# Match This

Due to considerable market growth, biosimilar clinical trials are rising in popularity. One key example relates to rituximab, and the development of its biosimilars is currently leading the way in clinical research

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The global biologics market is worth $190 million, with the US being the largest market for biologics and biosimilars. The EU is also an important market, with 20 biosimilars currently approved and in use. The 'Global and USA Biosimilar Market Analysis to 2021' report, published in 2015, predicts that biosimilars will account for 4-10% of the total US biologics market by 2020 (1). Rituximab (Rituxan®/MabThera®) is currently one of the top five biologics targeted by biosimilar developers (2).

Completion of Phase 3 trials is one of the main requirements in biosimilar development and therefore has a major impact on cost and time to market. This article reviews the Phase 3 trial environment and trends in key parameters for rituximab biosimilar clinical trials; it also considers non-originator biological versions of rituximab that are available in some countries. These differ from biosimilars in that they do not necessarily undergo the same rigorous testing and demonstration of equivalent efficacy and safety required by regulatory authorities such as the FDA and EMA.

## Market Players

Global sales of rituximab were $7.4 billion in 2014 (compound annual growth rate 1% from 2012 to 2014), with 79% of sales in the US and the European Union Five (EU5) (France, Germany, Italy, Spain and the UK). The patent expired in the EU in 2013 and Japan in 2014, and will expire in the US in September 2016.

Its high sales potential and patent expiry make rituximab a key target for biosimilar manufacturers, with approximately 30 biosimilars under development in 2013 (3). To date, Celltrion is the only company that has submitted a marketing authorisation application for a rituximab biosimilar in the EU (on 10 November 2015) and none have yet been approved.

The first movers in rituximab biosimilar development can be divided into three groups (4):

### Generic Pharmaceutical Companies

Organisations such as Sandoz or Teva were among the first to embark on the development of a rituximab biosimilar. A joint

| | Companies | Disease | Phase | Number of patients | Endpoints |
|---|---|---|---|---|---|
| Group 1 | Sandoz | RA | 1/2 | 164 | E, PD, PK, S |
| | | FL | 3 | 618 | E, S |
| | Teva | RA | 3 | 544 | E, S |
| Group 2 | Pfizer | RA | 1/2 | 210 | PK, PD, E, S, I |
| | | RA | 3 | 157 | E, S |
| | | FL | 3 | 394 | E, S |
| | Boehringer Ingelheim | RA | 3 | 306 | E, PK |
| | Merck & Co | RA | 1 | 180 | PK, S |
| | | NHL | 1 | 22 | PK, S, E |
| Group 3 | Samsung Bioepis | RA | 1/3 | 500 | PK, E, PD, S, I |
| | Celltrion | DLBCL | 1 | 10 | S |
| | | RA | 1 | 147 | PK |
| | | RA | 1/3 | 300 | PK, E, S |
| | | FL | 1/3 | 134 | PK, E, S, I |
| | | FL | 3 | 174 | E, S |
| | Mabion SA | RA | 3 | 863 | E, S, I |
| | | DLBCL | 1 | 140 | PK |
| | Biocad | RA | 3 | 160 | E, S |
| | mAbxience SA | FL | 3 | 250 | E, S |

Table 1: Rituximab biosimilar clinical trials (DLBCL: diffuse large B-cell lymphoma; E: efficacy; FL: follicular lymphoma; I: immunogenicity; NA: not available; NHL: non-Hodgkin lymphoma; PD: pharmacodynamics; PK: pharmacokinetics; RA: rheumatoid arthritis; S: safety)

| Country | Number of sites | % of total sites | Number of studies | Total number of studies | Ratio of number to total number of studies | % Contribution |
|---|---|---|---|---|---|---|
| US | 131 | 21.48 | 1 | 3 | 0.33 | 7.16 |
| Brazil | 40 | 6.56 | 3 | 3 | 1.00 | 6.56 |
| Russia | 39 | 6.39 | 3 | 3 | 1.00 | 6.39 |
| India | 38 | 6.23 | 3 | 3 | 1.00 | 6.23 |
| Italy | 32 | 5.25 | 2 | 3 | 0.67 | 3.50 |
| Japan | 30 | 4.92 | 2 | 3 | 0.67 | 3.28 |
| Ukraine | 18 | 2.95 | 3 | 3 | 1.00 | 2.95 |
| South Africa | 18 | 2.95 | 3 | 3 | 1.00 | 2.95 |
| Argentina | 21 | 3.44 | 2 | 3 | 0.67 | 2.30 |
| Spain | 19 | 3.11 | 2 | 3 | 0.67 | 2.08 |
| Romania | 19 | 3.11 | 2 | 3 | 0.67 | 2.08 |
| Malaysia | 12 | 1.97 | 2 | 3 | 0.67 | 1.31 |
| Poland | 12 | 1.97 | 2 | 3 | 0.67 | 1.31 |
| France | 11 | 1.80 | 2 | 3 | 0.67 | 1.20 |
| UK | 10 | 1.64 | 2 | 3 | 0.67 | 1.09 |
| Turkey | 20 | 3.28 | 1 | 3 | 0.33 | 1.09 |
| Mean | 15.25 | 2.50 | 1.68 | 3.00 | 0.56 | 1.55 |
| SD | 21.32 | 3.49 | 0.69 | 0.00 | 0.23 | 1.91 |

Table 2: Percentage contribution of countries to rituximab biosimilar clinical trials in follicular lymphoma (only countries with a percentage contribution higher than 1% are listed)

venture between Teva and the Swiss company Lonza halted clinical trials of its rituximab biosimilar in 2012. Sandoz began its Phase 3 study in December 2011, and expects final data collection in December 2017.

**Multinational Organisations**

As an example, Boehringer Ingelheim, Merck & Co and Pfizer use innovative biologics to generate large revenues. They may regard biosimilars as an attractive market due to cost savings in the early phase of drug development and the desire to target a competitor's markets. Boehringer Ingelheim began developing a rituximab biosimilar, but halted its rheumatoid arthritis global trial in October 2015. Pfizer is also performing rituximab biosimilar clinical trials in rheumatoid arthritis and follicular lymphoma.

**Regional Businesses and New Entrants**

These include companies like Archigen, Celltrion and Samsung Bioepis. Celltrion, founded in 2002, started as a contract manufacturing organisation of biologics and expanded its portfolio to include biosimilars, targeting major markets by carrying out clinical trials. Celltrion is currently conducting three rituximab biosimilar studies: two Phase 1/3 trials in rheumatoid arthritis and follicular lymphoma and one Phase 3 trial in follicular lymphoma, mainly in India and the EU. Samsung Bioepis has halted its rituximab biosimilar programme, while Archigen – which is now a joint venture of Samsung Biologics and AstraZeneca US – resumed the development of its biosimilar in 2015.

Ten companies have conducted 19 biosimilar studies, involving 12 Phase 1/3 or 3 trials (five in follicular lymphoma and seven in rheumatoid arthritis: see Table 1, page 46), to demonstrate equivalent efficacy and safety to Rituxan/MabThera and to meet regulatory requirements. Patient numbers in the Phase 3 studies ranged from 157-863 per trial.

## Non-Originator Biologicals

In India, a non-originator biological version of rituximab – marketed as Reditux® by Dr Reddy's Laboratories since April 2007 – was the first generic version of rituximab available globally, while also being introduced in Bolivia, Chile and Peru. Other non-originator biological versions of rituximab include Kikuzubam®, Zytux™ and AcellBia™. Kikuzubam is marketed by the Mexican company Probiomed in Mexico, Bolivia, Chile and Peru, and was launched before biosimilar regulations were implemented in April 2012. Zytux has been marketed by Aryogen Biopharma in Iran since January 2014. AcellBia was launched in Russia by the Russian biotechnology business BIOCAD in April 2014, and with distribution partners, it is also available in Armenia, Cambodia, Indonesia, Kenya, Kyrgyzstan, Morocco, Myanmar, Pakistan, South Africa, Turkey, Ukraine, Uzbekistan and Vietnam. The availability of these non-originator biological versions may influence whether or not a company developing a rituximab biosimilar targets these countries as potential markets, and whether or not they may be suitable for conducting clinical trials.

## Follicular Lymphoma Studies

Potential markets and dynamics for biosimilar rituximab were examined using publicly available data for three of the four global rituximab biosimilar clinical trials in follicular lymphoma.

| Trial parameter | Follicular lymphoma (n=6) Median (range) | Rheumatoid arthritis (n=5) Median (range) |
|---|---|---|
| Study period (months)* | 33 (26-73) | 33 (26-44) |
| First patient in to last patient in (months) | 23 (14-49) | 20 (9-32) |
| Primary endpoint (months) | 6 (3-14) | 6 (6-35) |
| Secondary endpoint (months) | 12 (6-24) | 11 (6-35) |
| Number of patients | 322 (134-740) | 300 (157-863) |
| Number of countries | 26 (10-28) | 8 (4-16) |
| Number of sites | 145 (52-396) | 66 (40-85) |
| Enrolment rate (per site) | 4 (1-5) | 4 (2-17) |
| Enrolment rate (per month) | 12 (5-28) | 17 (8-27) |
| Enrolment rate (per site per month) | 0.09 (0.07-0.23) | 0.22 (0.20-0.52) |

*Study period = study completion date - study start date

Table 3: Rituximab biosimilar global Phase 3 clinical trial parameters

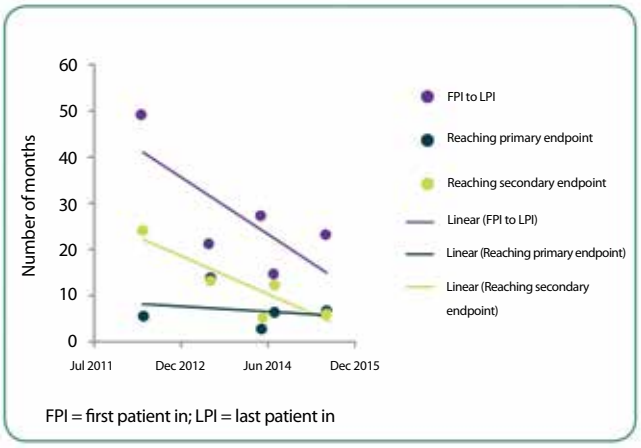
The three follicular lymphoma trials were carried out at 610 sites in 40 countries. There is insufficient data available for the clinical trials in rheumatoid arthritis. To analyse the participation of countries in clinical trials, the percentage contribution value was used (see Table 2, page 48). Markets were divided into major (US, EU5 and Japan), BRICS (Brazil, Russia, India, China and South Africa) and MIST (Mexico, Indonesia, South Korea and Turkey) markets. For example, the US has 131 of 610 global sites (21.48%) involved in one of the three studies, giving it a 7.16% contribution to follicular lymphoma biosimilar trials. Most of the countries in the major and BRICS markets have a higher than average contribution (1.55%). The top five countries are the US, Brazil, Russia, India and Italy. The total percentage contribution for the major markets, BRICS and MIST are 22.20%, 22.21%, and 1.7% respectively.

Eleven global Phase 3 clinical trials for a rituximab biosimilar (six in follicular lymphoma and five in rheumatoid arthritis) that are available on public websites were analysed to determine the mean values of specific parameters and their trends (see Table 3). The median study period for follicular lymphoma Phase 3 trials is 33 months, with a median number of 322 patients from 145 sites in 26 countries. The monthly enrolment rate per site is 0.09 subjects. Rheumatoid arthritis trials have the same median study period of 33 months, with a similar number of patients (n=300) but using a much lower median number of sites (n=66) and countries (n=8). With the lower number of sites, the monthly enrolment rate per site for rheumatoid arthritis trials (0.22 patients) is higher than that for follicular lymphoma studies.

A significant investment of time and cost is required to perform such Phase 3 trials. The overall study period is mainly driven by the recruitment period (first patient in to last patient in). Therefore, effective country and site selection is key to ensure a favourable patient/site ratio.

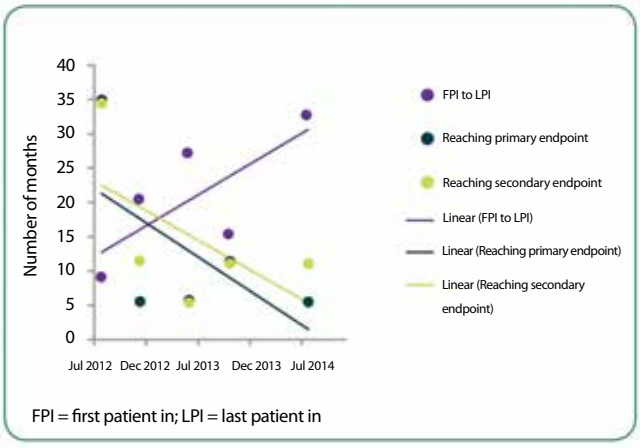
## Study Results

Trend analyses for some of the parameters that have the greatest impact on study timelines show that, in follicular lymphoma studies, there is a negative trend for the recruitment period and time to measurement of primary and secondary endpoints (see Figure 1). This indicates that over the past five years, it has taken less time to enrol patients and achieve study endpoints. Similar developments were observed for primary




FPI = first patient in; LPI = last patient in

Figure 1: Trends in clinical trials of follicular lymphoma




FPI = first patient in; LPI = last patient in

Figure 2: Trends in clinical trials of rheumatoid arthritis

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and secondary endpoints in rheumatoid arthritis studies, but not for the recruitment period (see Figure 2). The recruitment period shows a positive trend, so between July 2012 and April 2014, the time taken to recruit patients increased. This may be related to the fact that in rheumatoid arthritis studies, the median number of study sites is less than half that of follicular lymphoma (66 versus 145), meaning that it takes longer to enrol patients.

The percentage contribution analysis suggests that most of the countries in the major and BRICS markets have a higher than average contribution (1.55%) to rituximab biosimilar Phase 3 clinical trials, and that the top five countries are the US, Brazil, Russia, India and Italy. This analysis helps to indicate which countries are preferred locations for rituximab biosimilar clinical trials. Pharma companies aim to have exposure of their biosimilar in key markets, in order for their data to be available at launch to support uptake of the drug. Although clinical trials can help provide this exposure, it can still be very challenging to gain market share due to the unfamiliarity of prescribers with biosimilars. The support of influential opinion leaders, who have had a positive experience with a biosimilar in a trial, may facilitate market uptake.

It may also be that a high percentage contribution for a country is due to a number of other factors, such as how easy or straightforward it is to conduct a clinical trial, whether there is a good supply of study sites and investigators, or whether there is a large patient population. Time and cost are important considerations for any clinical trial, so countries that have good recruitment rates are able to expedite a trial, helping to reduce the overall time and cost of clinical development. As expenses are usually lower in emerging or developing markets, these countries are likely to be key locations for clinical trial programmes.

## Conclusion

The development of rituximab biosimilars is currently a major area of clinical research, with generic, multinational and regional pharma companies all involved. The majority of clinical trials are Phase 3 studies in follicular lymphoma and rheumatoid arthritis. The most common countries involved in three of the four follicular lymphoma studies are the US, Brazil, Russia, India and Italy, representing both developed and developing pharmaceutical markets. In general, over the past six years, there has been a downward trend in the time required for the overall study and patient enrolment.

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