# Novartis announces FDA and EMA filing acceptances of BEOVU® for patients with diabetic macular edema

Oct 13, 2021

- *Regulatory decisions for BEOVU® (brolucizumab-dbll) in diabetic macular edema (DME) are expected in mid-2022 in the US and Europe*
- *DME is the leading cause of blindness in adults in developed countries; unmet needs in DME include improving fluid resolution and addressing the burden of frequent treatment schedules*[1-3]
- *The regulatory applications are based on year one data from the Phase III KESTREL and KITE trials investigating BEOVU 6 mg versus aflibercept 2 mg in DME patients*[4]
- *In KESTREL and KITE, BEOVU was non-inferior to aflibercept in change in BCVA from baseline and showed potential for fluid resolution in more DME patients with fewer injections*[4]
- *BEOVU demonstrated a favorable benefit-risk profile in KESTREL and KITE*[4]
- *The Japanese PMDA also accepted an application for BEOVU in DME*

**East Hanover, October 13, 2021** — Novartis today announced that the US Food and Drug Administration (FDA) has accepted the company's supplemental Biologics License Application (sBLA) and that the European Medicines Agency (EMA) has validated the type-II variation application for BEOVU® (brolucizumab-dbll) 6 mg for the treatment of diabetic macular edema (DME). Additionally, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) accepted an application for BEOVU in the treatment of DME. Regulatory decisions for BEOVU in DME are expected in mid-2022 for the US and Europe.

If approved, DME would be the second indication for BEOVU following its approval for wet age-related macular degeneration in October 2019 (FDA) and February 2020 (European Commission)[5,6]. DME is the leading cause of blindness in adults in developed countries, affecting 12% of people with type 1 diabetes and 28% of those with type 2 diabetes[1]. Consistently high blood sugar levels associated with diabetes can damage small blood vessels in the eye, causing them to leak fluid[1]. Unmet needs in DME include improving fluid resolution and addressing the burden of frequent treatment schedules[1-3].

"People living with diabetes often need to manage multiple comorbidities related to diabetes and there is a significant need to provide better disease management. If approved, BEOVU has the potential to provide better fluid resolution and fewer injections during the loading phase and throughout maintenance treatment," said Jill Hopkins, SVP and Global Development Unit Head, Ophthalmology, Novartis Pharmaceuticals. "We look forward to bringing this potential new treatment option that may help to address unmet needs in the DME patient population."

The regulatory applications are based on year one data from the Phase III, randomized, double-masked KESTREL and KITE* studies, which met their primary endpoint of non-inferiority in change in best corrected visual acuity (BCVA) from baseline versus aflibercept at year one[4]. In KESTREL and KITE, following the loading phase, over half of patients in the BEOVU 6 mg arm remained on a 12-week dosing interval through year one[4]. Fewer eyes treated with BEOVU had intraretinal and/or subretinal fluid (IRF/SRF) at week 32 and week 52 versus eyes treated with aflibercept[4]. The KESTREL and KITE trials are the first pivotal trials to assess an anti-VEGF treatment on six-week dosing intervals in the loading phase, suggesting BEOVU may offer fewer injections from the start of treatment[4].

Overall, BEOVU demonstrated a favorable benefit-risk profile in KESTREL and KITE[4]. The most common ocular and non-ocular adverse events (≥5%) in KESTREL and KITE were conjunctival hemorrhage, nasopharyngitis and hypertension[4]. IOI rates in KESTREL were 4.7% for brolucizumab 3 mg (including 1.6% retinal vasculitis), 3.7% for BEOVU 6 mg (including 0.5% retinal vasculitis), and 0.5% for aflibercept 2 mg[4]. IOI rates in KITE were equivalent (1.7%) between the BEOVU 6 mg and aflibercept 2 mg arms with no retinal vasculitis reported[4]. Retinal vascular occlusion was reported in KESTREL for brolucizumab 3 mg (1.1%) and 6 mg (0.5%), and in KITE for brolucizumab and aflibercept (0.6% each)[4]. The majority of these events were manageable and resolved with or without treatment[4].

Novartis remains committed to bringing BEOVU to the patients who may benefit most from this important medicine.

**About the KESTREL and KITE clinical trials**

KESTREL and KITE are global, randomized, double-masked, Phase III, two-year studies comparing the safety and efficacy of BEOVU and aflibercept in the treatment of DME[4,7,8].

KESTREL and KITE involved 926 patients in 36 countries[7,8]. In the loading phase of both trials, patients in the BEOVU arms were treated every six weeks for a total of five doses; patients in the aflibercept arms were treated every four weeks for a total of five doses, in line with its label at the start of the studies[7,8]. Following the loading phase, patients in the BEOVU arms were subsequently treated every 12 weeks, with those demonstrating disease activity moved to dosing every eight weeks for the remainder of the study[7,8].

At week 72 of KITE, BEOVU patients dosed every 12 weeks could be extended to dosing every 16 weeks, and patients dosed every eight weeks could be extended to every 12 weeks[8]. As in year one, those demonstrating disease activity were moved to dosing every eight weeks for the remainder of the study[8]. Through the entirety of both two-year trials, patients in the aflibercept arms were treated every eight weeks[7,8].

**About diabetic macular edema (DME)**

DME is a common microvascular complication in patients with diabetes that may have a debilitating impact on visual acuity, eventually leading to blindness[1]. DME is the leading cause of blindness in adults in developed countries, affecting 12% of patients with type 1 diabetes and 28% of those with type 2 diabetes[1].

Consistently high blood sugar levels associated with diabetes can damage small blood vessels in the eye, causing them to leak fluid[1]. This damage leads to an excess of vascular endothelial growth factor (VEGF)[1,9]. VEGF is a protein that stimulates the growth of blood vessels[1,9]. At elevated levels in DME, VEGF stimulates the growth of abnormal, leaky blood vessels[1,9]. The resulting accumulation of fluid (known as edema) in the macula can lead to vision loss[1,9]. The macula is the area of the retina responsible for sharp, central vision[9]. Early symptoms of DME include blurry or wavy central vision and distorted color perception, although the disease can also progress without symptoms at early stages[9,10].

**About BEOVU (brolucizumab-dbll)**

BEOVU (brolucizumab, also known as RTH258) 6 mg is approved for the treatment of wet age-related macular degeneration (AMD) in more than 70 countries, including in the US, EU, UK, Japan, Canada and Australia[5,6,11-13]. Additional trials, which study the effects of brolucizumab in patients with wet AMD, diabetic macular edema (DME), and proliferative diabetic retinopathy (PDR), are currently ongoing.

**INDICATIONS AND USAGE**

BEOVU® (brolucizumab-dbll) injection is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

BEOVU is contraindicated in patients with ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

**WARNINGS AND PRECAUTIONS**

**Endophthalmitis and Retinal Detachment**

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

**Retinal Vasculitis and/or Retinal Vascular Occlusion**

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of BEOVU. Patients should be instructed to report any change in vision without delay.

**Increase in Intraocular Pressure**

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

**Thromboembolic Events**

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

**ADVERSE REACTIONS**

Serious adverse reactions including endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion, increases in intraocular pressure, and arterial thromboembolic events have occurred following intravitreal injections with BEOVU.

The most common adverse events (≥5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain.

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU. The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

Please see full Prescribing Information.

**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.

**Kite Pharma, Inc. is neither a sponsor of nor associated with Novartis' KITE trial.*

**About Novartis**

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of 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 employs nearly 15,500 people in the United States. For more information, please visit https://www.novartis.us.

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**Novartis Media Relations**

E-mail: media.relations@novartis.com

**Amy Wolf**
Novartis External Communications
+41 79 57607 23
amy.wolf@novartis.com

**Vicki Crafton**
Novartis US Division Communications
+1 201 213 6338
vicki.crafton@novartis.com

**Julie Masow**
Head, US External Engagement
+1 862 579 8456

julie.masow@novartis.com

**Novartis Investor Relations**

E-mail: investor.relations@novartis.com

**North America**
**Sloan Simpson**
+1 862 778 5052

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