcia Kayath, Global Head of Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals. “Even with the great advancements made in treating wet AMD, data shows 50% of patients have unresolved fluid and a third require monthly injections, highlighting the persistent unmet need that Beovu may help address[3,4].”

In a post-hoc unmasked assessment of the Phase III HAWK and HARRIER data, there was an observed trend toward increased incidence of RV/RO in patients with treatment emergent (boosted/induced) anti-drug antibodies (ADAs)[2]. Further analyses of the data presented and additional data collection are ongoing.

Novartis has five presentations at the congress including results from a post-hoc HAWK and HARRIER analysis showing Beovu is associated with greater and sustained reduction in Pigment Epithelial Detachments and Subretinal Hyper-reflective Material compared with aflibercept[5]. Novartis also sponsored a symposium including description of US real-world wet AMD patient case studies with Beovu.

Beovu is now approved in more than 50 countries, including in the US, EU, UK, Japan, Canada and Australia, based on the results of the HAWK and HARRIER clinical trials[6-10]. Novartis is confident that Beovu continues to represent an important treatment option for patients with wet AMD, with an overall favorable benefit/risk profile.

About Beovu (brolucizumab)
Beovu (brolucizumab, also known as RTH258) is the first advanced humanized single-chain antibody fragment (scFv) approved for clinical use[11,12,13]. 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[13-15].

The proprietary innovative structure results in a small molecule (26 kDa) with potent inhibition of, and high affinity to, all VEGF-A isoforms[14]. Beovu is engineered to deliver a high concentration of drug, thus providing more active binding agents[11,12,13]. In preclinical studies, Beovu inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction[14-16]. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema[17]. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and suppress endothelial cell proliferation and vascular permeability[17].

About the HAWK and HARRIER studies
With more than 1,800 patients across nearly 400 centers worldwide, HAWK (NCT02307682) and HARRIER (NCT02434328) are the first global head-to-head trials in patients with wet AMD that prospectively demonstrated efficacy of Beovu at week 48 using an innovative q12w/q8w regimen, with a majority of patients on q12w immediately following the loading phase[11,12]. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of Beovu[11,12]. 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 wet AMD[11,12]. The most common adverse events (≥5% of patients) with Beovu were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain[11,12].

About the coalition
In early 2020, following post-marketing reports of vasculitis, Novartis initiated a review of post-marketing safety case reports and together with an external review committee confirmed a safety signal of uncommon adverse events termed as “retinal vasculitis” and/or “retinal vascular occlusion” that may result in severe vision loss. As a result, Novartis initiated worldwide label updates to reflect this adverse event information.

Novartis is dedicated to examining the root causes and potential risk factors associated with these adverse events and has convened a fully dedicated team of Novartis research, drug development and medical specialists, who are working with an external team of top global experts to thoroughly investigate risk factors and identify mitigation strategies and treatment protocols.

About wet age-related macular degeneration
Wet AMD 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 million people worldwide[18-20]. Wet AMD occurs when abnormal blood vessels form underneath the

macula, the area of the retina responsible for sharp, central vision[21,22]. These blood vessels are fragile and leak fluid, disrupting the normal retinal architecture and ultimately causing damage to the macula[21,22].

Early symptoms of wet AMD include distorted vision (or metamorphopsia) and difficulties seeing objects clearly[23]. Prompt diagnosis and intervention are essential[24]. As the disease progresses, cell damage increases, further reducing vision quality[24]. This progression can lead to a complete loss of central vision, leaving the patient unable to read, drive or recognize familiar faces and potentially depriving them of their independence[24,25]. Without treatment, vision can rapidly deteriorate[26].

About Novartis in ophthalmology
At Novartis, our mission is to discover new ways to improve and extend people's lives. In ophthalmology, we develop and deliver life-changing medicines and therapies for diseases and conditions from front to back of the eye, enabled by data and transformative technologies. Our ophthalmic solutions reach more than 150M people per year, from premature infants to the elderly.

Disclaimer
This media update contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this media update, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations 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 the investigational or approved products described in this media update will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products 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; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, 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 media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update as a result of new information, future events or otherwise.

About Novartis
Novartis is reimagining medicine to improve and extend people’s lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world’s top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding

innovative ways to expand access to our latest treatments. About 110,000 people of more than 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at **https://twitter.com/novartisnews**
For Novartis multimedia content, please visit **https://www.novartis.com/news/media-library**
For questions about the site or required registration, please contact media.relations@novartis.com

References

1. Ip M, et al. The Brolucizumab Experience Thus Far: A Health Economics and Outcomes Research Analysis. Presented at: American Academy of Ophthalmology 2020 Virtual Congress. November 2020.
2. Heier JS, et al. Assessing characteristics of patients with or without intraocular inflammation (IOI) in the brolucizumab treatment arms from the HAWK and HARRIER, Phase 3 studies. Presented at: American Academy of Ophthalmology 2020 Virtual Congress. November 2020.
3. Singer M. Two-Year Real-World Treat and Extend Patterns and Fluid Outcomes Among Neovascular Age-Related Macular Degeneration Patients Treated With Anti-VEGFs. Presented at the American Society of Retina Specialists (ASRS) Annual Meeting (Virtual). July 24–26 2020.
4. Khanani AM, et al. SIERRA-AMD: A Retrospective, Real-World Evidence Study of Patients With Neovascular Age-Related Macular Degeneration in the United States. *Ophthalmol Retina*. 2020;4:122–133.
5. Sadda S, et al. Pigment Epithelial Detachments and Subretinal Hyper-reflective Material: A HAWK and HARRIER Analysis. Presented at: American Academy of Ophthalmology 2020 Virtual Congress. November 2020.
6. Beovu [US prescribing information] East Hanover, NJ. Novartis: 2019.
7. Beovu [summary of product characteristics] Basel, Switzerland. Novartis: 2020.
8. Pharma Japan. National Health Insurance Pricing. Available at: https://pj.jiho.jp/sites/default/files/pj/document/2020/05/New%20Drugs%20to%20Be%20Added%20to%20NHI%20Price%20List%20on%20May%2020_1.pdf. Accessed September 2020.
9. Canadian Agency for Drugs and Technologies in Health. CADTH Canadian Drug Expert Committee Recommendation. Available at: https://cadth.ca/sites/default/files/cdr/complete/SR0632%20Beovu%20-%20CDEC%20Final%20Recommendation%20%E2%80%93%20May%2025%2C%202020_for%20posting.pdf. Accessed September 2020.
10. Beovu [prescription medicine decision summary] Australia. Novartis: 2020.
11. Dugel P, Koh A, Ogura Y, et al; HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *J Ophthalmol*. 2020;127(1):72-84
12. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: 96-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration [published online ahead of print]. *J Ophthalmol*. 2020. https://doi.org/10.1016/j.ophtha.2020.06.028.
13. Nimz EL, et al. Intraocular and systemic pharmacokinetics of brolucizumab (RTH258) in nonhuman primates. Presented at: Association for Research in Vision and Ophthalmology (ARVO) annual meeting. 2016. Abstract 4996
14. Escher D, et al. Single-chain antibody fragments in ophthalmology. Presented at: EURETINA congress. 2015. Abstract.
15. Gaudreault J, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. *Invest Ophthalmol Vis Sci* 2012;53:3025.
16. Tietz J, et al. Affinity and Potency of RTH258 (ESBA1008), a Novel Inhibitor of Vascular Endothelial Growth Factor A for the Treatment of Retinal Disorders. IOVS. 2015; 56(7):1501.
17. 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.
18. 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.
19. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and met analysis. *Lancet Glob Health*. 2014;2:106-16.
20. Singer M. Advances in the management of macular degeneration. *F1000Prime Rep*. 2014;6:29.
21. MedlinePlus. Age-related macular degeneration. Available at: https://medlineplus.gov/genetics/condition/age-related-macular-degeneration/. Accessed November 2020.
22. World Health Organization. Priority eye diseases: Age-related macular degeneration. Available at http://www.who.int/blindness/causes/priority/en/index7.html. Accessed November 2020.
23. Healthline. What is metamorphopsia? Available at https://www.healthline.com/health/metamorphopsia. Accessed November 2020.
24. NHS Choices. Macular degeneration - Symptoms. Available at http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Symptoms.aspx. Accessed November 2020

25. Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. *Health Qual Life Outcomes*. 2006;4:97.
26. van Lookeren Campagne M, et al. Mechanisms of age-related macular degeneration and therapeutic opportunities*. J Pathol*. 2014; 232(2):151-64.

# # #

Novartis Media Relations
E-mail: media.relations@novartis.com

Peter Zuest
Novartis External Communications
+ 41 79 899 9812 (mobile)
peter.zuest@novartis.com

Amy Wolf
Novartis Division Communications
+ 41 79 576 07 23 (mobile)
amy.wolf@novartis.com

Eric Althoff
Novartis US External Communications
+1 646 438 4335
eric.althoff@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	Sloan Simpson	+1 862 778 5052
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		