

New Novartis Phase III data for brolucizumab demonstrate reliability of 12-week treatment interval

Apr 30, 2018

- - Patients identified for brolucizumab 12-week treatment interval in Phase III HAWK and HARRIER trials had an 87% and 83% probability of successfully continuing on a 12-week interval through week 48
- - Predictability data increase confidence in reliability of brolucizumab 12-week dosing regimen and potential of a simplified treatment plan

EAST HANOVER, N.J., April 30, 2018 /PRNewswire/ -- Novartis announced new positive brolucizumab (RTH258) data in neovascular age-related macular degeneration (nAMD) from a pre-specified secondary analysis of the Phase III HAWK and HARRIER trials. The findings showed that patients assessed as appropriate for a 12-week treatment frequency during the first 12-week cycle after loading could reliably stay on that quarterly interval through week 48. This is the first time a high level of reliability has been prospectively demonstrated for a pre-specified secondary endpoint of a 12-week dosing interval with an anti-vascular endothelial growth factor (VEGF) therapy in Phase III trials. These additional data were presented at the Association for Research in Vision and Ophthalmology (ARVO) 2018 Annual Meeting. Last June, the company announced positive results from these two Phase III studies of brolucizumab showing non-inferiority to aflibercept in mean change in BCVA from baseline to week 48.

Previously reported findings demonstrated that a majority of brolucizumab 6 mg patients in the trials – 57% in HAWK and 52% in HARRIER – were maintained on a 12-week dosing interval following the loading phase through week 48. The new findings showed that brolucizumab 6 mg patients who were suitable for 12-week treatment intervals during the first 12-week cycle after the loading phase had an 87% (HAWK) and 83% (HARRIER) probability of remaining on this quarterly treatment interval through week 48. The ability to reliably assess the likelihood of patients remaining on quarterly dosing could help physicians and patients better manage, personalize and optimize treatment plans.

"The ability to quickly identify patients who can maintain a 12-week interval has the potential to simplify treatment plans for nAMD patients," said Glenn J. Jaffe, M.D., Chief of Retinal Ophthalmology, Duke University, and an author of the presentation. "These robust data may offer physicians confidence that when 12-week dosing with brolucizumab is initially successful, there is high probability that the patient will maintain this interval through the first year of treatment."

"HAWK and HARRIER previously demonstrated non-inferiority in the primary endpoint of visual acuity and superiority in several secondary endpoints assessing key anatomical outcomes versus aflibercept, with a majority of brolucizumab patients maintained on an every-12-week dosing interval following the loading phase through week 48¹," said Dirk Sauer, Development Unit Head, Novartis Ophthalmology. "Here we show that success early on with brolucizumab appears strongly predictive of the ability of these patients to successfully maintain this 12-week treatment interval² through week 48. We look forward to continuing to advance brolucizumab through regulatory approvals as a welcome new option for treatment of nAMD, which is a leading cause of blindness."

Brolucizumab safety was comparable to aflibercept with the overall incidence of adverse events balanced across all treatment groups in both studies³. The most frequent ocular adverse events (greater than 5% of patients in any treatment arm) for brolucizumab 3 mg, 6 mg and aflibercept, respectively, in HAWK were reduced visual acuity (8.7%, 6.9% and 8.9%), conjunctival hemorrhage (8.4%, 6.4% and 5.6%), vitreous floaters (6.7%, 5.0% and 3.1%) and eye pain (5.9%, 4.4% and 4.2%)⁴. The incidences of these events for brolucizumab 6 mg and aflibercept, respectively, in HARRIER were reduced visual acuity (5.9% and 6.2%), conjunctival hemorrhage (1.9% and 3.3%), vitreous floaters (3.0% and 0.8%) and eye pain (2.7% and 3.3%)⁴. The most frequent non-ocular adverse events were typical of those reported in an nAMD population; there were no notable differences between arms⁴. The incidence of arterial thrombotic events (ATE) was 3.9%, 2.5% and 5.6% (brolucizumab 3 mg, brolucizumab 6 mg and aflibercept respectively) in HAWK and 2.7% and 4.3% (brolucizumab 6 mg and aflibercept, respectively) in HARRIER².

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^{4,5,6}.

The proprietary innovative structure results in a small molecule (26 kDa) with potent inhibition of, and high affinity to, all VEGF-A isoforms^{4,7}. In preclinical studies, brolucizumab inhibited activation of VEGF receptors through prevention of the ligand-receptor interaction^{4,5,6,7}. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema⁸. 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 diseases⁹.

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 phase¹⁰. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of brolucizumab^{10,11}.

The studies were designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg and 3 mg (HAWK only) versus aflibercept 2 mg in patients with nAMD^{10,11}. 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^{10,11}.

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 significance¹. Additionally, brolucizumab demonstrated superiority in three secondary endpoints considered key markers of nAMD: central subfield retinal thickness, retinal fluid (intraretinal fluid and/or subretinal fluid) and disease activity³. These results were achieved while a majority of brolucizumab patients—57% in HAWK and 52% in HARRIER—were maintained on a q12w dosing interval immediately following the loading phase through week 48³.

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^{12,13}. 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^{14,15,16}.

Early symptoms of nAMD include distorted vision or metamorphopsia and difficulties seeing objects clearly¹⁷. 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 faces¹⁴. Without treatment, vision can rapidly deteriorate¹⁸.

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, approximately 200 million patients worldwide were treated with Novartis ophthalmic products.

Disclaimer

This press release 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," "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 press release, 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 press release 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; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality 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 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

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation is an affiliate of Novartis which 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 124,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For

more information, please visit <http://www.novartis.com> (link is external).

Novartis is on Twitter. Sign up to follow @Novartis at <http://twitter.com/novartis>

For Novartis multimedia content, please visit www.novartis.com/news/media-library

For questions about the site or required registration, please contact media.relations@novartis.com

References

1. Dugel P, et al. HAWK & HARRIER: 48-week results of 2 multi-centered, randomized, double-masked trials of brolucizumab versus aflibercept for neovascular AMD. Presented at: The American Academy of Ophthalmology 2017 Annual Meeting on November 10, 2017, New Orleans.
2. Dugel P, et al. A Comparison of the Anatomical Efficacy of Brolucizumab and Aflibercept in Neovascular Age-related Macular Degeneration (nAMD): An Analysis over 16 Weeks of Matched Treatment in the HAWK and HARRIER Studies. Presented at: the Association for Research in Vision and Ophthalmology (ARVO) 2018 Annual Meeting, Honolulu, HI.
3. Data on file.
4. Escher D, et al. Single-chain antibody fragments in ophthalmology. Oral presentation at EURETINA congress. 2015. Abstract. Available at: <http://www.euretina.org/nice2015/programme/free-papers-details.asp?id=4072&day=0> (link is external). Accessed November 2017.
5. Nimz EL, et al. Intraocular and systemic pharmacokinetics of brolucizumab (RTH258) in nonhuman primates. The Association for Research in Vision and Ophthalmology (ARVO) annual meeting. 2016. Abstract 4996.
6. Gaudreault J, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. ARVO Annual meeting abstract. Invest Ophthalmol Vis Sci 2012;53:3025. <http://iovs.arvojournals.org/article.aspx?articleid=2354604> (link is external).
7. 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.
8. Qazi Y, et al. Mediators of ocular angiogenesis. J. Genet. 2009;88(4):495-515.
9. 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.
10. ClinicalTrials.gov. Identifier NCT02307682. Available at <https://clinicaltrials.gov/ct2/show/NCT02307682> (link is external). Accessed November 2017.
11. ClinicalTrials.gov. Identifier NCT02434328. Available at <https://clinicaltrials.gov/ct2/show/NCT02434328>(link is external). Accessed November 2017.
12. 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.
13. Chopdar A, et al. Age related macular degeneration. BMJ. 2003;26(7387):485-488.
14. World Health Organization. Priority eye diseases: Age-related macular degeneration. Available at <http://www.who.int/blindness/causes/priority/en/index7.html> (link is external). Accessed November 2017.
15. NHS Choices. Macular Degeneration. Available at <http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Introduction.aspx> (link is external). Accessed November 2017.
16. National Eye Institute. Facts About Age-Related Macular Degeneration. Available at https://nei.nih.gov/health/maculardegen/armd_facts (link is external). Accessed November 2017.
17. NHS Choices. Macular degeneration - Symptoms. Available at <http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Symptoms.aspx> (link is external). Accessed November 2017.
18. van Lookeren Campagne M, et al. Mechanisms of age-related macular degeneration and therapeutic opportunities. J Pathol. 2014; 232(2):151-64. doi: 10.1002/path.4266.

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

Eric Althoff

Martin DeBenedetto

Novartis Global Media Relations Director, Communications

+41 61 324 7999 (direct) (862) 778-7619 (direct)

+41 79 593 4202 (mobile) (973) 738-4104 (mobile)

eric.althoff@novartis.com

martin.debenedetto@novartis.com

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

North America

Richard Pulik +1 212 830 2448

Cory Twining +1 212 830 2417

SOURCE Novartis

Source URL: <https://prod1.novartis.com/us-en/news/media-releases/new-novartis-phase-iii-data-brolucizumab-demonstrate-reliability-12-week-treatment-interval>

List of links present in page

1. <https://prod1.novartis.com/us-en/us-en/news/media-releases/new-novartis-phase-iii-data-brolucizumab-demonstrate-reliability-12-week-treatment-interval>
2. <http://www.novartis.com/>
3. <http://twitter.com/novartis>
4. <http://www.novartis.com/news/media-library>
5. <mailto:media.relations@novartis.com>
6. <http://www.euretinia.org/nice2015/programme/free-papers-details.asp?id=4072&day=0>
7. <http://iovs.arvojournals.org/article.aspx?articleid=2354604>
8. <https://clinicaltrials.gov/ct2/show/NCT02307682>
9. <https://clinicaltrials.gov/ct2/show/NCT02434328>
10. <https://clinicaltrials.gov/ct2/show/NCT02434328>
11. <http://www.who.int/blindness/causes/priority/en/index7.html>

12. <http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Introduction.aspx>
13. https://nei.nih.gov/health/maculardegen/armd_facts
14. <http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Symptoms.aspx>
15. <mailto:media.relations@novartis.com>
16. <mailto:eric.althoff@novartis.com>
17. <mailto:martin.debenedetto@novartis.com>
18. <mailto:investor.relations@novartis.com>