Use of Marketed Drugs in Retinal Disease Studies

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Background on Lucentis and Eylea

Lucentis (ranibizumab injection), first approved in the U.S. in 2006, is manufactured and distributed by Genentech in the United States; outside of North America, Lucentis is distributed by Novartis. As described in its prescribing information, Lucentis is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intracocular use. It binds and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Lucentis is available as a single-use prefilled syringe or a single-use 2-mL vial to deliver 0.05 mL of ranibizumab solution (concentrations vary) via an intravitreal injection directly into the eye. Lucentis must be refrigerated at 2º–8ºC and cannot be frozen. Patients may receive injections via various treatment regimens as frequently as monthly.

Eylea (aflibercept) was co-developed by Regeneron and Bayer and gained its first U.S. approval in 2011. It’s prescribing information lists that it is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. It binds VEGF-A and PlGF, blocking activities of both growth factors. The Regeneron version marketed in North America is a single-use glass vial to deliver 0.5 mL of 40 mg/mL solution (2 mg) via intravitreal injection; outside of North America, Bayer’s Eylea is a single-use syringe. Eylea must be refrigerated at 2º–8ºC and cannot be frozen. Dosing frequency for Eylea is disease- and timepoint-dependent, but patients may receive injections as frequently as once per month.

Both drugs are readily available and actively marketed in many countries. In addition to the treatment burden for patients using the anti-VEGF therapies—regular, often monthly, intrawcular infections for life—each costs approximately $1,000–$2,000 per dose for the drug alone.}

Background on Lucentis and Eylea (continued)

Price varies widely by location and retail source, but annualized costs are generally north of $8,000 per patient. Lucentis and Eylea are considered safe and effective for the majority of target patients, but the high cost means reimbursement is variable dependent upon regional health economics policies, specific formularies and local insurance practices. Even in countries where these drugs are readily available, treatment can be cost-prohibitive for many individual sufferers, leading to continued vision loss and eventually blindness.

Lucentis and Eylea have had impressive success toward improving vision and quality of life for patients suffering from common retinal disorders; the two drugs combined for $8 billion in global sales during 2016. With an aging global population, drugs for treating age-related retina diseases are a big business; gaining even a fraction of this market has potential blockbuster implications.

For all these supply- and demand-side reasons, and despite the excellent health outcomes from both Lucentis and Eylea, there remains strong interest for development of less burdensome and/or lower cost alternatives. There continues to be a healthy pipeline of novel treatments in development which may be administered in combination with either Lucentis or Eylea, be delivered via an alternative modality (e.g., eye drop or oral), or provide sustained vision improvement via fewer applications. In all of these cases, clinical trials for retina disease require that Lucentis or Eylea be available as a comparator or adjunct therapy for research purposes.

Case Study 1

A U.S. biotech required accelerated startup to achieve a key “first patient in” milestone that had been promised publicly. The central supply was not going to be ready to meet the critical deadline. The study team was able to fast-track a few select sites and negotiated a direct reimbursement rate for Eylea into each of their grants. These sites activated early and enrolled their first patients using Eylea from their clinic pharmacy, which was reimbursed by the sponsor during a routine site payment. Subsequent enrollment at all sites was then facilitated by the central supply when it became available a few weeks later.

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**Case Study 2**

A biosimilar developer negotiated with the FDA to gain agreement on a global Phase III trial using U.S.-sourced Lucentis. The sponsor was interested to conduct the study primarily in Asia and Eastern Europe, but with a U.S. component to support future regulatory submissions in all regions. Unfortunately, FDA’s expectations are not required to correlate with commercial realities. In this case, Genentech strictly prohibits export of Lucentis from the U.S. for any purposes, including clinical research. Thus, the sponsor was forced to source Lucentis for its global trial from the secondary market in the U.S. at a 35 percent premium, an incremental cost of $3 million for the drug alone. And this came with batch variability, lower assurance of supply, higher logistical complexity and increased administrative costs.

**Procurement Strategies for a Marketed Drug in Clinical Trials**

When Lucentis or Eylea is included in a research trial, it must be provided or paid for by the sponsor for the duration of the clinical protocol. There are basically three options for handling the marketed drug, regardless of the study design. These include:

1. The site may obtain a marketed drug from its local supply and seek reimbursement from the sponsor directly.
2. The marketed drug may be sourced by the sponsor from regional wholesalers for distribution to some or all sites. This may be managed within a specific country or across a region, e.g., the European Union.
3. The sponsor may negotiate with the manufacturer (directly or via a third-party drug supply specialist) to procure and distribute the marketed drug centrally.

Any one or a combination of these approaches may be used within a single study and there are considerations for the ideal sourcing model—cost, availability, logistics, cold-chain and risk management to name a few. Working directly with the manufacturer may provide more confidence in the supply, but can be difficult and requires added administrative efforts. Commercial interests of a manufacturer may create a conflict for their willingness to support potentially competing clinical research. Relying on sites to supply their own drug reduces control, but can allow for more flexibility. The table on page 5 demonstrates various considerations for each approach.
Comparator Handling for Biosimilar Trials

For biosimilar studies, the situation is even more complex. According to FDA guidance on the use of U.S.-licensed product for biosimilar research, “…analytical studies and at least one clinical PK study… intended to support a demonstration of biosimilarity… must include an adequate demonstration of biosimilarity… must include an adequate demonstration of biosimilarity.” Thus, even for studies conducted outside U.S., the FDA’s requirement is to use U.S. originator, unless further bioequivalence is confirmed between the U.S. and ex-U.S. products. It is possible to create an analytical and PK bridge of U.S.-to-Europe originator, but this requires incorporation of 3-arm Phase I portion into a Phase III study, or a separate Phase I study altogether.

To work around this, some sponsors are choosing the easiest path: to use U.S.-sourced originator globally, which is generally acceptable to EMA. But this has other material implications for the cost of research.

U.S.-sourced Lucentis or Eylea is approximately twice the cost as that from Europe. The added cost of using a U.S.-only drug on a large study or one running many months, of which both factors are common in retinal disease biosimilar studies, can run into the millions or even tens-of-millions of dollars over the course of any trial.

With this, it is essential for sponsors to consider all the cost and time implications of various approaches. There is potential cost savings from using a European-sourced originator, but it has to be ensured that the drug’s quantity is available when trying to source locally or via wholesalers in smaller countries. It is also necessary to understand the acceptability by regulators to gain subsequent approvals (see Case Study 2).

Masking for Marketed Drugs

For most double-masked studies (any use of “blinded,” “blinding” terminology is generally avoided for ophthalmology projects), all forms of the investigational agent and/or its placebo are prepared with identical packaging and labeling in order to prevent anyone who may handle or even simply view the drug from knowing its contents. For studies involving an already marketed drug, even with best efforts, it is nearly impossible to manufacture and package an investigational agent that closely matches vial and bottle shape, stopper material, cap color, container size and other attributes of an already marketed product. Further, the manufacturer of a marketed product may occasionally alter one or more elements of the container packaging for various reasons. For Lucentis and Eylea, this is further complicated because both products are also available as pre-filled syringes.

Masking for retinal disease studies is complex and needs careful consideration in order to maintain subject safety and data integrity. This is most often achieved in two ways:

1. Every attempt may be made to simulate the container and packaging of the marketed product. Minimally, this will mean that the boxes, cartons and all labeling are identical between the comparator drug (e.g., Lucentis or Eylea) and the investigational agent, even if the vial or syringe itself cannot be matched. Still, direct handling of the individual units will most likely create an unmasking situation, so these steps are just precautionary and cannot alone create a fully masked situation.

2. All direct handling of the drug may be managed by an unmasked team. This includes those who prepare and ship the Lucentis or Eylea for clinical trials use, site representatives who handle and record individual usage, investigators performing injections and clinical monitors who perform investigational product accountability.

During site selection for a retinal study involving Lucentis or Eylea, sites must demonstrate that they have sufficient staff to handle both the masked and unmasked roles, physical facilities to securely store the drug and prevent access to masked personnel, and standard operating procedures (SOPs) that ensure proper drug management. The clinical teams need to include unmasked monitors to perform drug accountability separately from those doing source document review. The entire process requires careful logistics planning to establish firewalls for communications and documentation, as well as an escalation pathway in the event of a problem.

Conclusions and Tips from the Field

It is critical that clinical trial planning includes a strategy for the handling of a marketed drug. For a study involving Lucentis or Eylea, the marketed drug alone can represent a third of the total trial budget. Particularly for multinational studies, there are significant implications to the ongoing logistics throughout the duration of the protocol. Working with a service provider who understands the pros and cons of various sourcing strategies and masking procedures can be important considerations to control costs and de-risk a complex component of the trial execution.

To close, consider some useful tips from the field:

No single sourcing strategy is “right” or “wrong.” There are reasons to consider each, and for any single trial, multiple approaches may be appropriate. As an example, Case Study 1 demonstrates that site-level reimbursement can help accelerate study startup, and may also provide better control of early study costs. Site reimbursement early in a trial can also help align the comparator distribution with actual enrollment; you won’t be stuck with unused marketed product at sites that aren’t enrolling.

Collection of drug documentation is easier when dealing directly with the manufacturer rather than a wholesaler (and nearly impossible to obtain from a site). The manufacturer can routine provide full documentation reflecting the chain of custody from the source to the designated point of delivery, along with full product documentation including certificates of analysis, certificates of conformity, package inserts, GMP compliance, equivalency data, material safety data sheets (MSDS), and TSE/BSE documentation. The amount and type of documentation varies from country to country, but all should be gathered to minimize regulatory delays.

Labeling requirements for a multinational study are variable and complex. A centralized sourcing strategy can provide confidence that label requirements, including all translations for each required language, are applied accurately. There needs to be close attention to version control for all labeling documentation.

Be certain to verify that sites have adequate facilities and refrigeration equipment during the site identification and qualification stages. Also, for studies with special masking procedures, evaluate that sites have sufficient staff and documented masking procedures for receipt, handling and accountability of both the investigational and marketed products. You don’t want to learn that a site doesn’t have an appropriately monitored refrigerator or unmasked pharmacist after product has already been sent.

Whoever is monitoring the trial also requires specialized masking procedures. It is recommended anyone who directly views or handles the drug be unmasked with firewalls in place to ensure information is not shared with the masked team. This even includes those handling invoices that will indicate the quantity and dates of comparator drug usage.

Initial planning for supply utilization requires detailed patient recruitment projections at the country and site levels. These forecasts should be routinely reviewed at least quarterly with the supplier/packager to ensure that adequate drug is available and appropriately distributed for the forthcoming 3-6 months as recruitment advances.
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