White Paper

Biosimilars for Retinal Vascular Diseases:

Considerations for clinical trials of anti-VEGF biosimilars in a crowded landscape

CHARU MANAKTALA, MD, head, Biosimilars Center of Excellence
KATHLEEN GORDON, MD, senior medical director, co-chair, Ophthalmology Center of Excellence
AMY DEL MEDICO, therapeutic strategy director, co-chair, Ophthalmology Center of Excellence

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Executive summary

Treatment for retinal vascular diseases – which are a major cause of visual impairment and blindness – has greatly improved since the approval of anti-VEGF therapies, with sight restoration now a standard treatment goal. However, these therapies are expensive and access to treatment is variable. With patent expiries for Lucentis® (ranibizumab) in 2020 and Eylea® (aflibercept) in 2023, the development landscape for biosimilars for these originator biologics, with potential to reduce prices and expand access, is becoming increasingly congested, with close to 20 candidate biosimilars in development. In this White Paper, IQVIA experts share their insights on how the biosimilar development process can be optimized despite the high level of competition for clinical trial participants and sites.

Introduction

Multiple biosimilars across various therapeutic areas have been approved and launched in the Europe and US markets since 2006 and 2015, respectively. The introduction of biosimilar competition has resulted in significant savings in European markets, though the impact has varied across different products and markets. Biosimilars comprised 9% of the total biologics market in Europe in 2020 with a CAGR of 58%. In the US, the savings from biosimilars were slow to materialize in the initial years. However, the recent biosimilar launches for oncology biologics are projected to capture as much as 60% of the market by end of second year of launch.[1,2]

Against this background, the upcoming patent expiries for the anti-vascular endothelial growth factor (VEGF) therapies Lucentis® (ranibizumab) in 2020 and Eylea® (aflibercept) in 2023 hold promise for expanded access to these extremely useful therapies through the introduction of biosimilars.[3,4] At this time, multiple biosimilars of Lucentis and Eylea are in development.[3,4]

Vascular diseases of the retina remain a significant cause of visual impairment and acquired blindness.[5] The number of patients with diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal vein occlusion, is steadily increasing in the United States, according to a recent study.[6,7] The number of Americans with DR is projected to increase from 7.7 million in 2010 to 14.6 million in 2050;[8] worldwide, DR affects 126.6 million people.[9] The number of Americans with AMD is forecast to rise from 2.07 million in 2010 to 5.44 million in 2050;[10] and AMD affects 170 million individuals worldwide.[11] Some 1.1 million Americans have retinal vein occlusion;[12] and worldwide, the total affected population is estimated at 16 million.[13]

Lucentis and Eylea are now frequently used for several retinal conditions, including neovascular AMD (nAMD), a more severe form of AMD characterised by new and abnormal blood vessel growth.[14,15] These therapies target vascular endothelial growth factor (VEGF), which stimulates the production of blood vessels[16]

and has been implicated in retinal vascular diseases.[17] The recent (2019) approval of Beovu® (brolucizumab) was expected to benefit patients with a less frequent 8 to 12 week treatment administration. However, emerging safety concerns have impacted the use of Beovu.[18] In addition to these, bevacizumab (Avastin® and its biosimilars) is another anti-VEGF that is used extensively for off-label treatment of retinal vascular diseases.[19]

These anti-VEGF therapies have changed the treatment paradigms for a host of retinal vascular diseases since U.S. Food and Drug Administration (FDA) approval of Lucentis in 2006[20] and Eylea in 2011.[21] Before these became available, patients' options were limited to treatments such as laser therapy, which often leads to poorer vision following treatment.[22 23] With anti-VEGF agents, sight restoration has become the standard treatment goal.[24] However, these agents are expensive and access to treatment varies across geographies.

Considerations for the design of a clinical efficacy and safety trial

Development of biosimilars follows a sequential process of establishing analytical biosimilarity, followed by non-clinical (where needed) and clinical development. At each step, biosimilarity is established based on studies that compare the proposed biosimilar with its reference biologic.

Establishing analytical biosimilarity, based on a comprehensive battery of physicochemical assays and in vitro assays of biological activity, forms a firm foundation for development of biosimilars that allows for an abbreviated development process compared with that required for the innovator biologic.[25] For biosimilars of most monoclonal antibody proteins, the clinical program comprises a pharmacokinetic (PK) endpoint bioequivalence trial (phase I) in healthy volunteers followed by an efficacy and safety (including immunogenicity) trial in a selected sensitive indication.

In this context, biosimilars of Lucentis and Eylea present a unique challenge. As these products are administered directly into the eye via intravitreal injection, resulting in very limited systemic exposure, a conventional PK endpoint bioequivalence trial measuring systemic PK would not be relevant.[26] In addition, a trial with administration as per labelled conditions (intravitreal injection) with evaluation of PK exposure in the vitreous would not be ethical, safe or feasible.

In view of the above unique challenges, regulators have accepted clinical evaluation of these biosimilars in a single trial designed to evaluate efficacy, safety and immunogenicity in a selected indication.

As many of these studies are first-in-human (FIH) for the proposed biosimilar, special attention must be paid to having in place very robust analytical data that demonstrates a high degree of similarity between the proposed biosimilar and its reference product; and include an early masked review of the safety data from the study.

Both Lucentis and Eylea are approved for several retinal conditions that include neovascular (wet) age related macular degeneration (nAMD), diabetic macular edema (DME), diabetic retinopathy (DR) in patients with DME, macular edema following retinal vein occlusion (RVO) and myopic choroidal neovascularization (myopic CNV).[20, 21] It is important for companies to select a single indication that is sensitive enough for the evaluation of clinical biosimilarity and can also support extrapolation of the safety and efficacy conclusion to the entire spectrum of indications approved for the reference biologic. nAMD and DME both qualify as appropriate indications for this purpose. Given that the efficacy is exerted through the same receptors/mechanism of action and the safety profiles are comparable across indications, either of these indications could be studied.

Key considerations for the design of a phase III trial of an Eylea or Lucentis biosimilar include the need for:

- A primary efficacy endpoint of mean change in the best corrected visual acuity (BCVA) from baseline in

the trial eye, assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) charts,[27] which is well accepted.

- A primary efficacy endpoint assessment at eight or 12 weeks, which is generally well accepted.
- Alternative endpoints such as the change in central subfield thickness (CST) have the advantage of an early readout of the primary efficacy endpoint (as early as four weeks) but are not universally accepted.
- The equivalence margin for calculation of sample size needs to be justified on statistical grounds as well as on a difference that would be considered clinically insignificant and therefore acceptable; generally, a difference of three or four letters in the mean change in BCVA is accepted.
- Total duration of patient participation in the trial needs to be at least one year.
- Limited systemic PK sampling is needed in a subset of patients to evaluate safety rather than to establish bioequivalence.
- Anti-drug antibody (ADA) sampling is needed, with an ADA testing strategy following the standard tiered approach and all confirmed samples being evaluated for neutralization potential.
- Only one eye can be included as the study eye, and this is often required to be treatment naïve.
- For patients who meet eligibility criteria in both eyes, the eye with the worse visual acuity will be selected as the trial eye; if both eyes have equal visual acuity, the eye with better visual prognosis will be selected at the Investigator's discretion.
- In some cases, there may be requirement to include a certain proportion of patients with light-colored irises.
- There is a need to define the permissible treatment options for the fellow eye which should be consistent with standard of care.
- Standardization of various assessments including the BCVA (assessed using EDTRS charts) and optical coherence tomography (OCT) is crucial.

MEASURING THE PRIMARY EFFICACY ENDPOINT

In these clinical trials, BCVA is the primary efficacy endpoint, as measured using ETDRS charts (of which there are a variety of formats such as Roman alphabet, European Wide, number, Landolt-C or Tumbling E). A change in ETDRS letters read from baseline to week eight is an accepted endpoint and hence the use of standardized charts in the form of ETDRS is imperative to the integrity of the data. The type of ETDRS chart used should reflect the alphabet that patients are familiar with and should be consistent within a country. The European Wide ETDRS chart is a good alternative for Europe since it uses optotypes common to the Roman, Cyrillic and Greek alphabets. Landolt C, Tumbling E and Number Charts are more commonly used in the Asia Pacific region. While repeatability and reliability are a concern when using different charts in the same trial, there is documented correlation between optotypes, particularly amongst patients with retinal disease.

In addition, biostatistical considerations support the use of these charts. An alternative approach to the use of multiple charts within a single study is to provide patients who are unable to recognise the optotypes with a large print, handheld card, enabling them to point at the letters they can read on the ETDRS chart. While this approach has been used in past clinical trials, drawbacks may include:

An increase in the time taken for the assessment, and the potential to result in patient fatigue, which could cause variability.

- The alphabet sheet has large letters so the impact of presbyopia should be limited, yet the fact that all 26 letters of the alphabet are shown can cause confusion. Since the letters are not familiar to the patient, the wrong one might be selected e.g. a Japanese patient might have difficulty distinguishing between European characters.

- The lack of published articles to support the use of these cards; only anecdotal evidence is available to evaluate variability.

These are important considerations given the current competitive landscape, which is pushing trials into non-traditional regions where the Roman alphabet is less likely to be familiar to participants.

All examination rooms and visual acuity examiners should be certified by a specialized vendor prior to study start-up and recertified after 12 months or retrained earlier should this be necessary. This helps ensure consistency in BCVA testing and integrity of the data collected for the endpoint.

Regulatory considerations

Regulatory expectations for biosimilars development are well defined and clearly presented, particularly in the EU and USA.[28 29] As described above, in general, regulators expect biosimilar clinical programs to comprise a phase I PK trial and phase III efficacy and safety trial.

However, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has laid out a different approach in its recently released guidance document: Guidance on the licensing of biosimilar products,[30] which states that: "Although each biosimilar development needs to be evaluated on a case by case basis, it is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach. Therefore, a well-argued justification for the absence of an efficacy trial should be appended to CTD Module 1 of the submitted application."

Even with the MHRA guidance, biosimilars development for ophthalmology is expected to be different, because conduct of a phase I trial in healthy volunteers is neither feasible nor ethical in these indications. As such, a phase III trial should be sufficient to support a marketing application for this type of biosimilar. This approach is recognised by EMA and US FDA, as demonstrated by the agencies' acceptance by both agencies of the marketing authorisation application for SB11, Samsung's proposed biosimilar to Lucentis [31 32 33] This biosimilar application is supported by a phase III trial that compares SB11 (proposed ranibizumab biosimilar) to Lucentis in patients with nAMD.[34] With regulatory expectations for biosimilar clinical development being clearly established, the biggest challenge that sponsors face is the generation of data that unequivocally demonstrate similarity of the proposed biosimilar to the reference product.

Operational considerations: location of trial conduct

There are several considerations for developing a country and site strategy for a biosimilar clinical trial involving the retina. Availability of reference product has a significant impact on both participant and investigator interest in such trials. Broadly speaking, access to anti-VEGF therapies is good in Western Europe and North America, with varying access in Asia Pacific and more limited access in Eastern Europe and Latin America. For this reason – and in part due to the historically long start-up times in Latin America – Eastern Europe is currently the preferred region for the conduct of these trials. However, this has resulted in an increasingly competitive landscape in Eastern Europe, limiting site availability and hence recruitment potential.

Regions with high levels of experience with trials involving the retina, but better access to reference product, such as Western Europe or North America, usually see a significantly lower overall investigator and participant interest and recruitment rates. In cases where the sponsor wishes to recruit a proportion of participants from such regions, it becomes important to identify specific sites with a higher insurance co-pay burden, where applicable, as patients and investigators in such sites may still have a high degree of interest in participating in biosimilar trials.

Start-up times in many Latin American countries are now decreasing significantly, and the availability of

retina specialists and treatment naïve participants make this a region worth considering, given the current competitive landscape.

Some trials require a proportion of participants to have light coloured irises, although there is not a consistent message from regulatory authorities on this point. This requirement can be managed by the inclusion of European countries where light coloured irises are prevalent in the population and the development of operational tools which track and limit the proportion of participants with dark coloured irises that are recruited. However, many countries where light coloured irises are more prevalent also have good access to standard of care. Planning should take account of potentially limited interest and reduced recruitment rates for patients with light coloured irises in these countries.

Operational considerations: competitive landscape

The development landscape for aflibercept and ranibizumab biosimilars is increasingly congested, with close to 20 products currently in phase III trials. Marketing authorization application for one bevacizumab intravitreal formulation has been submitted to EMA, and Samsung Bioepis' application for a Lucentis biosimilar has received positive opinion from the CHMP and is under review with the US FDA (Chart 1).

Chart 1: Summary of Current Landscape for Phase III non-innovative anti-VEGF Agents

ANTI-VEGF AGENT	SPONSOR COMPANIES
Lucentis (ranibizumab)	BioCND/QiLu, Gene Techno, Senju, Lupin, Chong Kun Dang, Reliance Life Sciences, Xbrane, Formycon
Eylea (aflibercept)	Samsung Bioepis/Biogen, Amgen, Alteogen/Kissei, Bioeq/Formycon, Momenta/Mylan, Sam Chun Dang Pharm. Co., Celltrion, Luye Pharma
Avastin (bevacizumab)	Laboratorio Elea, Outlook Therapeutics, Shanghai Henlius Biotech

These trials are often focused in Eastern Europe, because the region has more limited access to standard of care and hence higher levels of interest amongst participants and investigators. As a result, countries in this region are generally experienced in biosimilars research, but sites may be at capacity in terms of the number of clinical trials they can support. For this reason, companies developing biosimilars for retinal disease have several options: consider other regions or countries with less competition to conduct their trial; accept a lower-than-historical recruitment rate and site availability in Eastern Europe, meaning that more countries and sites would be required to meet already challenging recruitment timelines; or develop clinical trial naïve sites. Each approach has benefits and risks. The ongoing development of novel therapies also has an impact, with many sites preferring to be involved in these types of trials if given the opportunity.

Operational considerations: limiting barriers to site participation

Clearly, barriers to site participation should be addressed where possible. One important area is the selection of the central image reading vendor. Vendors accept varying optical coherence tomography (OCT) machine makes and models, and hence choosing a vendor with the broadest list of acceptable models allows the sponsor to work with the largest possible number of sites for their clinical trial.

Another consideration is the availability of tools required for safety and efficacy assessments. For example, in Russia and Ukraine, fluorescein dye cannot be sourced locally and has to be imported. This requires early planning to avoid delays during trial start-up. Goldmann applanation tonometers may also not be commonly used in clinical practice in some countries, and so may need to be provided if the protocol requires use of this instrument to measure ocular pressure. Alternatively, flexibility may be needed with regard to the instrument used to measure intraocular pressure, to enable a more familiar standard of care to be used.

Investigators will prioritize studies that offer competitive reimbursement, the ability to treat the fellow eye if necessary, and trial protocols that are easily interpreted and conducted.

Conclusion

With recent and upcoming patent expiries, the landscape for anti-VEGF biosimilars for retinal vascular diseases is more crowded than ever. Against this highly competitive backdrop, it is critical for biosimilar sponsors to make well-informed choices in several key areas:

- **Optimizing study design:** Regulators accept clinical evaluation of biosimilars for ranibizumab and aflibercept based on a single phase III trial that evaluates efficacy, safety and immunogenicity in a selected indication. This indication must be sufficiently sensitive to allow evaluation of clinical biosimilarity and to support extrapolation of the safety and efficacy findings to the reference product's full range of approved indications. Both nAMD and DME qualify as appropriate indications for this purpose.
- **Careful selection of sites and geographies:** Access to the reference biologic – which is generally good in Western Europe and North America, variable in Asia Pacific, and more limited in Eastern Europe and Latin America – has a major impact on participant and investigator interest in biosimilar trials. If sponsors wish to recruit in Western Europe or North America, it is vital to identify specific sites with higher insurance co-pay burdens, where there may still be a good level of interest in biosimilar trials. While Eastern Europe has historically been a preferred location, the landscape is now highly competitive. This leaves sponsors with a choice between accepting lower site and patient availability in Eastern Europe, focusing on geographies with less competition such as Latin America, or developing new, clinical trial naïve sites.
- **Overcoming barriers to participation:** Technology availability can be a barrier to site participation. It can be helpful for sponsors to select a central image reading vendor with the widest possible list of optical coherence tomography machine makes and models, thus leaving open the option to work with the largest possible number of sites. Availability of tools for safety and efficacy assessments is another factor, with early planning required to source fluorescein dye or Goldmann applanation tonometers in some geographies. Flexibility on the instrument used for intraocular pressure measurement can also help overcome barriers. Finally, investigators in all geographies may be more likely to participate in biosimilar studies for sponsors that offer competitive rates of reimbursement and a protocol that is straightforward to interpret and conduct and enables treatment of the fellow eye if necessary.

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About the authors

CHARU MANAKTALA, MD
head, Biosimilars Center of Excellence, IQVIA

With more than 25 years of healthcare and pharmaceutical industry experience, Charu has expertise across clinical development and post authorization lifecycle management. She has experience with clinical development of multiple biosimilars across different therapeutic areas and advises on global and/or region specific clinical and regulatory strategies for the development of biosimilars.

She holds a MD degree in pediatrics from the University of Delhi, India.

KATHLEEN GORDON, MD.
senior medical director
co-chair, Ophthalmology Center of Excellence, IQVIA

Kitty completed her medical degree and ophthalmology residency training at Cornell University Medical College and received fellowship training in ocular oncology at the University of California in San Francisco. She practiced clinical ophthalmology for 23 years during which time she was co-investigator for a variety of clinical trials, authored multiple publications, and has been an invited speaker at the state and national level.

She joined IQVIA's Immunology Internal Medicine Team three years ago as Medical Strategy Lead and as Co-Chair of the Ophthalmology Centre of Excellence.

AMY DEL MEDICO
therapeutic strategy director
co-chair, Ophthalmology Center of Excellence, IQVIA

Amy has 17 years experience in the pharmaceutical industry of which 15 have been with IQVIA. During this time Amy has been involved in project management, start-up, feasibility and strategic roles, mostly in phase I to III studies.

Amy currently co-chairs IQVIA's Ophthalmology Centre of Excellence where she specializes in strategy planning, operational delivery, account management and business development for ophthalmology customers and clinical trials. In this role she consults globally with small biopharma companies, larger pharma and key opinion leaders.

In previous roles at IQVIA Amy has been responsible for driving start-up and patient recruitment at partner sites and coordinating global, cross-functional teams to initiate, manage and review country level feasibility assessments for multi-country studies.

Prior to IQVIA, Amy worked in a central laboratory where she was responsible for the design, supply and management of central laboratory services for clinical trials.

CONTACT US
4820 Emperor Boulevard
Durham, NC 27703
United States

Omega, Embassy Tech Square
Marathahalli - Sarjapur Outer Ring Road
Kadubeesanahalli
Bangalore - 560 103
India
Charu.Manaktala@quintiles.com
iqvia.com