Axial spondyloarthritis (axSpA)

Forecast

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OVERVIEW

Description	Datamonitor Healthcare uses a patient-based approach to size the commercial potential of the axial spondyloarthritis (axSpA) market across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK). This analysis contains an assessment of key axSpA therapies on the market and in the late-phase pipeline, a discussion of axSpA market dynamics, and a 10-year patient-based sales forecast.
Recent forecast updates	Stelara's development program in axSpA has been discontinued due to failure to meet key endpoints (Q4 2017). Simponi Aria was approved in the US (October 2017). The anticipated launch of biosimilar adalimumab in the US has been delayed to Q1 2023 following news regarding ongoing litigation (September 2017).

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Highlights	Market growth will be driven by novel biologics and US price increases, despite biosimilar erosion During the forecast period, the axSpA market will see downward pressure from the arrival of biosimilars of the key marketed anti-tumor necrosis factor (TNF) biologics Enbrel and Humira, which will be marketed at a lower cost than the reference brands. Despite this, Datamonitor Healthcare forecasts overall growth, partly due to the launch and increasing uptake of novel, high-cost biologics, namely the interleukin (IL)-17A inhibitors, as well as due to annual price increases in the US. Datamonitor Healthcare forecasts the axSpA market to grow from $3.6bn in 2016 to $4.7bn in 2025, representing a compound annual growth rate of 2.97%. Cosentyx will successfully establish its position as the preferred biologic in the post-TNF setting Cosentyx, the first-in-class IL-17A inhibitor, is forecast to successfully establish its position as the preferred biologic for patients who are refractory to TNF inhibition, by 2025. Although the anti-TNF biologics have demonstrated strong efficacy in axSpA, a significant proportion of patients are inadequate responders or refractory to TNF inhibition. Datamonitor Healthcare expects Cosentyx to dominate the TNF-refractory market, with its growth fueled by the increasing availability of favorable long-term efficacy and safety data and its first-in-class status. By 2025, Cosentyx is forecast to achieve sales of $726.8m across the US, Japan, and five major EU markets, overtaking the second-generation anti-TNF biologics Cimzia and Simponi. Taltz's uptake will be limited due to its relatively late market entry in 2019, as well as its lack of differentiation from Cosentyx. Despite significant pressure from the increasing availability of cheaper biosimilars, Enbrel and Humira will remain the dominant biologics in axSpA While well-established anti-TNF biologics are facing significant competition from the increasing availability of cheaper biosimilars, Enbrel and Humira are forecast to retain their position as the preferred first-line biologics in axSpA. In 2016, Enbrel and Humira had sales of $1.1bn and $1.3bn, respectively, together accounting for approximately 67% of 2016 axSpA sales. Despite an overall decrease in Enbrel and Humira sales over the 10-year forecast period, the two brands will remain the leading therapies in axSpA due to their proven real-world efficacy, positive long-term safety data, and physician and patient familiarity.
Methodology	Patient-based forecasting methodology utilizing epidemiology data and primary research with 225 prescribing rheumatologists across the US, Japan, and five major EU markets. Pricing, dosing, and future event assumptions are added to create Datamonitor Healthcare's forecast.

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RECENT FORECAST UPDATES

The list below summarizes recent market-impacting events included in this latest update of Datamonitor Healthcare's axial spondyloarthritis (axSpA) forecast.

STELARA'S CLINICAL DEVELOPMENT IN AXSPA HAS BEEN DISCONTINUED DUE TO FAILURE TO MEET KEY ENDPOINTS (Q4 2017)

ClinicalTrials.gov lists all Phase III studies evaluating the safety and efficacy of Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) in axSpA as terminated, due to Stelara's inability to meet key endpoints (ClinicalTrials.gov identifiers: NCT02437162; NCT02438787; NCT02407223). Datamonitor Healthcare does not expect any further development in axSpA.

SIMPONI ARIA WAS APPROVED IN THE US MARKET (OCTOBER 2017)

In October 2017, Simponi Aria (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) received US approval for the treatment of active ankylosing spondylitis (Johnson & Johnson, 2017). The approval was based on positive data from the Phase III GO-ALIVE study (ClinicalTrials.gov identifier: NCT02186873). Simponi Aria became available for prescription for axSpA immediately upon approval since it had already been available in the US due to its prior approval in rheumatoid arthritis.

THE ANTICIPATED LAUNCH OF BIOSIMILAR ADALIMUMAB IN THE US HAS BEEN DELAYED TO Q1 2023 (SEPTEMBER 2017)

In September 2017, AbbVie announced a global resolution of all intellectual property-related litigation with Amgen, which will delay the launch of Amjevita in the US until January 2023 (AbbVie, 2017). While this does not preclude other biosimilar developers from undertaking an at-risk launch, successfully challenging patents held by AbbVie, or designing around patents and using their own patent estate to support a biosimilar launch, Datamonitor Healthcare believes that a biosimilar adalimumab launch in the US is unlikely prior to 2023.

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MARKET DYNAMICS

Figure 1: **Axial spondyloarthritis – current and future market dynamics analysis**

Current dynamic	Market opportunity
• Conventional DMARDs continue to dominate first-line therapy due to their low cost, despite lack of evidence for efficacy in axSpA and absence from treatment guidelines • Anti-TNF biologics remain the mainstay of treatment for patients with persistently high disease activity despite conventional DMARD therapy • Humira (adalimumab) and Enbrel (etanercept) share first-line biologic status due to their proven efficacy and physician familiarity with the brands • Cosentyx (secukinumab) has seen strong uptake due to its positive efficacy and safety profiles, and the need for novel, non-TNF biologics	• Cosentyx could demonstrate superiority to adalimumab in the SURPASS trial to drive prescribing early in the treatment algorithm • Indication expansion to include nr-axSpA • Develop agents for TNF-refractory patients or patients with contraindications to TNF inhibitors; could prove commercially rewarding due to the unmet medical need in this patient population and limited axSpA pipeline
Threat of substitution	**Payer pressure**
• Second-generation anti-TNF biologics Cimzia (certolizumab pegol) and Simponi (golimumab) are threatened by drugs with differentiated mechanisms of action, notably Cosentyx and Taltz (ixekizumab) • Increasing availability of anti-TNF biosimilars, which will erode market share from the originator brands	• Strong pricing competition introduced by the availability of biosimilars of leading anti-TNF brands • Anti-TNFs have secured preferred first-line biologic status based on formulary placement, limiting use of newer drugs to later lines of therapy

axSpA = axial spondyloarthritis; DMARDs = disease-modifying antirheumatic drugs; nr-axSpA = non-radiographic axial spondyloarthritis; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

The figure below depicts Datamonitor Healthcare's assessment of the clinical and commercial attractiveness of key marketed and pipeline drugs profiled as therapies for axSpA.

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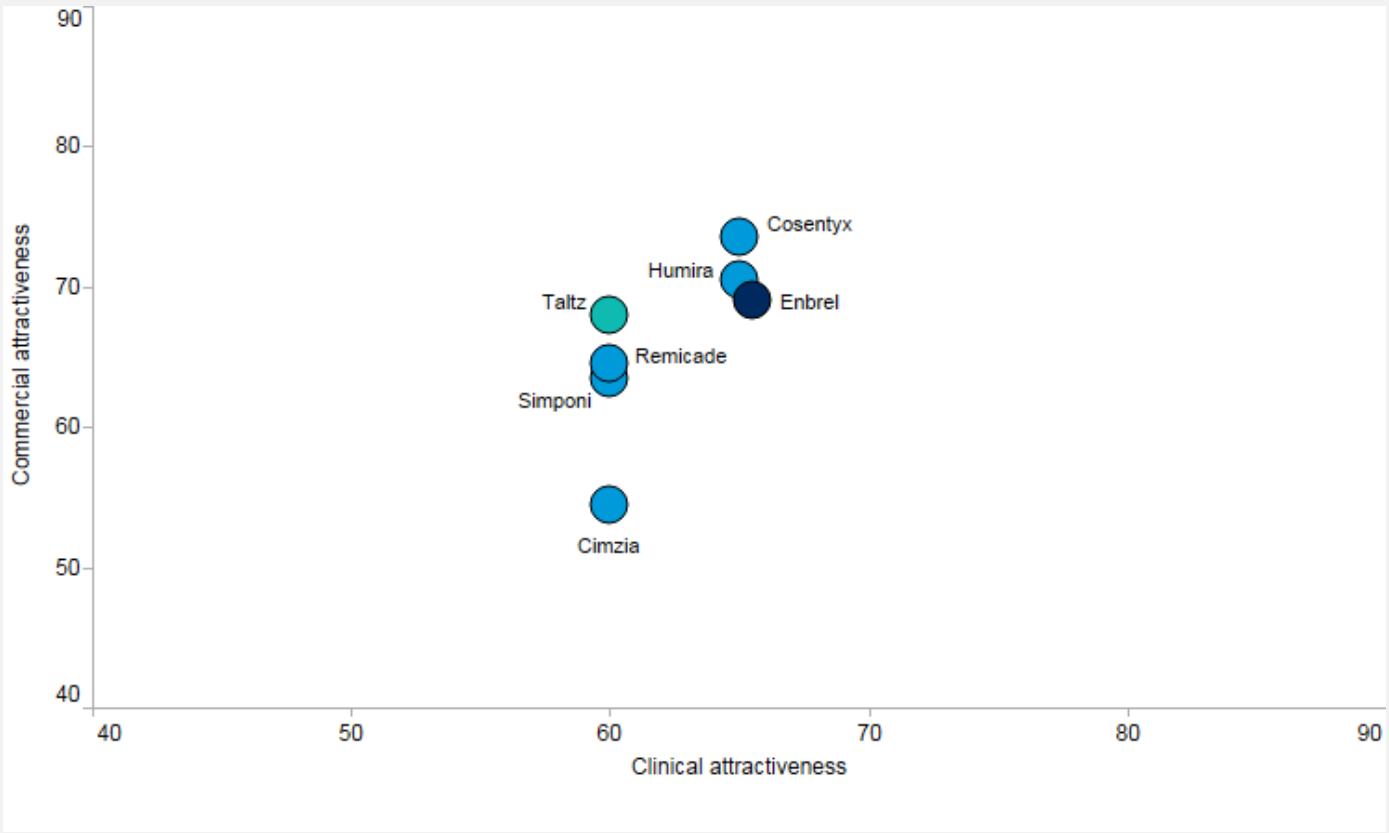
Figure 2: **Datamonitor Healthcare's assessment summary of key marketed and pipeline drugs for axial spondyloarthritis**



Source: Datamonitor Healthcare

HUMIRA SHARES FIRST-LINE BIOLOGIC STATUS WITH ENBREL, WITH PRESCRIBING TRENDS VARYING BETWEEN MARKETS

Datamonitor Healthcare's proprietary market research reveals that Humira (adalimumab; AbbVie/Eisai) has successfully penetrated the first-line biologic setting in the axSpA market, sharing this position with Enbrel (etanercept; Amgen/Pfizer/Takeda). While Humira launched in June 2006, after Enbrel and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), it has been able to establish its position as one of two preferred first-line TNF inhibitors in axSpA due to its proven efficacy and safety. Key opinion leaders have highlighted that the long-term data available for Humira, which provides superior efficacy compared to Enbrel, drive its use in patients with active axSpA and no extra-articular manifestations.

"If it is just primary axial spondylitis without any extra-articular manifestation, then I would probably go to adalimumab... it has been around longest along with etanercept, compared to the other TNF inhibitors."

Anonymous key opinion leader

Based on Humira's position in current prescribing practices and treatment guidelines, Datamonitor Healthcare expects that the brand will remain among the preferred first-line biologic agents for the foreseeable future.

REMICADE'S IV ADMINISTRATION IS LARGELY A DISADVANTAGE, DESPITE FAVOR AMONG SOME PHYSICIANS

Despite being favored in certain niche patient subgroups, overall Remicade's intravenous (IV) administration is a major drawback for the brand given that all of the other anti-TNF biologics are offered as subcutaneous (SC) formulations. Physicians and patients find the IV route of administration inconvenient and expensive compared to the SC formulation, which negatively impacts Remicade's clinical attractiveness and has hindered uptake of the brand. Key opinion leaders have highlighted the logistical obstacles resulting from Remicade's IV administration, which have led to competitors Enbrel and Humira being positioned earlier in the treatment algorithm by physicians.

"Infliximab has logistical impedances like the fact that it is IV and needs to be infused."

Anonymous key opinion leader

"Those three [Enbrel, Humira, and Remicade] have been around the longest but we tend not to go to infliximab unless needed... no incentive for me to infuse someone."

Anonymous key opinion leader

However, Remicade's IV administration is considered an advantage for a small subgroup of patients due to dose titration, which benefits patients partially failing other TNF inhibitors and those with significant variation from the average weight, providing an option currently not available with the other anti-TNF biologics.

"I do think infliximab has the benefit of being dose and frequency titrated, and that definitely in some patients is necessary when you cannot dose titrate with the other drugs... I have definitely had more response with infliximab when patients are partially failing other TNF inhibitors, because of that ability."

Anonymous key opinion leader

"In people that are obese where you can really increase the dose differently – I think there are some benefits."

Anonymous key opinion leader

COSENTYX HAS ENJOYED A STRONG LAUNCH IN AXSPA, WITH INCREASING AVAILABILITY OF LONG-TERM DATA EXPECTED TO FURTHER DRIVE ITS USE

Cosentyx (secukinumab; Novartis) has seen strong uptake since its launch in axSpA due to its convincing clinical profile and the fact that it meets the need for novel biologic agents suitable for the TNF-failure population, or for patients with contraindications to TNF inhibitors. Cosentyx's strong performance to date was reflected in Novartis's annual 2017 financial report, with Cosentyx reported to have achieved annual global sales of $2.1bn (Novartis, 2018a). Discussions with key opinion leaders have revealed that, based on its clinical performance in axSpA so far, Cosentyx's efficacy and safety profile is considered to be on par with those of the TNF inhibitors.

"It [Cosentyx] is a very promising new type of treatment that is probably as effective as a TNF inhibitor, maybe even a little more."

Anonymous key opinion leader

"The data seen from the Phase III clinical trial was indeed very good; actually it [Cosentyx] showed a better profile than the first Phase III trial data with TNF inhibitors... so that looks at least very good."

Anonymous key opinion leader

The increasing availability of long-term efficacy and safety data for Cosentyx will boost physicians' confidence in the brand and further drive prescribing. Long-term data from the MEASURE 1 trial (ClinicalTrials.gov identifier: NCT01358175) showed that almost 80% of patients treated with Cosentyx showed no radiographic progression of the spine, as measured by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), at 208 weeks. The study also showed sustained improvements in signs and symptoms in patients with active axSpA through week 208, measured using several endpoints, including ASAS 20/40, BASDAI, BASFI, BASMI, and ASDAS inactive disease (Braun et al., 2017; Novartis, 2017). Discussions with key opinion leaders have revealed that inhibition of radiographic spinal changes is one of the key unmet needs in axSpA. With no conclusive evidence that anti-TNF agents have a protective effect on radiographic progression in axSpA, these new data differentiate Cosentyx from its well-established competitors (Machado, 2013).

"The most important question with regards to efficacy is whether it will be able to inhibit structural or radiographic progression, which would be new in comparison to TNF inhibitors... if inhibition of radiographic progression can be shown, it would be an efficacy advantage."

Anonymous key opinion leader

Cosentyx is currently primarily prescribed for patients following the failure of at least one TNF inhibitor. With the head-to-head superiority trial of Cosentyx versus adalimumab (SURPASS), Novartis is aiming to boost prescribing of the IL-17A inhibitor earlier in the axSpA treatment algorithm (Novartis, 2018b).

SECOND-GENERATION ANTI-TNFS, CIMZIA AND SIMPONI, HAVE BEEN RELEGATED TO LATE LINES OF THERAPY DUE TO THEIR LATE MARKET ENTRY

Cimzia (certolizumab pegol; UCB/Astellas) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), the last of the anti-TNF biologics to be approved for the treatment of axSpA, have seen the lowest use within the anti-TNF class. Datamonitor Healthcare's proprietary axial spondyloarthritis survey highlights that Cimzia and Simponi have not successfully penetrated earlier lines of treatment in the US and five major EU markets (France, Germany, Italy, Spain, and the UK), indicating that rheumatologists are reluctant to change their prescribing behaviour, particularly when there are no clear efficacy or safety advantages associated with newer therapies. Key opinion leaders note that they use Enbrel and Humira in earlier lines of treatment due to their experience and familiarity with the two brands. In addition, Enbrel and Humira are often the preferred first-line biologics due to their favorable formulary status.

"It is a matter of historical use. There was a time when the only two SC [subcutaneous] drugs were Enbrel and Humira and it worked well, so I have most experience with them."

EU key opinion leader

"Choosing a biologic for first-line treatment [...] there are various factors that we think about, and I will almost always start with a TNF inhibitor because of the track record, and our general comfort with the medicines, and they have just been out a lot longer than some of the newest agents that just came out in the last few years [...] so one factor is whether a patient is able or capable to do self-injections, or have

someone inject for them versus infusion, that is kind of the first decision maker [...] Sometimes their insurance will mandate one over the other and that is particularly true in this country with regards to Humira and Enbrel, which tend to have a favorable status so that you have to go through a step, if you feel like Simponi would be just right for this patient, and you had the injectable Simponi or Cimzia, you often have to argue, really argue why you are not going to use Enbrel or Humira first."

EU key opinion leader

Cimzia and Simponi's market share primarily comes from patients with active axSpA who have failed or responded inadequately to first-line anti-TNF biologics, and from patients with active ankylosing spondylitis and co-morbidities such as inflammatory bowel disease.

"If I have someone with ankylosing spondylitis... and Crohn's, they are getting certolizumab... based on FDA approval."

Anonymous key opinion leader

"If someone has failed, or had a side effect, or not responded, or has ulcerative colitis... then they get switched [from first-line Enbrel and Humira to Simponi]."

Anonymous key opinion leader

Cimzia is also preferred by rheumatologists for women of childbearing age, due to data demonstrating little to no placental transfer of the biologic from mother to infant during pregnancy. Data also showed minimal transfer of Cimzia via the mother's breast milk to the infant during lactation (EMA, 2017; FDA, 2017).

"One other factor that weighs into my decision-making is if it is a young woman of childbearing age, we will tend to go to certolizumab, and sometimes if it is a new start TNF-naïve patient and they are a woman of childbearing age that is considering having kids, I will just go straight to certolizumab because of the fact that it does not cross the placenta as much."

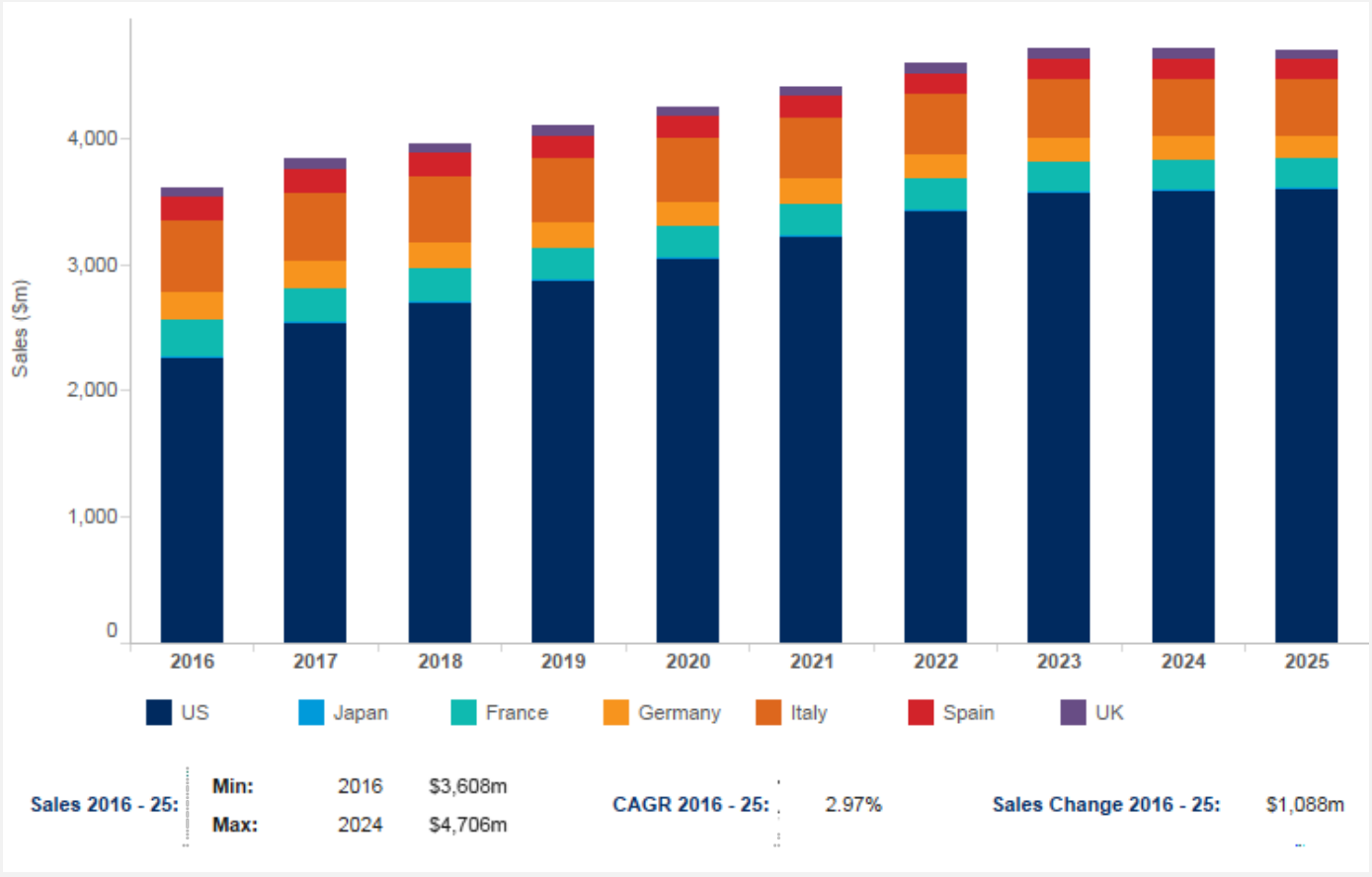
Anonymous key opinion leader

FORECAST AND FUTURE TRENDS

THE AXSPA MARKET WILL ONLY SEE MODERATE GROWTH OVER THE FORECAST PERIOD DUE TO BIOSIMILAR EROSION OF KEY BRANDS

Datamonitor Healthcare estimates the axial spondyloarthritis (axSpA) market to have been worth approximately $3.6bn in 2016 across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK). During the forecast period, the market will see downward pressure from the entry of biosimilars of the key marketed anti-tumor necrosis factor (anti-TNF) biologics, Enbrel (etanercept; Amgen/Pfizer/Takeda), Humira (adalimumab; AbbVie/Eisai), and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), which will be marketed at a lower cost than the reference brands. As a result, Datamonitor Healthcare forecasts moderate overall growth, with the axSpA market expanding to approximately $4.7bn in 2025, at a compound annual growth rate (CAGR) of 2.97%.

Figure 3: **Total market sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 1: **Total market sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	2,260.2	2,533.5	2,695.4	2,863.2	3,041.3	3,226.8	3,426.1	3,562.6	3,588.8	3,605.7
Japan	8.5	8.5	8.2	7.8	7.4	7.0	6.7	6.4	6.1	5.9
France	287.7	262.7	257.8	251.5	246.1	241.4	237.1	232.9	228.2	223.0
Germany	221.4	215.7	210.2	204.2	200.0	196.8	193.7	190.2	186.0	180.8
Italy	561.1	545.1	526.1	511.2	498.7	487.4	477.4	467.9	457.5	446.2
Spain	188.1	183.9	180.3	176.0	172.7	169.8	167.0	163.9	160.1	155.7
UK	80.9	80.5	80.2	79.5	79.4	79.6	79.9	80.0	79.5	78.5
Total	3,607.9	3,829.9	3,958.2	4,093.6	4,245.5	4,408.7	4,587.8	4,703.8	4,706.3	4,696.0

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

RISING US PRICES AND INCREASING UPTAKE OF PREMIUM-PRICED IL-INHIBITORS WILL LEAD TO NET GROWTH OF THE AXSPA MARKET

The overall growth seen in the axSpA market will be primarily driven by steep annual price increases in the US as well as the increasing uptake of high-cost interleukin (IL)-inhibitors, which respond to a key unmet need by offering new treatment options for patients that are not well-controlled with the marketed anti-TNFs, or who have contraindications to anti-TNF therapy. Novartis's first-to-market IL-17A inhibitor Cosentyx (secukinumab) is forecast to continue to see strong uptake over the forecast period as it is increasingly supported by positive long-term data. The anticipated launch of the second IL-17A inhibitor, Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical), will further contribute to market expansion.

The delayed arrival of the first biosimilar of a subcutaneous anti-TNF, Humira, in the US will also contribute to offsetting contracting sales in Japan and the five major EU markets. Total US sales revenues are forecast to reach $3.6bn in 2025, displaying a CAGR of 5.33% during 2016–2025.

EU MARKETS ARE EXPECTED TO DISPLAY A DECLINE IN SALES DUE TO PRICE EROSION CAUSED BY THE GROWING PRESENCE OF ANTI-TNF BIOSIMILARS

Unlike the US, the five major EU markets display a relatively fast decline in sales revenue over the forecast period, despite the increase in the total prevalent cases of axSpA patients and the increasing penetration of high-cost IL-inhibitors. This is due to the growing presence of anti-TNF biosimilars, and the subsequent price reductions for the reference brands. The first infliximab biosimilar launched in Europe in Q1 2015, while the first etanercept biosimilar launched in Q1 2016. The first adalimumab biosimilar is forecast to launch in Q4 2018, following the expiry of residual patent protection (Biogen, 2017). Total sales in the five major EU markets are forecast to decrease from $1.3bn in 2016 to $1.1bn in 2025, at a CAGR of -2.32%.

The figure below shows Datamonitor Healthcare's forecast of axSpA sales in the five major EU markets over 2016–25.

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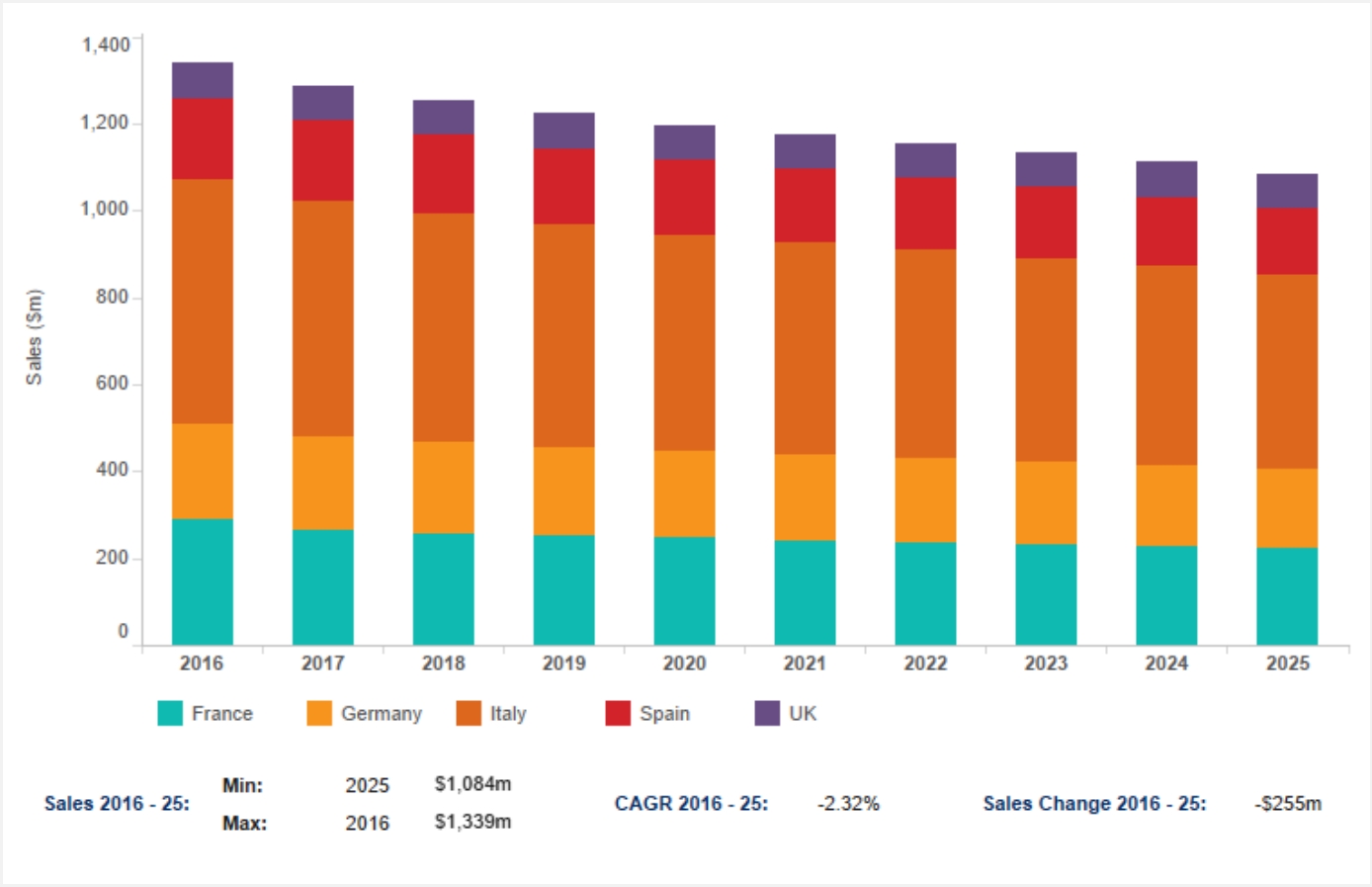
Figure 4: **Total axial spondyloarthritis sales across the five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

DESPITE COMPETITION FROM NOVEL BIOLOGICS WITH UNIQUE MODES OF ACTION, TNF INHIBITORS WILL CONTINUE TO DOMINATE THE MARKET DUE TO THEIR COST-EFFECTIVENESS

With the increasing availability of a number of low-cost anti-TNF biosimilars and the subsequent price reduction expected for the reference brands, anti-TNF biologics will offer a cost-effective option for patients in the early lines of therapy, resulting in a market dominated by one class of drug. This dominance of TNF inhibitors is reflected in their combined class sales across all seven markets, which are expected to reach $3.5bn in 2025, accounting for 75% of total sales in the axSpA market by the end of the forecast period.

The figure below shows Datamonitor Healthcare's forecast of total axSpA sales according to drug class, including TNF inhibitors, IL inhibitors, and conventional disease-modifying antirheumatic drugs (DMARDs), over 2016–25.

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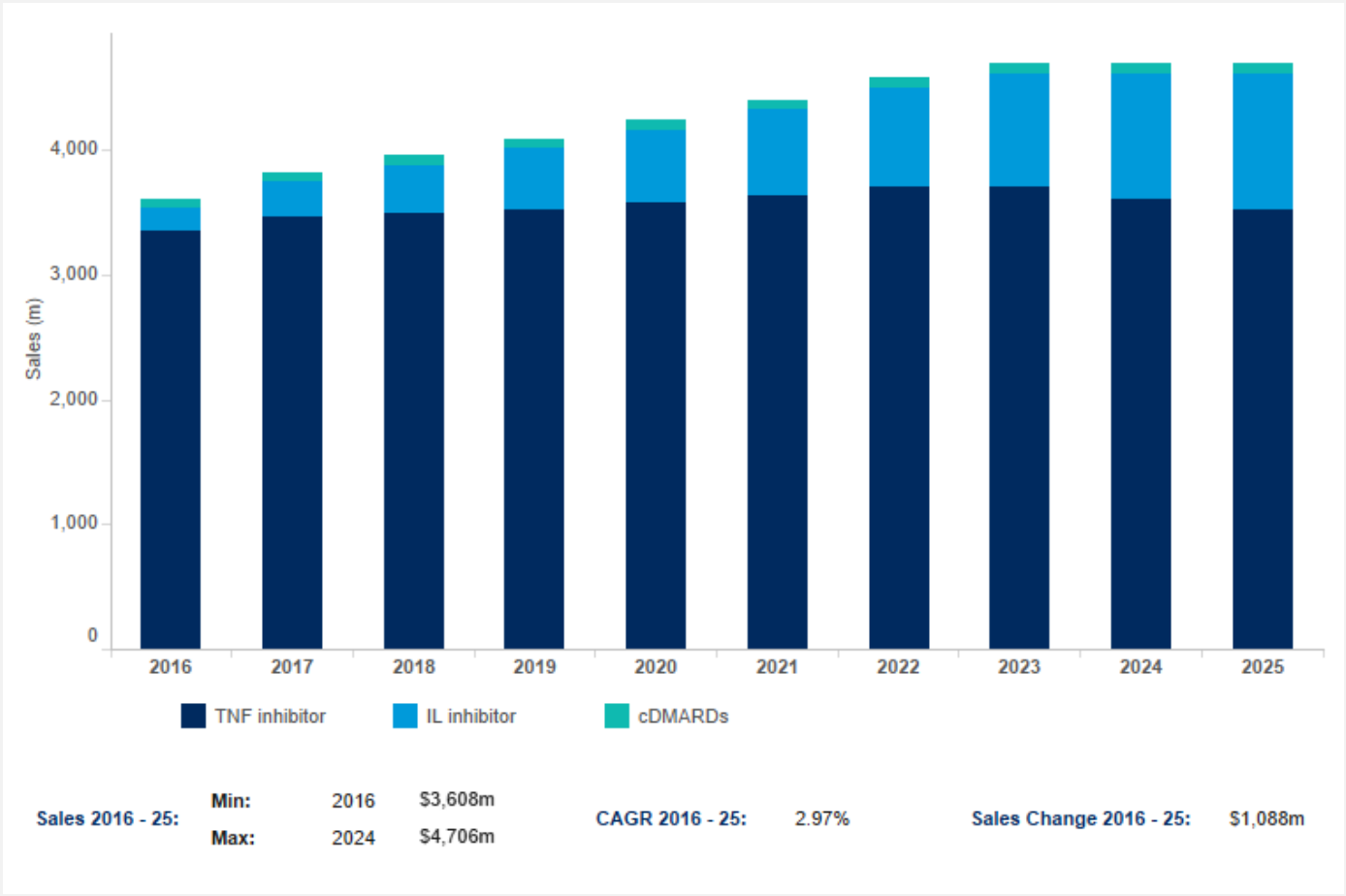
Figure 5: **Total axial spondyloarthritis sales according to drug class, 2016–25**



Sales 2016 - 25:	**Min:**	2016	$3,608m	**CAGR 2016 - 25:**	2.97%	**Sales Change 2016 - 25:** $1,088m
	Max:	2024	$4,706m			

Source: Datamonitor Healthcare

Table 2: **Total axial spondyloarthritis sales according to drug class ($m), 2016–25**

Drug class	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
IL inhibitors	179.6	278.6	386.1	488.5	588.9	693.0	800.3	915.4	1,011.4	1,084.7
TNF inhibitors	3,353.6	3,475.8	3,495.2	3,526.7	3,576.7	3,634.5	3,704.7	3,704.0	3,609.1	3,524.4
cDMARDs	74.7	75.4	76.9	78.3	79.9	81.3	82.8	84.4	85.8	87.0
Total	3,607.9	3,829.9	3,958.2	4,093.6	4,245.5	4,408.7	4,587.8	4,703.8	4,706.3	4,696.0

Note: totals may not sum due to rounding.

cDMARD = conventional disease-modifying antirheumatic drug; IL = interleukin; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

Key opinion leaders highlight that they expect pricing pressure to dictate rheumatologists' choice of first- and second-line biologics, with novel biologics such as the IL-17A inhibitors Cosentyx and Taltz expected to be relegated to late lines of therapy, primarily in patients who are refractory to TNF inhibition. IL inhibitors are considered unlikely to dominate the axSpA market unless they can match the reduced price of the anti-TNF biologics and display better efficacy in comparison to the market leaders Enbrel and Humira.

"Well, first of all, I think the drugs that are out there right now are quite effective [...] so you are going to have a hard time beating their efficacy, because as I have already mentioned, many, many – 90% of our patients – are going to respond favorably to one of the TNF inhibitors, and often in a very dramatic way. The patient with chronic symptoms, elevated CRP [c-reactive protein levels] and functionally very limited takes their first shot of Humira and two days later calls and says 'oh my goodness, what is this stuff?' They feel fantastically better, so it is hard to beat that, right? I am not saying everybody has that positive response but there is a lot of it. So, really, the only way to differentiate yourself in a favorable way [for the novel IL inhibitors] would be to make yourself less toxic, lower risk of infection, which is going to be tough to show. But you have to show at least similar efficacy, and then some degree of favorable safety, or cheaper. And that is where the biosimilars can at least do something."

US key opinion leader

DESPITE SIGNIFICANT PRESSURE FROM BIOSIMILARS, ENBREL AND HUMIRA ARE FORECAST TO REMAIN THE DOMINANT BIOLOGICS IN AXSPA

While leading TNF biologics Enbrel and Humira are expected to face strong competition from increasingly available biosimilars, they are still anticipated to remain the dominant therapies used to treat axSpA by 2025.

In 2016, Enbrel and Humira had sales for axSpA of $1.1bn and $1.3bn, respectively, and together accounted for approximately 67% of the 2016 axSpA sales. Over the 10-year forecast period, the increasing availability of cheaper biosimilars, particularly in Europe, is expected to result in a decline in the sales of both biologics, with Enbrel and Humira garnering overall 2025 sales of $1.06bn and $1.2bn, respectively, representing CAGRs of -0.43% for Enbrel and -0.81% for Humira. Despite this decline in sales and the strong competition posed by biosimilars, Datamonitor Healthcare expects Enbrel and Humira to remain the dominant biologics used to treat axSpA, with combined 2025 sales of $2.3bn, representing 48% of the total market.

Remicade was the first anti-TNF to face biosimilar competition. Celltrion's biosimilar infliximab (marketed as Remsima by Celltrion and Inflectra by Pfizer) launched for axSpA in Q1 2015 in Europe, and in Q2 2016 in Japan (Hospira, 2015; Nippon Kayaku, 2015). In the US, Celltrion/Pfizer's biosimilar infliximab was approved for use in all indications in Q2 2016, and launched at-risk in Q4 2016 (FDA, 2016; Pfizer, 2016). In Europe, the first etanercept biosimilar, Benepali (Biogen/Merck & Co/Samsung Bioepis), was launched in Q1 2016 (Biogen, 2016). As the launch of biosimilar etanercept in the US is dependent on successful litigation relating to multiple patents held by Amgen for Enbrel with expiry dates of 2028 and 2029, Datamonitor Healthcare does not assume a launch in the US at this time (United States Securities and Exchange Commission, 2015). In Europe and the US, Humira is set to face biosimilar competition in Q4 2018 and Q1 2023, respectively. Datamonitor Healthcare forecasts biosimilars to launch with up to a 30% discount compared to their branded counterparts, offering payers, physicians, and patients a lower-cost value proposition. Key opinion leaders highlight that the chief advantage of biosimilars is their cost savings potential.

"For etanercept [biosimilar] I would use it as I use Enbrel right now [...] it would definitely be first line. Benepali [etanercept biosimilar] is the one coming out now and it is definitely something I would prescribe first line [...] I feel comfortable switching patients from the brand to the biosimilar [...] why should we not? We are saving money. We can treat four instead of three patients for the same price."

US key opinion leader

"Yes, I think it is not a real problem; since they [biosimilars] have been evaluated by the EMA [European Medicines Agency] usually the rheumatologists consider that this is a correct guideline and correct evaluation. So, we do not have too many concerns regarding the efficacy and safety profile [...] currently, it is only a price decision, the advantage of biosimilars is not medical or scientific, it is purely a cost decision to use biosimilars, and this is the only advantage they have."

EU key opinion leader

While up to 55% of patient share is forecast to be lost to biosimilars, this erosion is anticipated to be relatively slow initially as a result of expected physician hesitation to prescribe biosimilars, particularly for patients already receiving the brand. Additionally, Datamonitor Healthcare believes that companies will aim to resist biosimilar erosion by leveraging the proven real-world efficacy, positive long-term safety data, and physician and patient familiarity associated with their products. However, prescribing of biosimilars is expected to expand with the increasing availability of long-term safety data and switching studies.

"You know, at the beginning when we started using biosimilar infliximab we decided not to switch, because we do not have that many data on the switch. So for eighteen months, we have not switched. But I know that some hospitals have decided to switch due to the price difference, we have not done that yet but we could do that in the future because I am quite reassured regarding the data that we currently have, and I do not think there is any concern to switch."

EU key opinion leader

The figure below shows Datamonitor Healthcare's forecast for sales of brand leaders Enbrel and Humira versus the other available biologics in axSpA, across the US, Japan, and five major EU markets during 2016–25.

Figure 6: **Sales of Enbrel and Humira versus other established biologics within axial spondyloarthritis in the US, Japan, and five major EU markets, 2016–25**

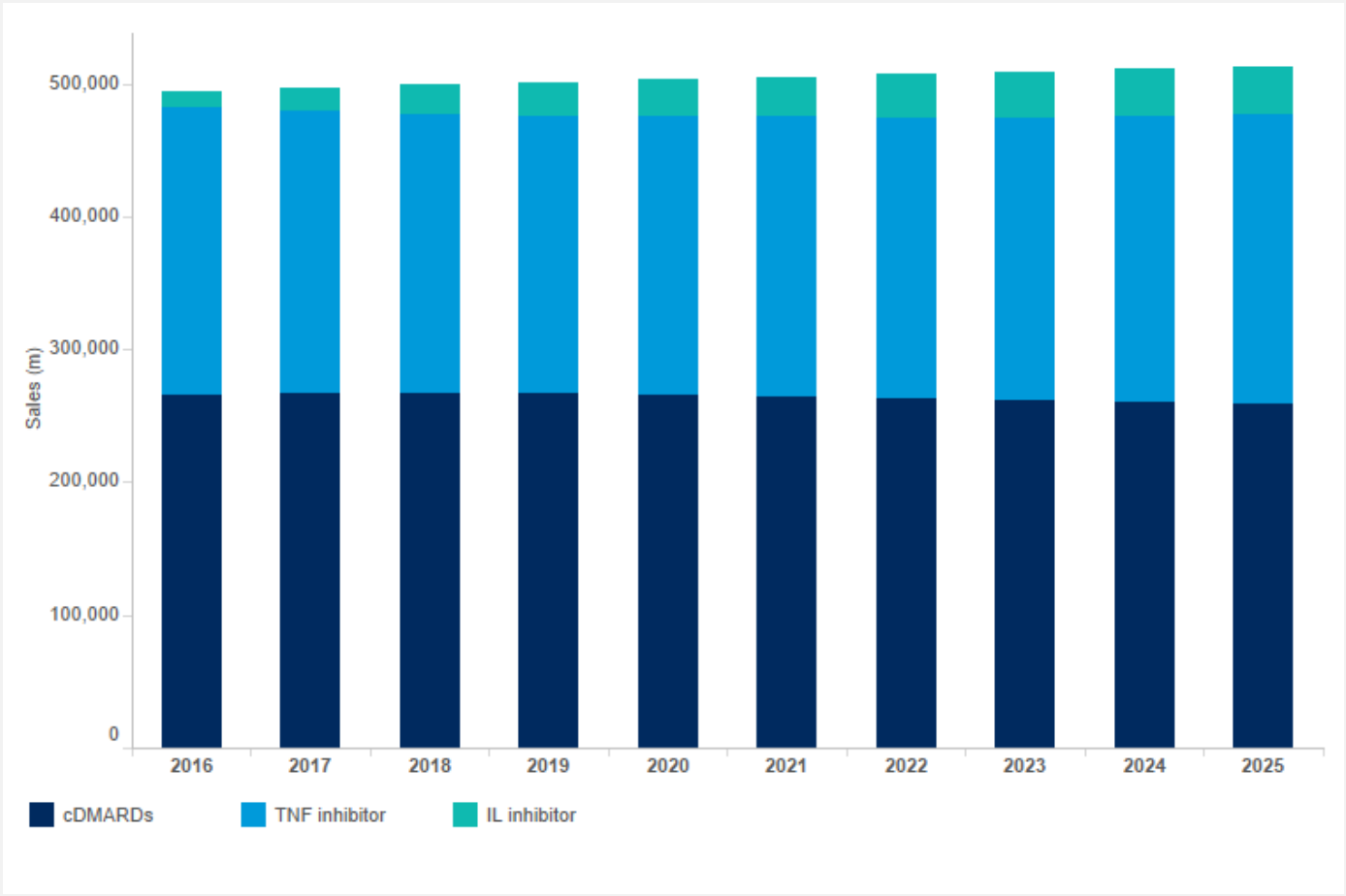
Source: Datamonitor Healthcare

CONVENTIONAL DMARDS CLAIM A HIGH PATIENT SHARE DESPITE LACK OF EVIDENCE SUPPORTING THEIR EFFICACY IN AXSPA

Despite current guidelines (including the 2016 European League Against Rheumatism and the 2015 American College of Rheumatology recommendations) advocating against the use of conventional DMARDs methotrexate and sulfasalazine, this drug class is expected to continue to claim a high patient share during the forecast period across all seven markets (van der Heijde et al., 2017; Ward et al., 2016). Despite a lack of evidence supporting their efficacy in axSpA, the low costs associated with conventional DMARDs in comparison to the more expensive biologics are driving this trend (Caso et al., 2015). Conventional DMARDs are forecast to capture up to 51% of patient share across all markets by 2025.

The figure below shows Datamonitor Healthcare's forecast of total axSpA patient numbers according to drug classes – including TNF inhibitors, IL inhibitors, and conventional DMARDs – in the US, Japan, and five major EU markets during 2016–25. Please note that the patient numbers shown in the table are inflated as patients have been counted separately for each drug class, despite some patients receiving combination therapy.

Figure 7: **Total axial spondyloarthritis patients across the US, Japan, and five major EU markets, by drug class, 2016–25**



Source: Datamonitor Healthcare

Table 3: **Total axial spondyloarthritis patients across the US, Japan, and five major EU markets, by drug class, 2016–25**

Drug class	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
IL inhibitors	11,250	16,687	21,498	25,088	28,160	30,432	32,485	34,242	35,132	35,343
TNF inhibitors	216,666	213,040	210,403	209,525	209,751	210,705	211,839	213,334	215,437	217,869
cDMARDs	266,163	266,878	267,067	266,706	265,787	264,243	262,876	261,486	260,243	259,172
Total	494,080	496,605	498,968	501,318	503,698	505,381	507,201	509,062	510,812	512,384

Note: totals may not sum due to rounding. The patient numbers shown in the table are inflated as patients have been counted separately for each drug class, despite some patients receiving combination therapy.

cDMARD = conventional disease-modifying antirheumatic drug; IL = interleukin; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

Key opinion leaders note that the use of conventional DMARDs is heavily influenced by cost, and that payers often have a requirement to use conventional DMARDs prior to biologics.

"Yes, in axial disease I think it [use of conventional DMARDs] may be driven by – just maybe kind of mandated by – either insurance or payers. I think it is a pretty futile effort in most circumstances, and the data supports that, I mean, for axial disease if you have a patient with ankylosing spondylitis, I think you are just wasting your time if you put them on methotrexate or sulfasalazine. I think the payers are just hoping that something is going to happen favorably, or they are just trying to make it harder to – they have been delaying it for three months and they have saved money."

Anonymous key opinion leader

However, despite this high patient share across all markets, the low annual treatment cost associated with conventional DMARDs is reflected in this class of drugs having the lowest sales revenue in the axSpA market, totaling $87m in 2025, which represents just 2% of the total axSpA sales. The table below shows Datamonitor Healthcare's sales forecast for two conventional DMARDs, methotrexate and sulfasalazine, in the axSpA market across the US, Japan, and five major EU markets during 2016–25.

Table 4: **Total sales of cDMARDs methotrexate and sulfasalazine across the US, Japan, and five major EU markets ($m), 2016–25**

Drug	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
methotrexate	43.3	43.4	44.3	45.2	46.1	47.0	47.9	48.9	49.7	50.4
sulfasalazine	31.5	32.0	32.6	33.2	33.8	34.3	34.9	35.5	36.1	36.5
Total	74.7	75.4	76.9	78.3	79.9	81.3	82.8	84.4	85.8	87.0

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

COSENTYX IS FORECAST TO SEE STRONG GROWTH, SUCCESSFULLY ESTABLISHING ITS POSITION AS THE PREFERRED BIOLOGIC IN THE POST-TNF SETTING

Over the 2016–25 forecast period, Cosentyx is expected to garner sales that will exceed $726m across the US, Japan, and five major EU markets. Cosentyx's anticipated strong growth will be driven by the increasing availability of positive long-term efficacy and safety data and its novel mechanism of action, which addresses the need for a novel biologic agent that is suitable for the TNF-failure population, or for patients with contraindications to TNF inhibitors. Discussions with key opinion leaders have revealed their positive outlooks on Cosentyx based on the drug's clinical performance to date in axSpA and other inflammatory diseases.

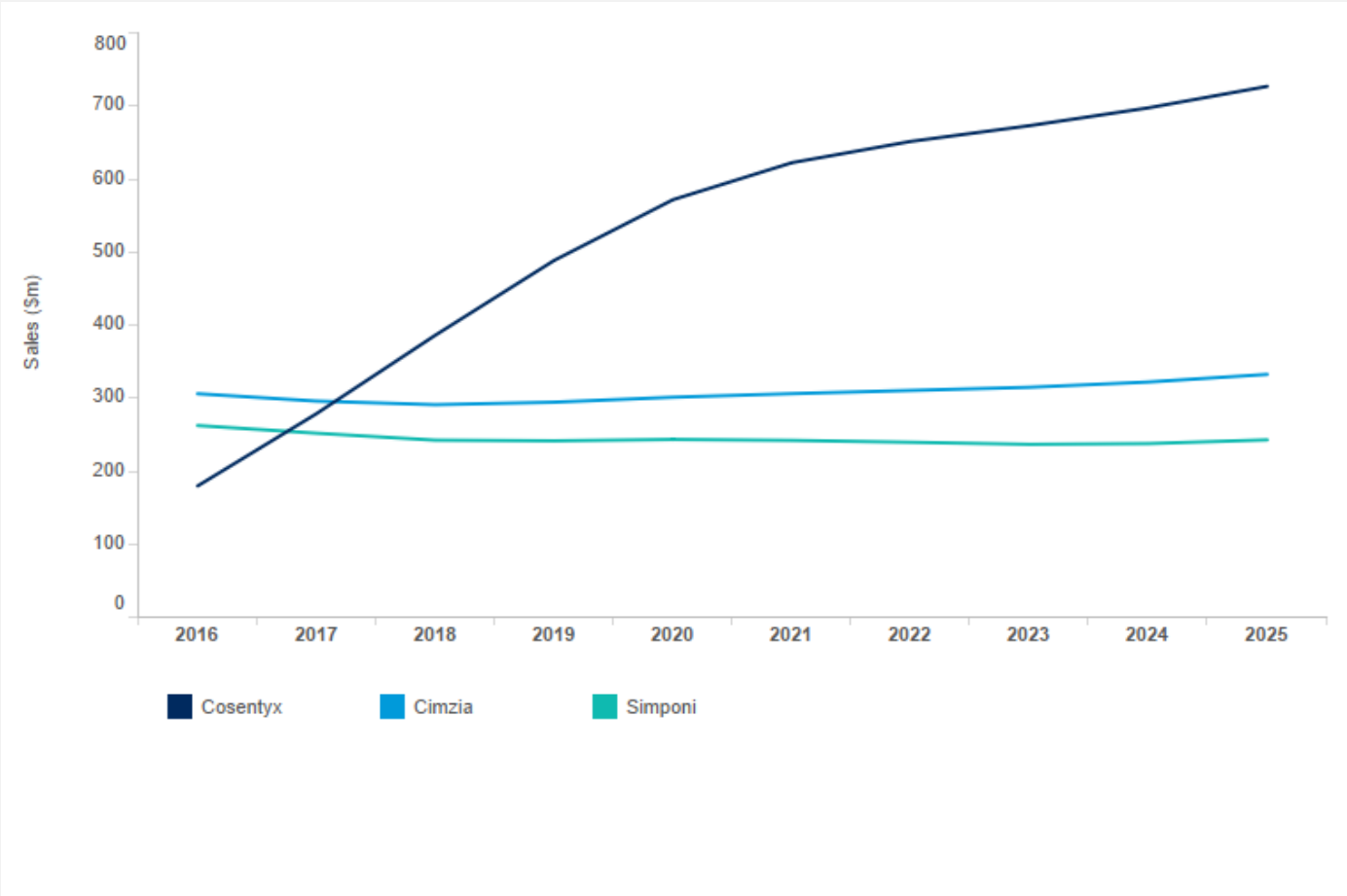
"I think it [Cosentyx] is an excellent drug, seriously. I do not want to sound too enthusiastic, but I think it is a bomb – in a good way. I think it is a very powerful drug. The data on psoriasis and psoriatic arthritis have really been exciting and the data on axial spondyloarthropathies are too. So, I think it could erode quite a bit of our, probably even our first-line prescriptions in the near future. I could see that happening. If you see a very tough patient you can tell these guys – you know, tough disease – that would probably be an excellent first choice for them."

EU key opinion leader

Datamonitor Healthcare forecasts Cosentyx to continue to be primarily used in TNF-experienced patients. Currently, Cosentyx predominantly competes with the second-generation anti-TNFs, Cimzia (certolizumab pegol; UCB/Astellas) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), which are typically used in patients who failed to respond or lost their initial response to a first-line anti-TNF, Enbrel or Humira. In late 2017, Novartis initiated the SURPASS trial, a head-to-head trial of Cosentyx versus a proposed biosimilar adalimumab, aiming to boost prescribing of the IL-17A inhibitor at early lines of therapy. Should Cosentyx demonstrate superiority to adalimumab in this trial, the increasing presence of low-cost anti-TNF biosimilars and physician familiarity with established first-line biologics will be major barriers to early-line penetration.

The figure below shows Datamonitor Healthcare's forecast for sales of IL-17A inhibitor Cosentyx in comparison to the second-generation TNF inhibitors Cimzia and Simponi in axSpA in the US, Japan, and five major EU markets during 2016–25.

Figure 8: **Total sales of Cosentyx versus Cimzia and Simponi for axial spondyloarthritis in the US, Japan, and five major EU markets, 2016–25**



Source: Datamonitor Healthcare

TALTZ'S SECOND-IN-CLASS STATUS AND LACK OF DIFFERENTIATION FROM COSENTYX WILL LIMIT ITS UPTAKE

Taltz's anticipated late market entry in Q4 2019 and the increasing availability of positive long-term data for the first-in-class IL-17A inhibitor Cosentyx will negatively impact Taltz's commercial prospects. Key opinion leaders interviewed by Datamonitor Healthcare highlight that Taltz is considered a "me-too" product, and is expected to have a similar efficacy and safety profile to Cosentyx.

"Taltz [...] is pretty much a second Cosentyx [...] It seems like kind of a me-too that just got to the race a little bit late, not that that disadvantages it necessarily, I mean it is only a little bit – it is like Enbrel [anti-TNF biologic] and Remicade [anti-TNF biologic] came out pretty close to each other way back then, although [with] different formulations: IV and subcutaneous but Taltz, it is going to probably end up just coming down to cost and insurance coverage, it is going to be one of those factors rather than any particular efficacy issue."

Anonymous key opinion leader

Aside from the lack of differentiation from Cosentyx, the increasing availability of anti-TNF biosimilars will also restrict Taltz's uptake, relegating it to late lines of therapy. Datamonitor Healthcare forecasts Taltz to achieve 2025 sales of $358m.

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Table 5: **Sales of Cosentyx versus Taltz for axial spondyloarthritis in the US, Japan, and five major EU markets ($m), 2016–25**

Biologic	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Cosentyx	179.6	278.6	386.1	488.5	571.6	622.3	651.4	673.0	697.4	726.8
Taltz	-	-	-	<0.1	17.3	70.7	148.9	242.4	314.1	357.8

Source: Datamonitor Healthcare

SIMPONI ARIA'S UPTAKE WILL BE RESTRICTED BY PHYSICIAN FAMILIARITY WITH REMICADE AND THE AVAILABILITY OF CHEAPER INFLIXIMAB BIOSIMILARS

Based on discussions with key opinion leaders, Datamonitor Healthcare expects uptake of Simponi Aria, the IV formulation of Simponi which launched in the US in Q4 2017, to be slow as it will be restricted by physician familiarity with Remicade as well as the availability of cheaper infliximab biosimilars.

"I'm not very interested in Simponi Aria because we already have infliximab on the market as an IV drug, and [...] very shortly we will have the first biosimilar infliximab on the market [...] so in all fairness we do not need it."

Anonymous key opinion leader

"I do not see which patients will use it [...] if there is a medical necessity we have infliximab and biosimilar infliximab [...] so I do not see the advantage."

Anonymous key opinion leader

Patient share for Simponi Aria is expected to come from physicians that prefer Simponi Aria to Remicade due to its relatively low immunogenicity; Simponi Aria provides an alternative IV anti-TNF biologic with a reduced risk of generating anti-drug antibodies.

"It would take over from Remicade [...] because it is fully humanized [...] if there is that option, then at least for the 65 [years] and older axSpA patients who require a TNF inhibitor it will become first line."

US key opinion leader

However, Datamonitor Healthcare believes that Simponi Aria's ability to cannibalize Remicade's existing patient share will be greatly limited by the availability of cheaper infliximab biosimilars. Johnson & Johnson will therefore need to offer significant discounts in order to match the price of biosimilars if Simponi Aria is to be considered a cost-effective alternative to infliximab.

By 2025, Simponi Aria is predicted to have sales of $24.6m in the US axSpA market.

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MARKET DEFINITION AND METHODOLOGY

MARKET DEFINITION FOR AXIAL SPONDYLOARTHRITIS

For the purposes of this patient-based forecast, Datamonitor Healthcare defines the axial spondyloarthritis (axSpA) market in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) as comprising the drug classes and molecules shown below. These have been identified as the key brands and molecules in the market, based on country-specific primary market research with prescribing rheumatologists, secondary research, and key opinion leader discussions.

Summary of brands and molecules included in Datamonitor Healthcare's patient-based axial spondyloarthritis forecast

Tumor necrosis factor (TNF) inhibitors:

- Cimzia (certolizumab pegol; UCB/Astellas)
- Enbrel (etanercept; Amgen/Pfizer/Takeda)
- Humira (adalimumab; AbbVie/Eisai)
- Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe)
- Simponi/Simponi Aria (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe)
- biosimilar adalimumab (multiple)
- biosimilar etanercept (multiple)
- biosimilar infliximab (multiple).

Interleukin (IL) inhibitors:

- Cosentyx (secukinumab; Novartis)
- Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical).

Conventional disease-modifying antirheumatic drugs (DMARDs):

- generic methotrexate (multiple)
- generic sulfasalazine (multiple).

PATIENT-BASED FORECAST METHODOLOGY

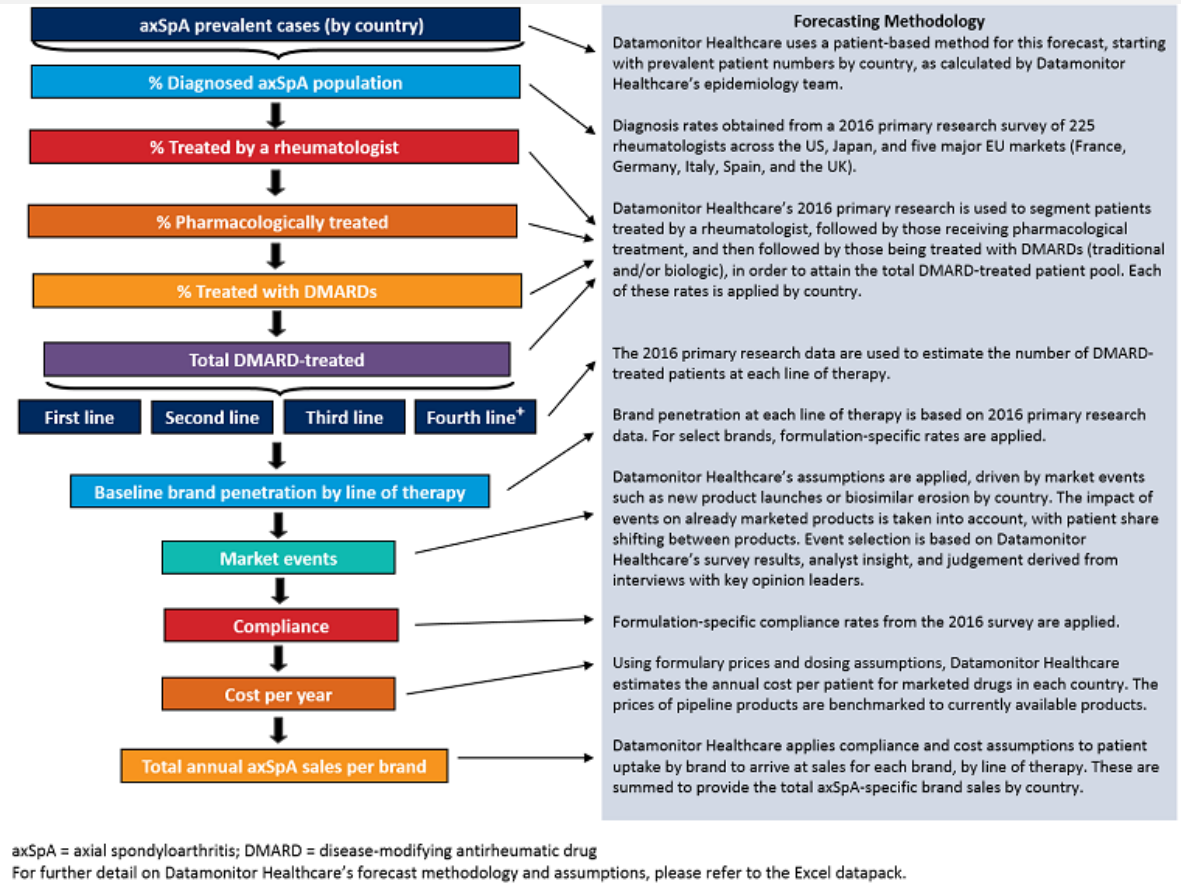
Datamonitor Healthcare has used a patient-based methodology in constructing its forecast of the axSpA market. The forecast is based on primary research, discussions with key opinion leaders, secondary sources, and Datamonitor Healthcare's epidemiology analysis. Datamonitor Healthcare's primary research includes a survey of 225 rheumatologists across the US, Japan, and five major EU markets, which was conducted in March 2016.

This patient-based forecast focuses on the competitive landscape of key treatments for axSpA, including conventional and biologic DMARDs.

Methodology flow

Datamonitor Healthcare's methodology for this forecast is summarized in the figure below, which shows how forecasts of each included product (marketed or pipeline) were calculated.

Figure 9: **Datamonitor Healthcare's axial spondyloarthritis forecast methodology**



axSpA = axial spondyloarthritis; DMARD = disease-modifying antirheumatic drug
For further detail on Datamonitor Healthcare's forecast methodology and assumptions, please refer to the Excel datapack.

Source: Datamonitor Healthcare

Epidemiology

The starting point for Datamonitor Healthcare's patient-based axSpA forecast is estimated diagnosed patient numbers by country during 2016–25, as calculated by Datamonitor Healthcare's epidemiology team. An in-depth discussion of the methodology used in calculating the estimated diagnosed patient population, as well as the age and gender splits, is available in Datamonitor Healthcare's Epidemiology: Axial Spondyloarthritis.

Percentage of patients diagnosed with axSpA

In this forecast, the percentage of diagnosed cases is determined from the results of Datamonitor Healthcare's 2016 primary market research survey. The diagnosis rate indicated by surveyed US rheumatologists has been adjusted downward based on secondary data sources that suggest diagnosis rates are lower than those indicated by the survey sample. According to the literature, axSpA presents a distinct diagnostic problem since it occurs in the context of a highly prevalent condition – lower back pain – in which it represents a small subset (O'Shea et al., 2007). This has also been highlighted during discussions with key opinion leaders, validating the downward adjustment.

"The percentage of patients who remain undiagnosed is really high due to multiple factors. I think one of the reasons is that back pain is common. So patients think they could self-treat because a lot of the therapies that work in axSpA include non-steroidal anti-inflammatories and exercise. People wake up with the symptoms and then they self-manage, and by midday they are feeling OK, especially if you have milder disease. So they do not go to the doctor. If they do go to the doctor depending on how early in the course of their disease they go to the doctor, the doctor may say 'Well back pain is common,' because they are not educated to the disease, or even if they think about it then they do an imaging study and it is negative, which it often is early in disease, they are told it is probably mechanical and they are sent off."

US key opinion leader

"Often the diagnosis [of axSpA] does get missed, or significantly delayed because the first symptoms may be just chronic low back pain, which a lot of people have, and the things I am looking for are to look out if the younger patient with chronic low back stiffness and achiness that is like an inflammatory type of back pain. I think women get delayed even more than men, because we think of this as a more predominantly male disease, and often I will see a woman who is older in her thirties, or forties before she gets the diagnosis, whereas men can be diagnosed in their teens, or twenties."

US key opinion leader

The diagnosis rate indicated by surveyed Japanese rheumatologists has also been adjusted downward based on secondary data sources that suggest diagnosis rates are lower than those indicated by the survey sample. According to the literature, there is a marked diagnostic delay among Japanese axSpA patients due to the low prevalence of the disease in Japan, the common occurrence of mechanical back pain in the general population, and a lack of clinical symptoms, signs, or biomarkers unique to axSpA (Nakashima et al., 2016).

Percentage of patients treated by rheumatologists

In this forecast, the country-specific percentages of patients whose treatment is managed by rheumatologists are determined from the results of Datamonitor Healthcare's 2016 primary market research survey. The survey exclusively targeted rheumatologists as Datamonitor Healthcare assumes the types of treatment included in this forecast would require specialist care. This trend is consistent with the literature, as well as the 2016 European League Against Rheumatism and 2015 American College of Rheumatology (ACR) recommendations for the management of axSpA, which suggest that rheumatologists primarily diagnose and treat the disease (van der Heijde et al., 2017; van Tubergen and Weber, 2012; Ward et al., 2016).

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The percentage of patients treated by rheumatologists that was indicated by surveyed US respondents has been adjusted downward based on secondary data sources and discussions with key opinion leaders; both of these sources suggest that the rate of treatment by a rheumatologist was overestimated by Datamonitor Healthcare's survey sample. Studies indicate that in the US, the majority of patients with low back pain consult general practitioners (GPs), and US primary care guidelines do not explicitly specify referral to a rheumatologist in cases of suspected axSpA (Herndon et al., 2015). Key opinion leaders highlight that although axSpA patients should be treated by a rheumatologist, this can depend upon rheumatologist availability.

"Of the diagnosed axSpA patients [...] most of them get some sort of pharmacologic treatment, hopefully they are under the care of a rheumatologist, but not always [...] it depends on availability of course. "

US key opinion leader

The percentage of patients treated by rheumatologists indicated by surveyed Japanese rheumatologists has also been adjusted downward based on secondary data sources that suggest that this rate was overestimated by Datamonitor Healthcare's survey sample. The low prevalence of axSpA in Japan is expected to lead to low disease awareness among GPs, which, in combination with a lack of clinical symptoms, signs, or biomarkers unique to axSpA, is expected to lead to patients primarily being treated by primary care physicians (Hukuda et al., 2001; Nakashima et al., 2016).

Percentage of patients receiving pharmacological treatment

Datamonitor Healthcare's 2016 primary market research survey asked rheumatologists to indicate the percentage of their axSpA patients receiving pharmacological therapy.

The pharmacological treatment rates indicated by respondents in the US market have been adjusted downward based on the 2015 ACR recommendations for the management of axSpA, which strongly recommend active physical therapy (Ward et al., 2016). This is substantiated by literature that suggests that various exercises, either individually or in a group and under supervision, and either land- or water-based, have positive effects on pain and the mobility function of axSpA patients (van den Berg et al., 2012). The availability of the Spondylitis Association of America, a national organization responsible for arranging support groups across the US, is expected to lead to a higher percentage of patients receiving non-pharmacological treatment, in the form of physical therapy.

The pharmacological treatment rates indicated by Japanese rheumatologists have also been adjusted downward based on literature which suggests that early, correct diagnosis, and treatment of axSpA in Japan remains a significant problem due to the very low prevalence of the disease, and a lack of awareness around the clinical symptoms associated with axSpA (Nakashima et al., 2016).

These adjustments were further validated by comparing the forecast outputs with company-reported sales.

Patients treated with conventional and biologic DMARDs

Datamonitor Healthcare's 2016 primary market research survey asked rheumatologists to indicate the percentage of their patients receiving conventional and biologic DMARDs, split by line of therapy. The percentage of DMARD-treated patients indicated by surveyed US rheumatologists has been adjusted downward based on discussions with key opinion leaders, which suggest that the rate of treatment with DMARDs was overestimated by Datamonitor Healthcare's survey sample in the US.

"I think when it comes to ankylosing spondylitis [active axSpA], 50% of them are treated with NSAIDs [non-steroidal anti-inflammatory drugs], and only a fraction is treated with a biological drug [...] We do not tend to prescribe traditional DMARDs, we do not have sound evidence that they are effective in AS [active axSpA]."

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Anonymous key opinion leader

The percentage of patients receiving conventional and/or biologic DMARDs indicated by Japanese rheumatologists has also been adjusted downward based on the restricted number of biologics licensed for axSpA in Japan, namely TNF inhibitors Humira and Remicade. As both biologics have the same mechanism of action, there is a lack of alternative treatment options available for those patients who are refractory to TNF inhibition. Based on this, the percentage of patients receiving conventional and/or biologic DMARDs has been adjusted downward.

These adjustments were further validated by comparing the forecast outputs with company-reported sales.

Brand penetration

For all marketed therapies included in this forecast, Datamonitor Healthcare applied a baseline brand penetration rate by line of therapy. The rate is estimated from Datamonitor Healthcare's 2016 primary research survey of 225 rheumatologists in the US, Japan, and five major EU markets. Penetration rates for biologics indicated by US and EU rheumatologists were adjusted downward and validated by comparing the forecast outputs with company-reported sales.

Market events

Datamonitor Healthcare applied events to the axSpA market by switching patients between products. Events in this forecast include new product launches and the impact of biosimilars. The selection of events and their impact is based on survey results, analyst insight, and judgment derived from interviews with key opinion leaders. Reviews of clinical trial data and conference materials are also incorporated. All events are applied by line of therapy and are country-specific. Different countries can have different launch dates and different rates of patient switching, both in terms of the percentage of patients switched and the speed of switching.

Events by brand are discussed in detail in the individual brand chapters and can be viewed in the Events tab of the accompanying Excel deliverable.

Compliance

Formulation-specific compliance rates for each country, obtained from the 2016 survey, are applied to Datamonitor Healthcare's axSpA forecast. As part of the primary market research, Datamonitor Healthcare asked leading rheumatologists to indicate how compliant their axSpA patients are with three different types of formulation: oral, subcutaneous, and intravenous. For example, if patients took half of their prescribed dose of oral tablets on average, this was defined as 50% compliance, while if patients attended three out of four of their intravenous therapy sessions on average, compliance was defined as 75%.

Price and dose assumptions

For this forecast, Datamonitor Healthcare calculates each product's price per year by disease severity, for each country. Datamonitor Healthcare determines dose assumptions for each product by reviewing the approved label for each marketed therapy and, where relevant, taking into account country-specific label differences. For pipeline products, assumptions are based on the dosing schedules used in clinical trials.

Datamonitor Healthcare then uses national formularies to gather pricing information per product. As the prices presented in formularies can differ, showing prices at different stages in the supply chain, Datamonitor Healthcare uses backing-out formulas to

adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for each country. The following figure outlines the sources and calculations used in the US and EU. For Japan, prices are taken from the National Health Insurance drug database. These prices are the retail price exclusive of consumption tax, and therefore, it is important to note that the sales given for Japan may be inflated compared to other countries, depending on the extent of price markups at different stages in the supply chain. However, Datamonitor Healthcare has validated its patient-based sales estimates with company-reported sales in Japan where available, and believes the impact to be minimal.

Figure 10: **Price sources and calculations, by country**

Country	Starting source	Formulary price	Net retail price formula	Ex-factory pharmacy price formula	Ex-factory wholesale price formula	Source for formulas	Note
US	Red Book	AWP	n/a	n/a	WP = AWP/1.2	Red Book (2015)	Assumes AWP is 120% of WP
France	Le Dictionnaire Vidal	Retail price inclusive of VAT				Eco-Santé France (2012) Patented Medicine Prices Review Board (2012)	Assumes VAT rate for reimbursed products applied to all
		If 0<RP<32.23	RPN = RP/1.021	PP = RPN/1.261	WP = PP/1.0993		
		If 32.23</=RP <211.08	RPN = RP/1.021	PP = RPN/1.1	WP = PP/1.06		
		If 211.09</=RP <562.89	RPN = RP/1.021	PP = RPN/1.06	WP = PP/1.02		
		If RP>562.89	RPN = RP/1.021	PP = RPN/1.06	WP = PP		
Germany	Die Lauer-Taxe	Retail price inclusive of VAT	RPN = RP/1.19	PP = (RPN - 8.35)/1.03	WP = (PP - 0.70)/1.0315	German Ministry of Health (2013)	
Italy	L'Informatore Farmaceutico	Retail price inclusive of VAT	RPN = RP/1.10	n/a	WP = 0.6665 x RPN	Patented Medicine Prices Review Board (2012)	
Spain	Catalogo de Medicamentos	Retail price inclusive of VAT				Vogler et al. (2009)	
		If 0<RP<143.04	RPN = RP/1.04	PP = RPN/1.279	WP = PP/1.076		
		If RP>143.04	RPN = RP/1.04	PP = RPN - 38.37	WP = PP - 7.54		
UK	British National Formulary	Ex-factory pharmacy price	n/a	n/a	WP = 0.875 x PP	Patented Medicine Prices Review Board (2012)	Assumes similar pricing presented in MIMS and BNF

ASP = average sales price; AWP = average wholesale price; BNF = British National Formulary; MIMS = Monthly Index of Medical Specialities; PP = pharmacy price; RP = retail price inclusive of VAT; RPN = net retail price; WP = wholesale price

Source: Datamonitor Healthcare; various (see above)

Using the calculated ex-factory wholesale price, the price per mg is calculated. This is multiplied by Datamonitor Healthcare's annual dosing assumptions in order to obtain an annual price per patient. Where possible, four years of historical prices are used to trend forward prices over the forecast period. In cases where four years of historical prices are unavailable, pricing changes have been assumed to follow the trends of other marketed drugs within the same class for which historical data are available. All prices are shown in US dollars, using the average 2017 exchange rate from Open Exchange Rates.

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Table 6: **Exchange rates used for calculating prices**

Currency	Local currency to USD
EUR	1.1067
GBP	1.3552
JPY	0.0092

Source: Open Exchange Rates, 2017

For pipeline products, prices have been benchmarked to branded products of the same class where applicable, taking into account premiums due to novelty or expected discounts. Prices are calculated individually for each product in each country. To see specific price assumptions by brand, please consult the individual brand sections or the accompanying datapack.

PRIMARY RESEARCH METHODOLOGY

PHYSICIAN RESEARCH

Datamonitor Healthcare conducted primary research with a sample of 225 rheumatologists in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK). The research was conducted in March 2016. The sample breakdown by country is shown in the table below, together with some key respondent metrics.

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Table 7: **Rheumatologists surveyed for the axial spondyloarthritis primary research study, 2016**

	US	Japan	France	Germany	Italy	Spain	UK
Sample size	35	30	33	31	34	31	31
Mean number of years in specialty	14.4	18.1	22.2	16.0	16.5	18.0	14.5
Mean number of hours per day spent in clinical practice	9.0	7.6	8.8	8.1	8.4	7.5	8.1
Mean number of axial spondyloarthritis patients respondents are clinically responsible for	119	19	105	140	116	108	150

Source: Datamonitor Healthcare's proprietary axial spondyloarthritis survey, March 2016

The primary research study was conducted online, with all the respondents self-completing a 30-minute questionnaire in their own language. The questionnaire was divided into three sections:

- screening questions
- main questionnaire
- demographic questions.

Datamonitor Healthcare's questionnaire was carefully designed and included a number of screening questions to ensure the most appropriate targeting of respondents for this study. Respondents needed to have clinical responsibility for the treatment and management of a minimum number of axial spondyloarthritis (axSpA) patients to ensure that responses were broadly representative of current treatment practices. The participating physicians also had to be working in clinical practice daily, have a minimum of three years' experience in their specialty, and to not work directly for a pharmaceutical company, other than involvement in clinical trials. All these criteria aimed to ensure, as far as possible, that respondents were experienced, practicing specialists with unbiased views.

The objectives of the main questionnaire for this study were to gain an understanding and insight into the following:

- key epidemiological datasets (diagnosis and treatment rates)
- patient management pathways
- patient segmentation by line of therapy
- prescribing behavior including the use of monotherapy and/or combination therapy, by line of therapy
- patient compliance
- prescribing influences
- product comparative performance and valued product attributes
- assessment of unmet treatment needs
- future trends and uptake of new therapies and their impact on the market.

The demographic questions that were asked at the end of Datamonitor Healthcare's survey helped to ensure that the sample was broadly representative of the treating physician population in each country.

Pilot interviews (consisting of online self-completion of the questionnaire) and subsequent telephone interviews with a Datamonitor Healthcare analyst were conducted with a small number of physicians in the US and UK. The purpose of piloting was to determine if the questionnaire:

- was "fit-for-purpose" and able to gather data that answered the research objectives
- was straightforward for the respondents to complete in the allocated time period

- covered all relevant aspects of treatment and management for axSpA.

After the mainstage fieldwork was completed, the raw data at the respondent level were carefully reviewed and quality-checked by the research team prior to data processing and analysis.

KEY OPINION LEADER RESEARCH

Telephone interviews

Datamonitor Healthcare conducted telephone interviews with three key opinion leaders as part of the primary research undertaken for axSpA. Each interview lasted 60 minutes.

With the aid of a detailed discussion guide, the objectives of each interview were to gain an understanding and insight into the following:

- patient management
- influences on current prescribing practice
- treatment guidelines
- opinion on current therapies, including therapy comparisons and prescribing preferences
- opinion on pipeline drugs, including likely approval/uptake/impact on current therapies, likely target patient populations, and required trial endpoints
- treatment challenges and unmet needs.

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Product Profiles

Cimzia : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

As the fifth anti-tumor necrosis factor (TNF) biologic to enter a market already dominated by the blockbusters Enbrel (etanercept; Amgen/Pfizer/Takeda), Humira (adalimumab; AbbVie/Eisai), and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), Cimzia's (certolizumab pegol; UCB/Astellas) prospects are unfavorable. Cimzia's late market entry and its lack of differentiation in terms of efficacy and safety compared to the other TNF inhibitors negatively impact its commercial potential. In addition, UCB's lack of experience in immunology compared to its competitors' extensive resources in this therapy space further restricts Cimzia's market penetration. With competition from cheaper biosimilars and Novartis's interleukin (IL)-17A inhibitor Cosentyx (secukinumab), an agent with a novel mechanism of action, Datamonitor Healthcare expects Cimzia's uptake to remain low.

DRUG OVERVIEW

Cimzia is a PEGylated humanized monoclonal antibody fragment, with high affinity for both soluble and membrane-bound TNF-alpha. Celltech (now UCB) used its proprietary fragments of antibody (Fab) technology to develop Cimzia for use in chronic inflammatory diseases.

Cimzia is approved for use in several autoimmune indications, namely rheumatoid arthritis, Crohn's disease, psoriatic arthritis, and axial spondyloarthritis (axSpA).

Table 8: **Cimzia drug profile**

Molecule	certolizumab pegol
Mechanism of action	PEGylated humanized MAb fragment against TNF-alpha
Originator	Celltech (now UCB)
Marketing company	UCB (US); Astellas (Japan)
Formulation	SC injection
Alternative names	n/a

MAb = monoclonal antibody; SC = subcutaneous; TNF = tumor necrosis factor

Source: Datamonitor Healthcare; Pharmaprojects

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DEVELOPMENT OVERVIEW

Cimzia first gained US Food and Drug Administration (FDA) approval for the treatment of adult patients with active ankylosing spondylitis (AS) in October 2013 (UCB, 2013a). Within the EU, Cimzia was initially approved for the treatment of moderate to severe active rheumatoid arthritis (UCB, 2009), and was granted an indication extension in October 2013 for the treatment of adult patients with severe axSpA. This comprised adult patients with severe active AS or severe active non-radiographic (nr)-axSpA, who had an inadequate response to or were intolerant to non-steroidal anti-inflammatory drugs (EMA, 2013). Both approvals were based on data from the RAPID-axSpA Phase III trial (ClinicalTrials.gov identifier: NCT01087762), which showed that a significant percentage of patients with active axSpA treated with Cimzia achieved the ASAS20 response over 12 weeks in comparison to placebo (Landewé et al., 2013).

PIVOTAL TRIAL DATA

The Phase III study that supported Cimzia's approvals for axSpA is summarized below.

Table 9: **Cimzia pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
RAPID-axSpA (NCT01087762) (Phase III)	325	Patients with active axSpA, including patients with AS and nr-axSpA	Randomized, double-blind, placebo-controlled	CZP 200mg Q2W: 400mg at weeks 0, 2, and 4, followed by 200mg every two weeks from week 6 onwards CZP 400mg Q4W: 400mg at weeks 0, 2, and 4, followed by 400mg every four weeks; 156 weeks	Achieved ASAS20* response at week 12: CZP 200mg Q2W: 57.7% CZP 400mg Q4W: 63.6% Placebo: 38.3%	Landewé et al., 2013

*ASAS20 response at week 12 (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis international Society response criteria 20; axSpA = axial spondyloarthritis; CZP = certolizumab pegol; nr-axSpA = non-radiographic axial spondyloarthritis; Q2W = every two weeks; Q4W = every four weeks

Source: see above

ONGOING LATE-PHASE TRIALS

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Table 10: **Cimzia ongoing late-phase trial in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing	Primary endpoints	Study start/primary completion date
C-AXSPAND (NCT02552212) (Phase III)	300	Adult patients with active nr-axSpA with inadequate response to, or contraindication to, or intolerant to, ≥2 NSAIDs	Randomized, double-blind, placebo-controlled	CZP 400mg on weeks 0, 2, and 4, followed by CZP 200mg every two weeks; 52 weeks	Percentage of patients meeting ASDAS-MI* response criteria at week 52	September 2015/May 2018

*ASDAS-MI response is achieved when there is a reduction (improvement) of ≥2.0 in the ASDAS relative to baseline. The ASDAS is calculated as the sum of the following components: back pain, patient's global assessment of disease activity, duration of morning stiffness, peripheral pain/swelling, and fatigue, all assessed on a numerical scale (0–10 units).

ASDAS-MI = Ankylosing Spondylitis Disease Activity Score major improvement; CZP = certolizumab pegol; nr-axSpA = non-radiographic axial spondyloarthritis; NSAID = non-steroidal anti-inflammatory drug

Source: Trialtrove; ClinicalTrials.gov

SWOT ANALYSIS

Figure 11: **Cimzia for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Strong efficacy data observed for axSpA and nr-axSpA subpopulations • Data showing minimal transfer of Cimzia through the placenta and breast milk from mother to infant led to EU label expansion to include potential use in women during pregnancy and breastfeeding • Approved in EU for patients with nr-axSpA	• Black box warning for serious infections and malignancies • Me-too formulation; launched fifth in an already crowded anti-TNF market • UCB has less marketing experience in immunology than its competitors and lacks partners • Not approved in Japan
Opportunities	**Threats**
• Promote for patients who need a high initial load of anti-inflammatory treatment • UCB could initiate head-to-head trial with one of the other anti-TNF biologics in order to prove equal or superior clinical efficacy • Increasing prevalence of disease across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) • Potential for future indication expansion for nr-axSpA in US based on results of C-axSpAnd Phase III trial • Potential for future filing in Japan • Promote drug for women of childbearing age • Recommended by NICE for axSpA and nr-axSpA • Delayed biosimilar competition, potentially until 2024	• Physician familiarity and positive reimbursement status of the other anti-TNF biologics • Increasing availability of real-world data for Cosentyx (secukinumab) • Increasing availability of biosimilars of leading anti-TNF brands will intensify pricing competition • Competition from Enbrel (etanercept) and Humira (adalimumab) in nr-axSpA patients • Anticipated competition from Taltz (ixekizumab)

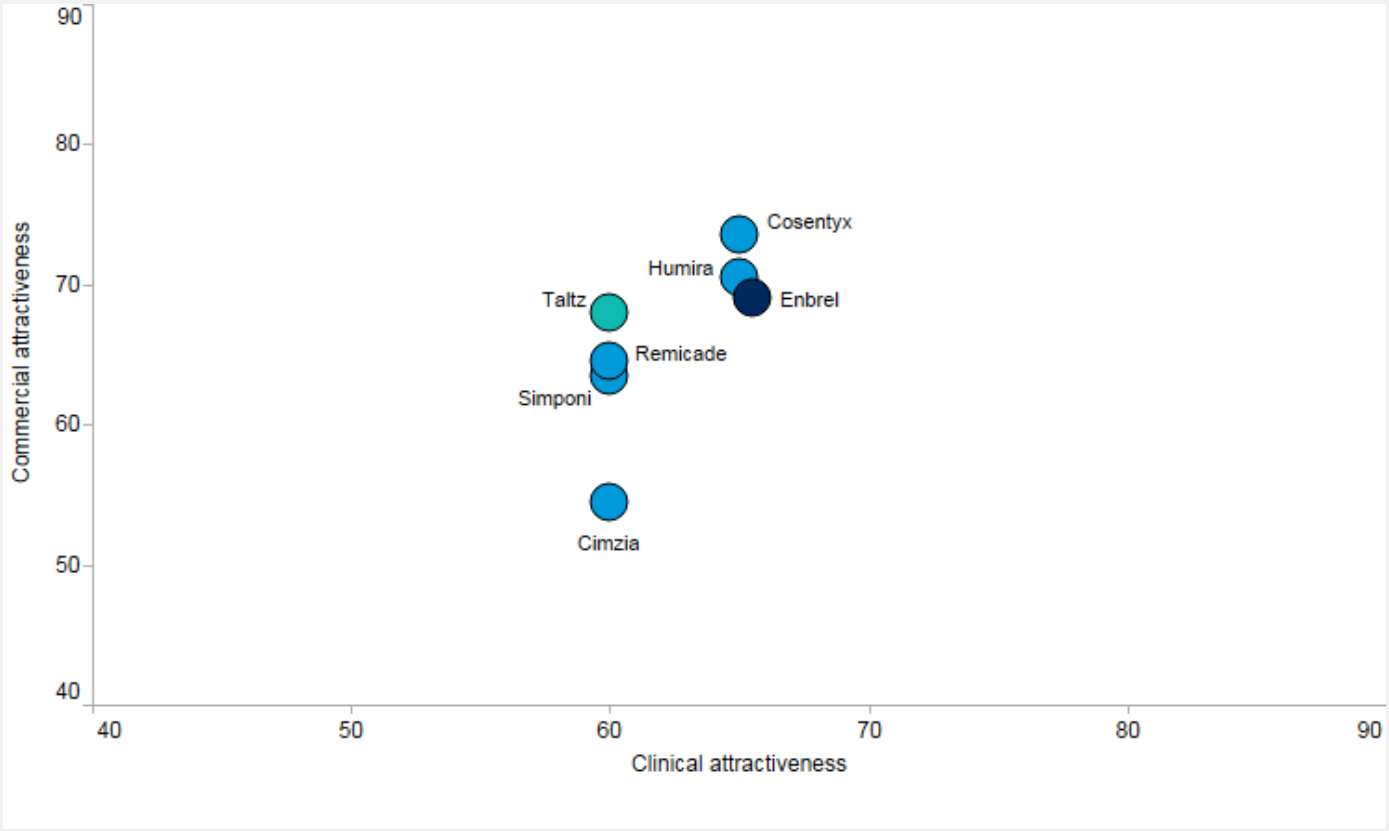
axSpA = axial spondyloarthritis; FDA = US Food and Drug Administration; NICE = National Institute for Health and Care Excellence; nr-axSpA = non-radiographic axial spondyloarthritis; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

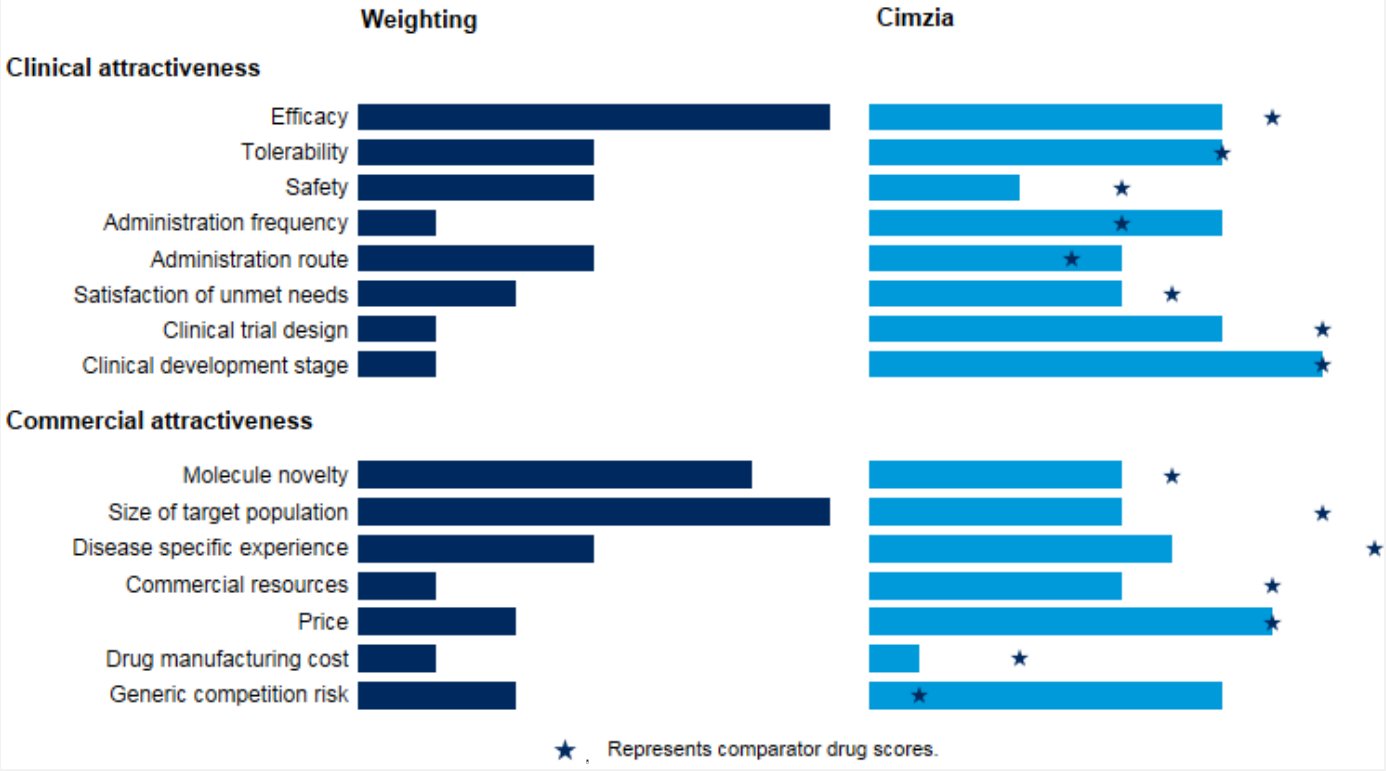
The figures below depict Datamonitor Healthcare's assessment of Cimzia's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel and all of the other key marketed and pipeline drugs profiled.

Figure 12: **Datamonitor Healthcare's drug assessment summary of Cimzia in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 13: **Datamonitor Healthcare's drug assessment summary of Cimzia in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Cimzia for axial spondyloarthritis:

REGULATORY

- The FDA approved Cimzia for the treatment of patients with active AS in October 2013 (UCB, 2013a). In the same month, the drug was approved by the European Medicines Agency (EMA) for the treatment of adults with severe active axSpA, comprising severe active AS and severe active nr-axSpA (UCB, 2013b).

- In January 2018, the EMA approved a label change for Cimzia to include its potential use in women with chronic rheumatic disease during pregnancy and breastfeeding. This label change was supported by post-marketing data from the CRIB and CRADLE studies, and pregnancy outcomes data. These studies included women with RA, PsA, axSpA, and CD (UCB, 2018).

- Datamonitor Healthcare forecasts Cimzia to gain US approval for nr-axSpA in Q2 2019. The Phase III C-AXSPAND trial (ClinicalTrials.gov identifier: NCT02552212), which aims to evaluate the safety and efficacy of Cimzia compared to placebo in patients with nr-axSpA, includes US sites. Based on the study's primary completion date of May 2018, Datamonitor Healthcare expects UCB to file for label expansion in the US in Q4 2018. Assuming the C-AXSPAND study generates positive data,

Datamonitor Healthcare expects US approval for use in nr-axSpA to be granted in Q2 2019.

- Datamonitor Healthcare does not forecast Cimzia to launch in Japan. UCB has not indicated intent to seek approval for Cimzia in this market (UCB, 2017).

COMPETITION

- As the fifth anti-TNF biologic to enter the market, Cimzia's late market entry and physician familiarity with market leaders Enbrel and Humira has restricted its market penetration. Cimzia competes mainly with Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) for patients with active axSpA who have failed or responded inadequately to first-line anti-TNF biologics, and patients with co-morbidities. Key opinion leaders emphasize that of the two anti-TNF agents, Cimzia is the preferred TNF inhibitor for women of childbearing age and pregnant women, due to data showing Cimzia has the lowest level of placental transfer to the fetus in comparison to other anti-TNF agents (Mahadevan et al., 2013). This key clinical attribute is highlighted by Cimzia's 2018 EU label expansion to include potential use in women with axSpA who are pregnant or breastfeeding (UCB, 2018).

"One other factor that weighs into my decision-making is if it is a young woman of childbearing age we will tend to go to certolizumab, and sometimes if it is a new-start TNF-naïve patient and they are a woman of childbearing age that is considering having kids, I will just go straight to certolizumab because of the fact that it does not cross the placenta as much."

Anonymous key opinion leader

- Datamonitor Healthcare believes that the increasing availability of cheaper anti-TNF biosimilars and the emergence of biologics with novel mechanisms of action are likely to further restrict Cimzia's uptake, with its sales prospects not expected to reach those of the leading brands by 2025.

- In the US, Cimzia is forecast to capture up to 5% of patient share from conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, at third-line and later following its indication expansion for nr-axSpA in Q2 2019.

- Cimzia is forecast to face strong competition from first-in-class IL-17A inhibitor Cosentyx, which is primarily prescribed to patients following the failure of at least one TNF inhibitor. Datamonitor Healthcare expects Cimzia to lose up to 30% of its patient share to Cosentyx across the US and five major EU markets (France, Germany, Italy, Spain, and the UK). Loss of patient share is expected to be greatest in the second and later lines of therapy.

"In the case of inadequate response to the first biologic, so the first TNF inhibitor, we have the choice between a second TNF or secukinumab [Cosentyx], which is the only one that is launched currently in spondyloarthritis, which is an anti-IL-17. Especially when we have primary failure with an anti-TNF, we prefer an anti-IL17 [...]"

EU key opinion leader

- Furthermore, Datamonitor Healthcare also expects Cimzia to lose up to another 5% of patient share across the US and five major EU markets to Cosentyx, as a result of the latter's indication expansion for nr-axSpA in Q4 2019. The loss of patient share is expected to be greatest at second and later lines of therapy in patients who are refractory to TNF inhibition, or in cases where anti-TNF therapy is not recommended due to a history of malignancy, or concerns around the side effect profiles of anti-TNFs.

- Cimzia is forecast to face competition from the second-to-market IL-17A inhibitor Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical). Cimzia is set to lose up to 10% of its patient share to Taltz. Loss of patient share will be greatest at the second and later lines of therapy.

DOSING

- Datamonitor Healthcare assumes dosing of 200mg every other week as described in Cimzia's prescribing information (EMA, 2017; FDA, 2017).

PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for Cimzia in each country. Historical prices are used to trend forward prices over the forecast period. The US price for Cimzia used in the axSpA patient-based forecast has been lowered by 30% to account for rebates and discounts. This assumption is based on Datamonitor Healthcare's discussions with key opinion leaders.

- Please view the accompanying datapack for a full table of drug costs per patient per year.

CIMZIA FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Cimzia in axial spondyloarthritis, by country, over 2016–25.

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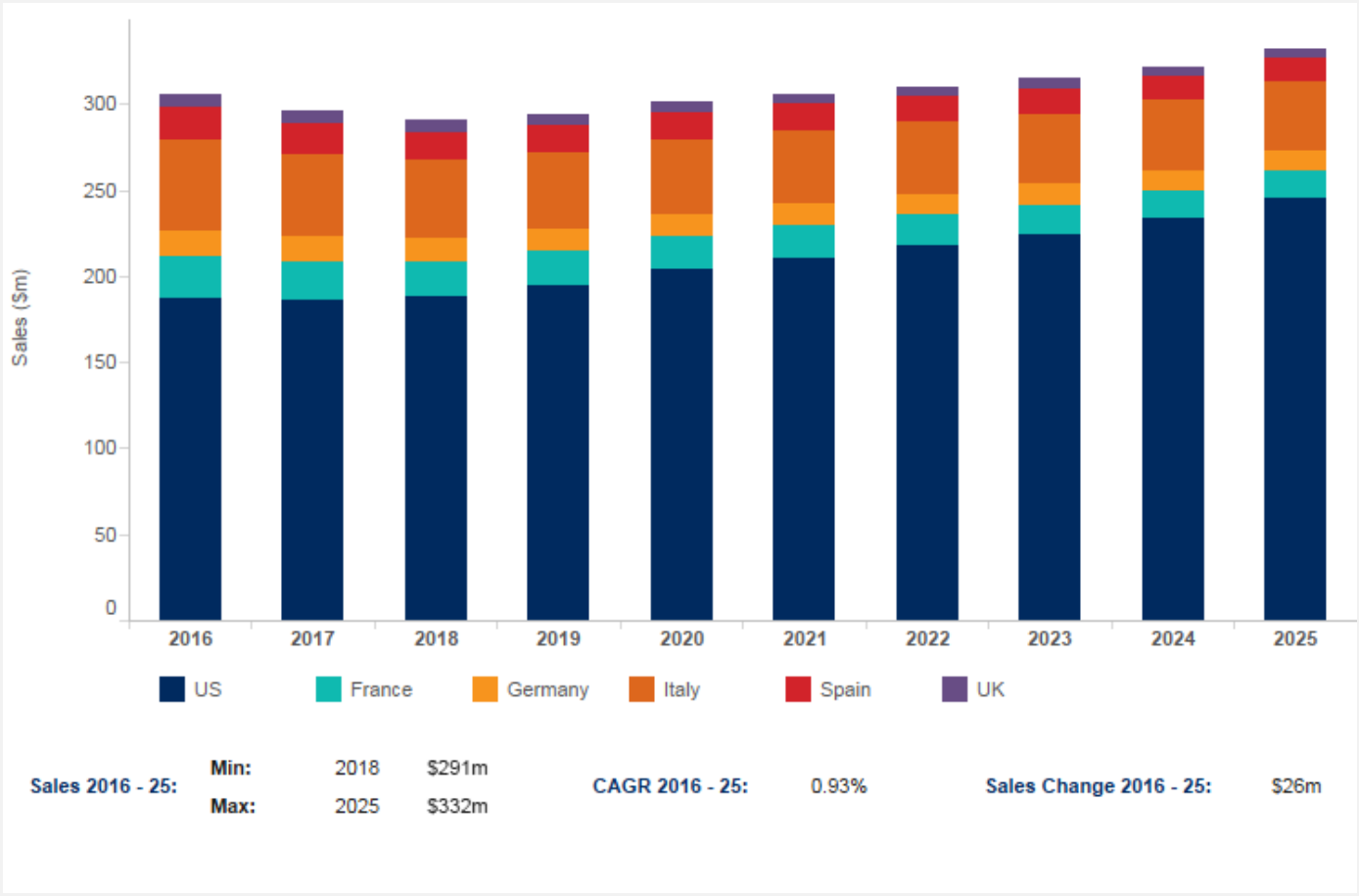
Figure 14: **Cimzia sales for axial spondyloarthritis across the US and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 11: **Cimzia sales for axial spondyloarthritis across the US and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	186.9	186.6	188.4	195.1	203.7	211.0	217.8	224.7	233.6	245.1
France	24.9	21.9	20.4	19.7	19.1	18.4	17.7	16.9	16.4	16.0
Germany	14.6	14.5	13.5	13.0	12.8	12.6	12.3	12.0	11.8	11.7
Italy	52.8	48.3	45.6	44.5	43.8	42.9	41.9	40.9	40.2	39.9
Spain	18.8	17.1	16.0	15.6	15.4	15.0	14.7	14.3	14.1	14.0
UK	7.9	7.6	7.0	6.6	6.3	6.2	6.0	5.9	5.8	5.8
Grand total	305.9	295.9	290.9	294.4	301.1	306.0	310.4	314.7	322.0	332.4

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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Cosentyx : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Cosentyx (secukinumab; Novartis), the first-to-market interleukin (IL)-17A inhibitor, has seen strong uptake since its launch in axial spondyloarthritis (axSpA) due to a favorable efficacy and safety profile. Cosentyx is backed by clinical data showing long-term inhibition of radiographic progression and spinal changes in axSpA patients. Unlike the longstanding anti-tumor necrosis factor (TNF) biologics, Cosentyx does not carry a black box warning of increased risk of malignancy. Novartis has initiated a head-to-head study of Cosentyx versus adalimumab biosimilar (SURPASS trial), aiming to directly compete with the anti-TNFs for a place early in the axSpA treatment algorithm. Datamonitor Healthcare anticipates that the increasing availability of positive real-world data for Cosentyx will boost physicians' confidence in the IL-17A inhibitor, further driving its uptake in the foreseeable future.

DRUG OVERVIEW

Cosentyx is a fully human monoclonal antibody which acts by neutralizing IL-17A, a key pro-inflammatory cytokine. It is indicated for the treatment of plaque psoriasis, psoriatic arthritis, and axSpA (EMA, 2017; FDA, 2017).

Table 12: **Cosentyx drug profile**

Molecule	secukinumab
Mechanism of action	Anti-IL-17 MAb
Originator	Novartis
Marketing company	Novartis
Formulation	SC injection
Alternative names	n/a

AS = ankylosing spondylitis; MAb = monoclonal antibody; SC = subcutaneous

Source: Datamonitor Healthcare; Medtrack; Pharmaprojects; Novartis, 2017b

DEVELOPMENT OVERVIEW

Cosentyx gained EU approval for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy, such as non-steroidal anti-inflammatory drugs (NSAIDs), in November 2015 (Novartis, 2015). In the US, Cosentyx was granted approval for the treatment of adults with active AS by the US Food and Drug Administration (FDA) in

January 2016 (Novartis, 2016). Both approvals were based on data from the MEASURE 1 (ClinicalTrials.gov identifier: NCT01358175) and MEASURE 2 (ClinicalTrials.gov identifier: NCT01649375) Phase III clinical trials, which showed that adult patients with active AS treated with Cosentyx demonstrated greater improvements in ASAS20 response compared to placebo at week 16 (Baeten et al., 2015).

PIVOTAL TRIAL DATA

The Phase III studies that supported regulatory approvals for Cosentyx in axSpA are summarized below.

Table 13: **Cosentyx pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Study design	Target patients	Dosing tested and duration	Results	Reference
MEASURE 1 (NCT01358175) (Phase III)	371	Randomized, double-blind, placebo-controlled	Adult patients with moderate to severe AS, who had an inadequate response to NSAIDs or an anti-TNFα therapy	IV infusion of secukinumab 10mg/kg at weeks 0, 2, and 4, followed by SC injection of secukinumab 75mg or 150mg every four weeks starting at week 8; 104 weeks	Achieved ASAS20* response at week 16: Cosentyx 75mg: 60% Cosentyx 150mg: 61% Placebo: 29%	Baeten et al., 2015
MEASURE 2 (NCT01649375) (Phase III)	219	Randomized, double-blind, placebo-controlled	Adult patients with moderate to severe AS, who had an inadequate response to NSAIDs or an anti-TNFα therapy	SC injections of secukinumab 75mg or 150mg at weeks 1, 2, and 3, then every four weeks starting at week 4; 156 weeks	Achieved ASAS20* response at week 16: Cosentyx 75mg: 41% Cosentyx 150mg: 61% Placebo: 28%	Baeten et al., 2015

*ASAS20 response at week 16 (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS20 = Assessment of Spondyloarthritis international Society response criteria 20; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; SC = subcutaneous; TNF = tumor necrosis factor

Source: see above

OTHER LATE-PHASE TRIALS

The table below summarizes other late-phase trials for Cosentyx in axSpA.

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Table 14: **Late-phase trials for Cosentyx in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Primary endpoints/ results	References
MEASURE 3 (NCT02008916) (Phase III)	226	Adult patients with moderate to severe AS with inadequate response to NSAIDs	Randomized, double-blind, placebo-controlled	Arm 1: 10mg/kg Cosentyx IV at weeks 0, 2, and 4 followed by Cosentyx SC 300mg every month; 16 weeks Arm 2: 10mg/kg Cosentyx IV at weeks 0, 2, and 4 followed by Cosentyx SC 150mg every month; 16 weeks Arm 3: Placebo	Proportion of patients achieving ASAS20* response at week 16 Arm 1: 60.5%** Arm 2: 58.1% *** Placebo: 36.8%	Pavelka et al., 2017
NCT02750592 (Phase III)	30	Adult Japanese patients with moderate to severe AS with an inadequate response/failure to respond/intolerance to NSAIDs and have experienced inadequate response to/intolerant to ≥1 anti-TNFα agent	Open-label, single-arm	150mg administered subcutaneously at weeks 1, 2, and 3, and every four weeks starting week 4; 60 weeks	Proportion of patients achieving ASAS40† response at week 16††	Trialtrove

Table 14: **Late-phase trials for Cosentyx in axial spondyloarthritis**

MEASURE 4 (NCT02159053) (Phase III)	350	Adult patients with moderate to severe AS with inadequate response to NSAIDs	Randomized, double-blind, placebo-controlled	Cosentyx SC 150mg at weeks 0, 1, 2, 3, and then every four weeks; Cosentyx SC 150mg once every four weeks; 16 weeks	Proportion of patients achieving ASAS20* response at week 16††	Trialtrove

*ASAS20 response (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

**p<0.01 vs placebo

***p<0.05 vs placebo

†ASAS40 response at week 16 (clinical primary endpoint) is defined as an improvement of ≥40% and ≥2 units on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥40% or 1 NRS unit) in the remaining area.

††Results are yet to be announced.

AS = ankylosing spondylitis; IV = intravenous; NSAIDs = non-steroidal anti-inflammatory drug; SC = subcutaneous

Source: various (see above)

ONGOING LATE-PHASE TRIALS

The table below summarizes ongoing late-phase trials for Cosentyx in axSpA.

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Table 15: **Ongoing late-phase trials for Cosentyx in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing	Primary endpoints	Study start/primary completion date
CAIN457H2315 (NCT02696031) (Phase III)	555	Adult patients with nr-axSpA with inadequate response to ≥2 different NSAIDs and inadequate response to ≤1 TNFα inhibitor	Randomized, double-blind, placebo-controlled	150mg administered subcutaneously at weeks 1, 2, and 3, and every month starting week 4; 52 weeks	Proportion of patients achieving ASAS40* response at week 16; proportion of patients achieving ASAS40 response at week 52	April 2016/April 2019
SURPASS (NCT03259074) (Phase III)	837	Adult patients with moderate to severe AS who have failed therapy with NSAIDS and/or DMARDs, who are biologic-naïve	Randomized, partially blinded	Arm 1: Cosentyx 150mg SC at weeks 1, 2, and 3, and every four weeks starting week 4 Arm 2: Cosentyx 300mg SC at weeks 1, 2, and 3, and every four weeks starting week 4 Arm 3: Biosimilar adalimumab 40mg every other week	Proportion of patients with no radiographic progression measured by mSASSS at week 104	January 2018/November 2021

*ASAS40 response at week 16 (clinical primary endpoint) is defined as an improvement of ≥40% and ≥2 units on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥40% or 1 NRS unit) in the remaining area.

Table 15: **Ongoing late-phase trials for Cosentyx in axial spondyloarthritis**

AS = ankylosing spondylitis; ASAS40 = Assessment of Spondyloarthritis international Society response criteria 40; DMARD = disease-modifying antirheumatic drug; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; nr-axSpA = non-radiographic axial spondyloarthritis; NSAID = non-steroidal anti-inflammatory drug; TNF = tumor necrosis factor

Source: Trialtrove; ClinicalTrials.gov

SWOT ANALYSIS

Figure 15: **Cosentyx for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Novel mechanism of action (IL-17A inhibitor) • Favorable long-term safety and efficacy profile • No black box warning for increased risk of malignancy, unlike anti-TNF biologics • Rheumatologists indicate a positive outlook for Cosentyx in axSpA • Novartis's resources and financial backing	• Novartis lacks market experience in immunology • Not currently approved in Japan • No current recommendation by ACR for use of Cosentyx in adult patients with axSpA • Updated EULAR guidelines recommend use of Cosentyx after failure of anti-TNF biologics • Not currently approved for use in patients with nr-axSpA
Opportunities	**Threats**
• Capitalize on first-in-class status in axSpA • Promote for patients refractory to TNF inhibition, and/or patients with a history of malignancy • Potential for indication expansion for nr-axSpA based upon results from CAIN457H2315 Phase III study • Potential for future filing in Japan • Increasing prevalence of disease across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) • Data from the SURPASS study could encourage uptake earlier in the treatment algorithm, should it demonstrate superiority to adalimumab • Cosentyx can compete with TNF inhibitors for first-line biologic status based on NICE 2016 guidelines, which recommend use of Cosentyx when treatment with NSAIDs or TNF inhibitors has failed or is not suitable • Patent protection until 2027 (US) and 2025 (EU)	• Physician and patient familiarity and experience with well-established anti-TNF inhibitors • Increasing availability of biosimilars of the leading anti-TNFs will intensify pricing competition • High cost may be prohibitive for the drug's uptake in TNF-naïve patients • Taltz (ixekizumab) is undergoing Phase III trials

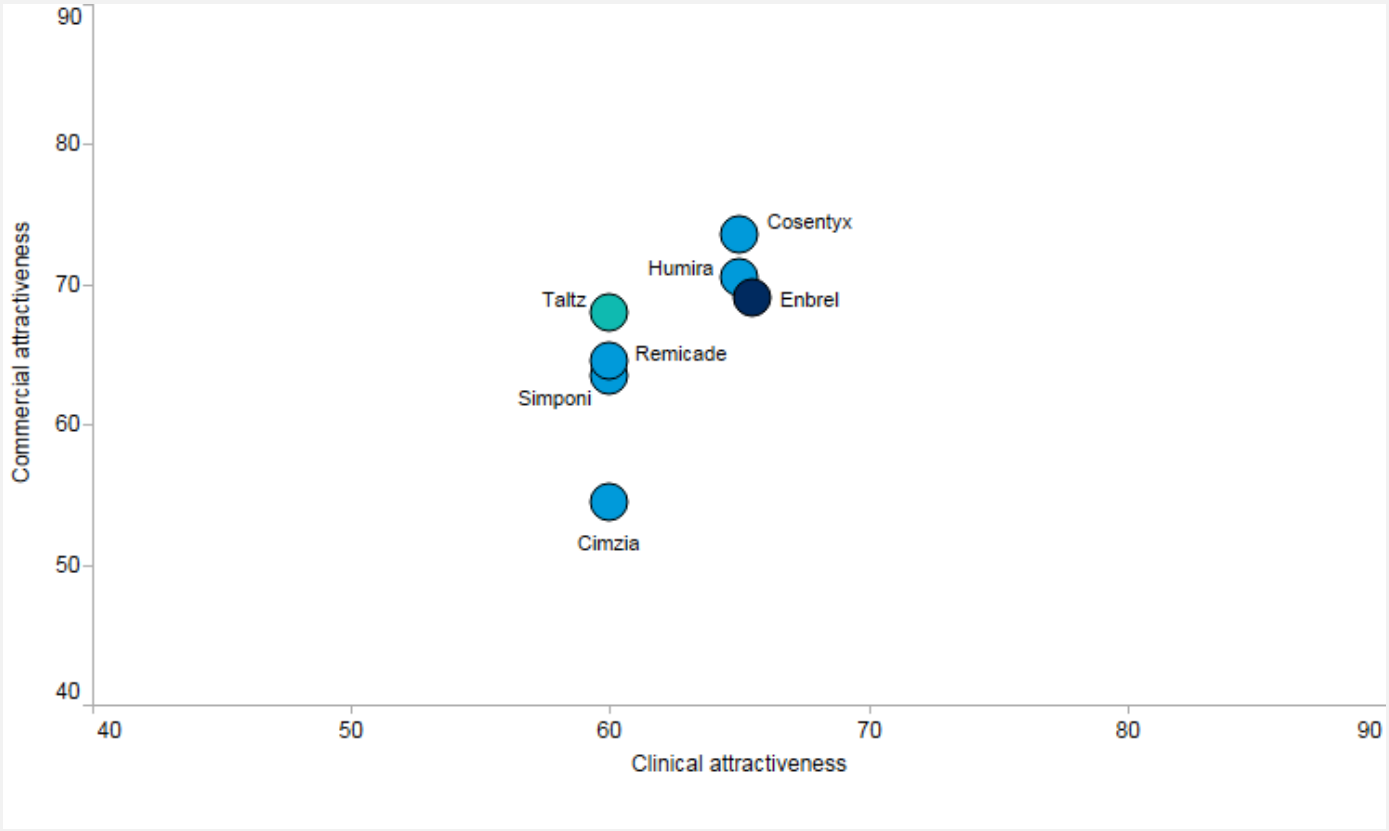
ACR = American College of Rheumatology; axSpA = axial spondyloarthritis; FDA = US Food and Drug Administration; IL = interleukin; NICE = National Institute for Health and Care Excellence; nr-axSpA = non-radiographic axial spondyloarthritis; NSAID = non-steroidal anti-inflammatory drug; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

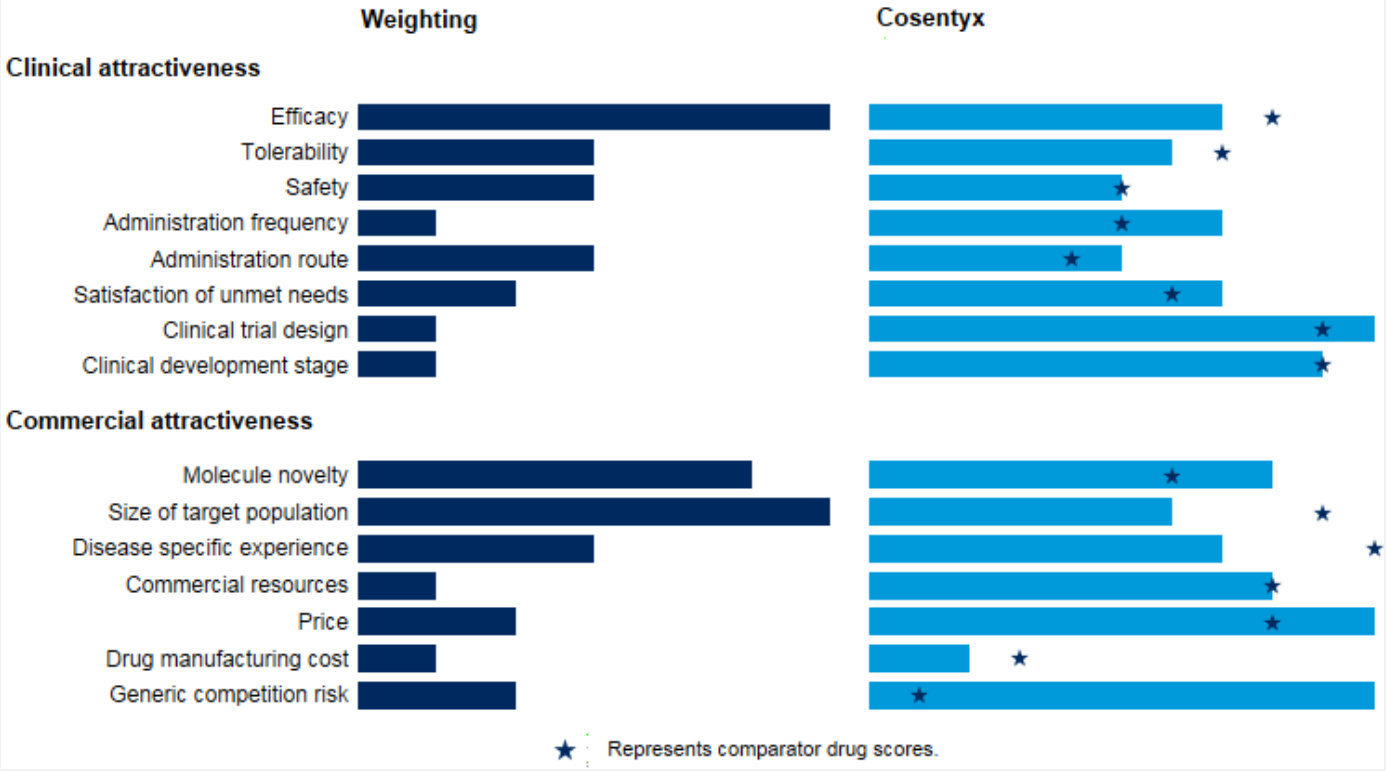
The figures below depict Datamonitor Healthcare's assessment of Cosentyx's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel (etanercept; Amgen/Pfizer/Takeda) and all of the other key marketed and pipeline drugs profiled.

Figure 16: **Datamonitor Healthcare's drug assessment summary of Cosentyx in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 17: **Datamonitor Healthcare's drug assessment summary of Cosentyx in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Cosentyx for axial spondyloarthritis:

REGULATORY

- Cosentyx was approved for the treatment of active AS in November 2015 by the European Medicines Agency; this was followed by FDA approval in January 2016 (Novartis, 2015; Novartis, 2016). Cosentyx launched in the US and five major EU markets (France, Germany, Italy, Spain, and the UK) in Q1 2016 following the conclusion of reimbursement decisions. Cosentyx's approval was based on positive results from the MEASURE 1 and MEASURE 2 (ClinicalTrials.gov identifiers: NCT01358175, NCT01649375) Phase III clinical trials.

- Cosentyx is currently undergoing a Phase III clinical trial evaluating its efficacy and safety in Japanese patients with active AS despite current or previous use of non-steroidal anti-inflammatory drugs and/or anti-TNF therapy (ClinicalTrials.gov identifier: NCT02750592). The data are expected to be used to support the registration of Cosentyx in Japan for the treatment of active AS. The estimated primary completion date for the clinical trial was Q3 2017, with Novartis expected to file for Japanese regulatory approval in the first half of 2018. Assuming a positive decision from regulators a year later, Datamonitor Healthcare anticipates launch in Q1 2019. The launch timings are based on historical development and launch timelines in autoimmune indications.

- Novartis has indicated that it plans to seek approval of Cosentyx for the treatment of nr-axSpA in 2019 (Novartis, 2017c). Novartis's supplemental Biologics License Application will likely be supported by data from the Phase III CAIN457H2315 study (ClinicalTrials.gov identifier: NCT02696031), which is evaluating the clinical efficacy, safety, and tolerability of Cosentyx in patients with nr-axSpA. The study includes sites in the US, Japan, and EU. Assuming this study generates positive data, Datamonitor Healthcare anticipates Novartis will receive label expansion approval from the US, Japanese, and EU regulators by Q4 2019.

COMPETITION

- Cosentyx has seen strong uptake since its launch in axSpA due to its favorable safety and efficacy profile, as well as its first-in-class status. Key opinion leaders highlight that Cosentyx is currently prescribed for patients following the failure of at least one TNF inhibitor, although this is likely to change in the future as rheumatologists gain more experience with the IL-17A inhibitor.

"We [...] start with TNF inhibitors when we decide to use a biologic. In the case of inadequate response to the first biologic, so the first TNF inhibitor, we have the choice between a second TNF or secukinumab, which is the only one that is launched currently in spondyloarthritis, which is an anti-IL17. Especially when we have primary failure with an anti-TNF, we prefer an anti-IL17, and in case of secondary failure, that means patients that have an initial response to the first TNF or who flare after a while, we then frequently try a second TNF before moving to Cosentyx."

Anonymous key opinion leader

- With the increasing availability of long-term data and post-marketing studies, Datamonitor Healthcare forecasts Cosentyx to continue to penetrate the axSpA space, establishing its position as the preferred agent for patients who are refractory to TNF inhibition.

- Datamonitor Healthcare forecasts Cosentyx to compete primarily with the TNF inhibitors Cimzia (certolizumab pegol; UCB/Astellas) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), which gain the majority of their share from patients with active axSpA who have failed or responded inadequately to first-line anti-TNF biologics. Key opinion leaders emphasize that of the two anti-TNF agents, Cimzia is the preferred TNF inhibitor for women of childbearing age and pregnant women, due to data suggesting Cimzia has the lowest level of placental transfer to the fetus in comparison to other anti-TNF agents (Mahadevan et al., 2013). Based on this, Cosentyx is expected to erode a larger patient share from Simponi compared to Cimzia. Datamonitor Healthcare predicts Cosentyx will erode up to 30% of patient share from Cimzia and up to 35% of patient share from Simponi across the US and five major EU markets, with loss of patient share greatest at the second and later lines of therapy.

- Datamonitor Healthcare expects the market leaders Enbrel and Humira (adalimumab; AbbVie/Eisai) to face competition from Cosentyx. Cosentyx is expected to erode up to 5% of patient share from Enbrel and Humira at first and second-lines, and up to 15% of their patient share at the third and later lines of therapy. Enbrel and Humira are likely to retain their status as the preferred biologics at early lines based on physician preference and formulary placement; hence erosion will be greatest at third and later lines of therapy.

"I think it is an excellent drug, seriously. I do not want to sound too enthusiastic, but I think it is bomb – in a good way. [...] I think it is a very powerful drug. So, I think it could erode quite a bit of our, probably even our first-line prescriptions in the near future. I could see that happening. If you see a very tough patient you can tell these guys – you know, tough disease – that would probably be an excellent first choice for them."

EU key opinion leader

- Datamonitor Healthcare expects conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, to face minimal competition from Cosentyx, which is expected to take just up to 5% of patient share from third and later lines of therapy across the US and five major EU markets.

- Datamonitor Healthcare expects Cosentyx's indication expansion for nr-axSpA to result in further competition with Cimzia and Simponi, with Cosentyx forecast to erode up to 5% and 10% patient share from Cimzia and Simponi, respectively, across the US and five major EU markets. Loss of patient share will be greater in second and later lines of therapy.

- Datamonitor Healthcare forecasts that the leading anti-TNF biologics Enbrel and Humira, their respective biosimilars, and the conventional DMARDs methotrexate and sulfasalazine, will face minimal competition from Cosentyx's indication expansion for nr-axSpA. Cosentyx is expected to erode just 5% of their patient share across the US and five major EU markets, from third and later lines of therapy.

- Cosentyx is forecast to face minimal competition from the second-to-market IL-17A inhibitor Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical), which is anticipated to launch in Q4 2019. Datamonitor Healthcare forecasts Taltz to capture up to 13% of Cosentyx's patient share, at second and later lines of therapy. No impact is expected at first line, where physicians will be reluctant to prescribe newer, undifferentiated agents such as Taltz.

- With a limited number of biologics licensed for axSpA in Japan, namely Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) and Humira, off-label use of other TNF inhibitors, including Enbrel and Simponi, is high. Cosentyx's arrival in the Japanese axSpA market is expected to curtail this off-label use, absorbing 25% and 30% of patient share from Enbrel and Simponi, respectively, across all lines of therapy.

- Exclusively in Japan, Datamonitor Healthcare forecasts Cosentyx to directly impact Remicade's patient share, as a result of the scarcity of approved biologics in axSpA. Cosentyx is expected to take up to 5% of second-line and beyond patient share from Remicade and biosimilar infliximab.

- As the leading anti-TNF biologic in Japan, Humira is forecast to face minimal competition from Cosentyx. Cosentyx is expected to take 5% of patient share from Humira at the first and second lines, and 10% of its patient share at the third and later lines of therapy.

DOSING

- Datamonitor Healthcare assumes dosing of 150mg every four weeks as described in Cosentyx's prescribing information (EMA, 2017; FDA, 2017).

PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for each country. Historical prices are used to trend forward prices over the forecast period.

- Please view the accompanying datapack for a full table of drug costs per patient per year.

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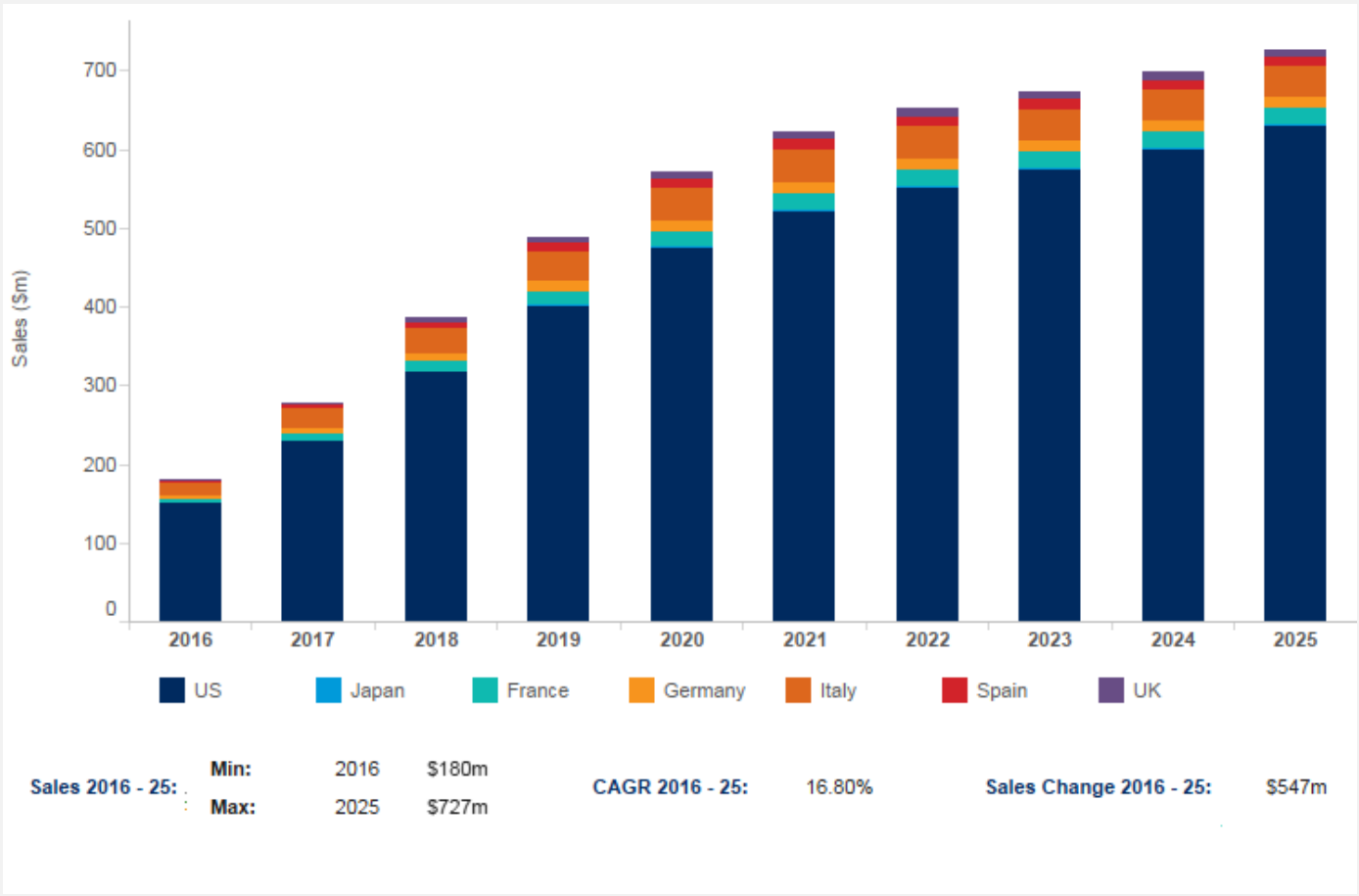
COSENTYX FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Cosentyx in axial spondyloarthritis, by country, over 2016–25.

Figure 18: **Cosentyx sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 16: **Cosentyx sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	149.6	228.2	315.8	401.8	475.5	522.7	552.3	575.3	601.1	631.7
Japan	-	-	-	<0.1	0.1	0.2	0.3	0.4	0.5	0.5
France	6.4	10.5	14.4	17.8	19.9	20.8	20.8	20.7	20.3	19.9
Germany	4.7	7.4	10.6	13.1	14.4	14.6	14.3	14.0	13.8	13.6
Italy	16.3	24.5	31.7	37.1	40.3	41.4	41.1	40.5	39.8	39.4
Spain	1.5	4.7	7.7	10.2	11.6	12.1	12.0	11.7	11.5	11.3
UK	1.2	3.3	5.9	8.4	9.9	10.4	10.5	10.4	10.3	10.3
Grand total	179.6	278.6	386.1	488.5	571.6	622.3	651.4	673.0	697.4	726.8

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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Enbrel : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Due to its first-to-market status, Enbrel (etanercept; Amgen/Pfizer/Takeda) has managed to maintain its positioning as one of two preferred first-line anti-tumor necrosis factor (TNF) biologics for use in axial spondyloarthritis (axSpA). Enbrel faces fierce competition from Humira (adalimumab; AbbVie/Eisai), which has been able to establish its position as the other preferred first-line anti-TNF biologic due to its proven efficacy and safety profile. Although anti-TNF biologics are considered largely comparable in terms of overall efficacy for axSpA treatment, key opinion leaders have highlighted that Enbrel has a slightly improved safety profile compared to other drugs in its class, including Humira. As a result, Datamonitor Healthcare has selected it as the comparator drug for this indication. Despite threats from biosimilars and Novartis's interleukin (IL)-17A inhibitor Cosentyx (secukinumab), Datamonitor Healthcare expects Enbrel to remain among the preferred first-line biologics for axSpA in the short-to-medium term.

DRUG OVERVIEW

Enbrel is a dimeric fusion protein consisting of the extracellular ligand-binding portion of TNF receptor linked to the Fc portion of human immunoglobulin G1. Enbrel binds specifically to circulating TNF and blocks its interaction with cell surface TNF receptors, thereby retarding TNF-mediated inflammation in autoimmune diseases. It is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system.

Enbrel is approved for use in several autoimmune indications, namely rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, and axSpA (EMA, 2017; FDA, 2017).

Table 17: **Enbrel drug profile**

Molecule	etanercept
Mechanism of action	TNF inhibitor
Originator	Amgen
Marketing company	Amgen (US); Pfizer (US, EU); Takeda (Japan)
Formulation	SC injection
Alternative names	n/a

SC = subcutaneous; TNF = tumor necrosis factor

Source: Source: Datamonitor Healthcare; Pharmaprojects

DEVELOPMENT OVERVIEW

Enbrel first gained US approval for the treatment of adult patients with active ankylosing spondylitis (AS) in July 2003 (Amgen, 2003). Within the EU, Enbrel was first granted approval in January 2004 for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy (EMA, 2004). Both approvals were based on data from a single Phase III study (ClinicalTrials.gov identifier: NCT00421915), which showed that a significant percentage of patients with active AS treated with Enbrel achieved the ASAS20 response over 24 weeks in comparison to placebo (Davis et al., 2003).

In July 2014, the European Medicines Agency (EMA) expanded Enbrel's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to NSAIDs, based on clinical data from the EMBARK Phase III trial (ClinicalTrials.gov identifier: NCT01258738) (EMA, 2014).

PIVOTAL TRIAL DATA

The Phase III studies that have supported approvals of Enbrel in axSpA are summarized below.

Table 18: **Enbrel pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
NCT00421915 (Phase III)	277	Patients with moderate to severe active AS	Randomized, double-blind, placebo-controlled	25mg twice weekly; 24 weeks	Achieved ASAS20* at week 12: Etanercept: 59% Placebo: 28% Achieved ASAS20 at week 24: Etanercept: 57% Placebo: 22%	Davis et al., 2003
EMBARK (NCT01258738) (Phase III)	215	Adult patients with active nr-axSpA that had not responded sufficiently to NSAIDs	Randomized, double-blind, placebo-controlled	50mg per week with continued background NSAID treatment; 12 weeks. After 12 weeks, open-label period, 50mg per week with continued background NSAID treatment; 92 weeks	Achieved ASAS40 at week 12: Etanercept: 32% Placebo: 16%	Dougados et al., 2014

*ASAS20 response at week 12 (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

Table 18: **Enbrel pivotal trial data in axial spondyloarthritis**

AS = ankylosing spondylitis; ASAS20/40 = Assessment of SpondyloArthritis international Society response criteria 20/40; nr-axSpA = non-radiographic axial spondyloarthritis, NSAID = non-steroidal anti-inflammatory drug

Source: Source: various (see above)

OTHER LATE-PHASE TRIAL DATA

The table below provides an overview of Enbrel's Phase IV ASCEND study in axSpA.

Table 19: **Enbrel late-phase trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
ASCEND (NCT00247962) (Phase IV)	566	Adult patients with active AS who have failed one or more NSAIDs taken for at least three months	Randomized, double-blind	Etanercept 50mg once weekly or sulfasalazine 3g daily; 16 weeks	Achieved ASAS20 at week 16: Etanercept: 75.9% Sulfasalazine: 52.9%	Braun et al., 2011

AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis international Society response criteria 20; NSAID = non-steroidal anti-inflammatory drug

Source: Source: see above

SWOT ANALYSIS

Figure 19: **Enbrel for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• First-to-market anti-TNF for AS • Recommended by NICE for AS and nr-axSpA • Better safety profile than its anti-TNF competitors • Preferred first-line anti-TNF agent for many physicians • Experienced marketing partnership between Pfizer and Amgen • Approved in EU for patients with nr-axSpA • Once-weekly dosing considered to be an advantage by physicians	• Black box warning for serious infections and malignancies • ACR guidelines recommend treatment with infliximab (Remicade/biosimilars) or Humira for patients with IBD or frequently recurrent uveitis instead of Enbrel • Not approved in Japan • Enbrel shares first-line biologic status with Humira
Opportunities	**Threats**
• Possible US patent protection through to 2029 • Could file for indication expansion for nr-axSpA in US on basis of EMBARK Phase III clinical trial • Potential for future filing in Japan • Increasing prevalence of disease across US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK)	• Sandoz's etanercept biosimilar Erelzi was approved by the FDA in August 2016, and Biogen's etanercept biosimilar Benepali launched in the EU in March 2016 • Availability of infliximab biosimilars in the US, Japan, and EU will intensify pricing competition • Adalimumab biosimilars are expected to launch from 2018 in Europe, and from 2023 in the US • Increasing availability of real-world data for Cosentyx (secukinumab)

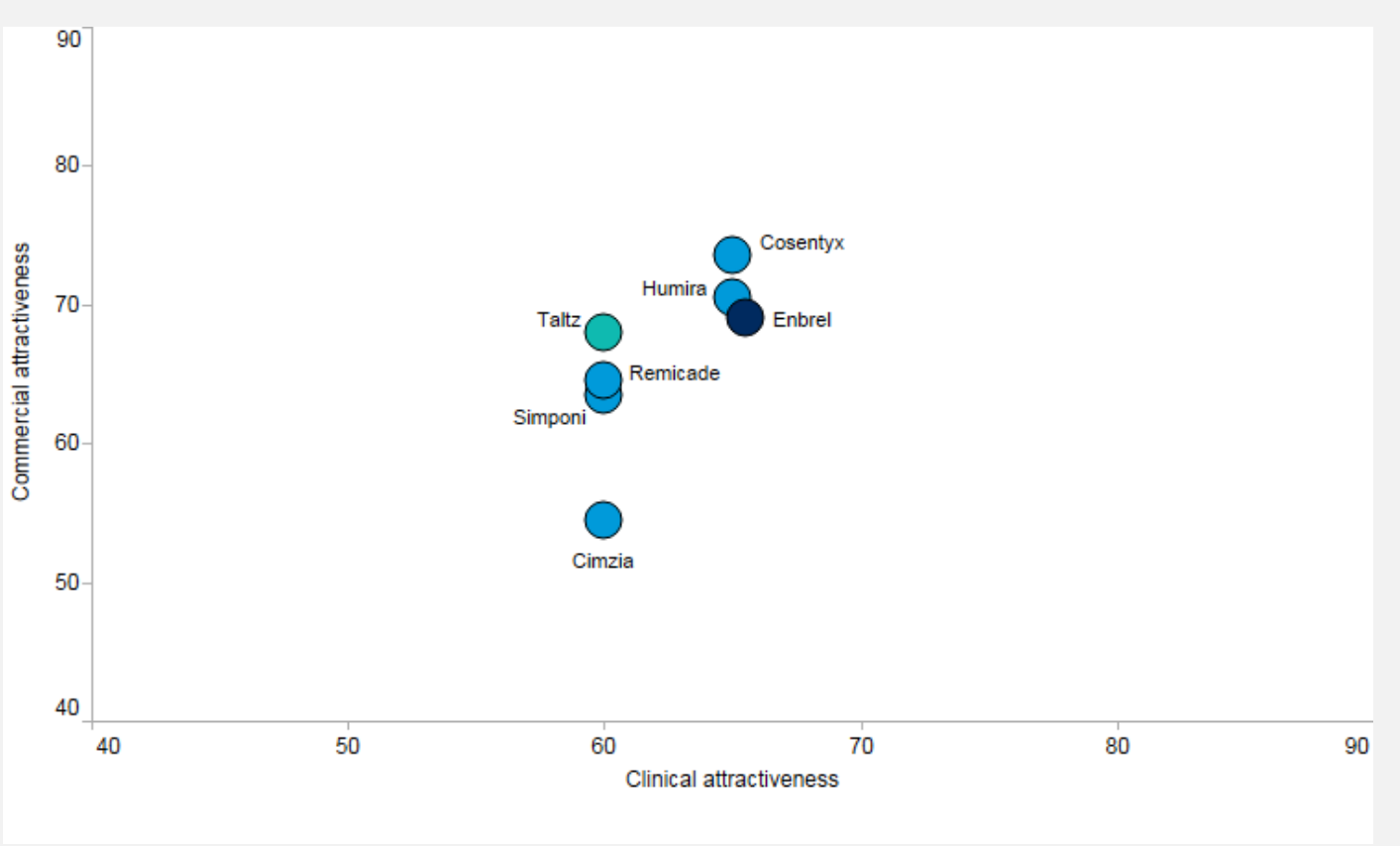
ACR = American College of Rheumatology; AS = ankylosing spondylitis; FDA = US Food and Drug Administration; IBD = inflammatory bowel disease; NICE = National Institute for Health and Care Excellence; nr-axSpA = non-radiographic axial spondyloarthritis; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

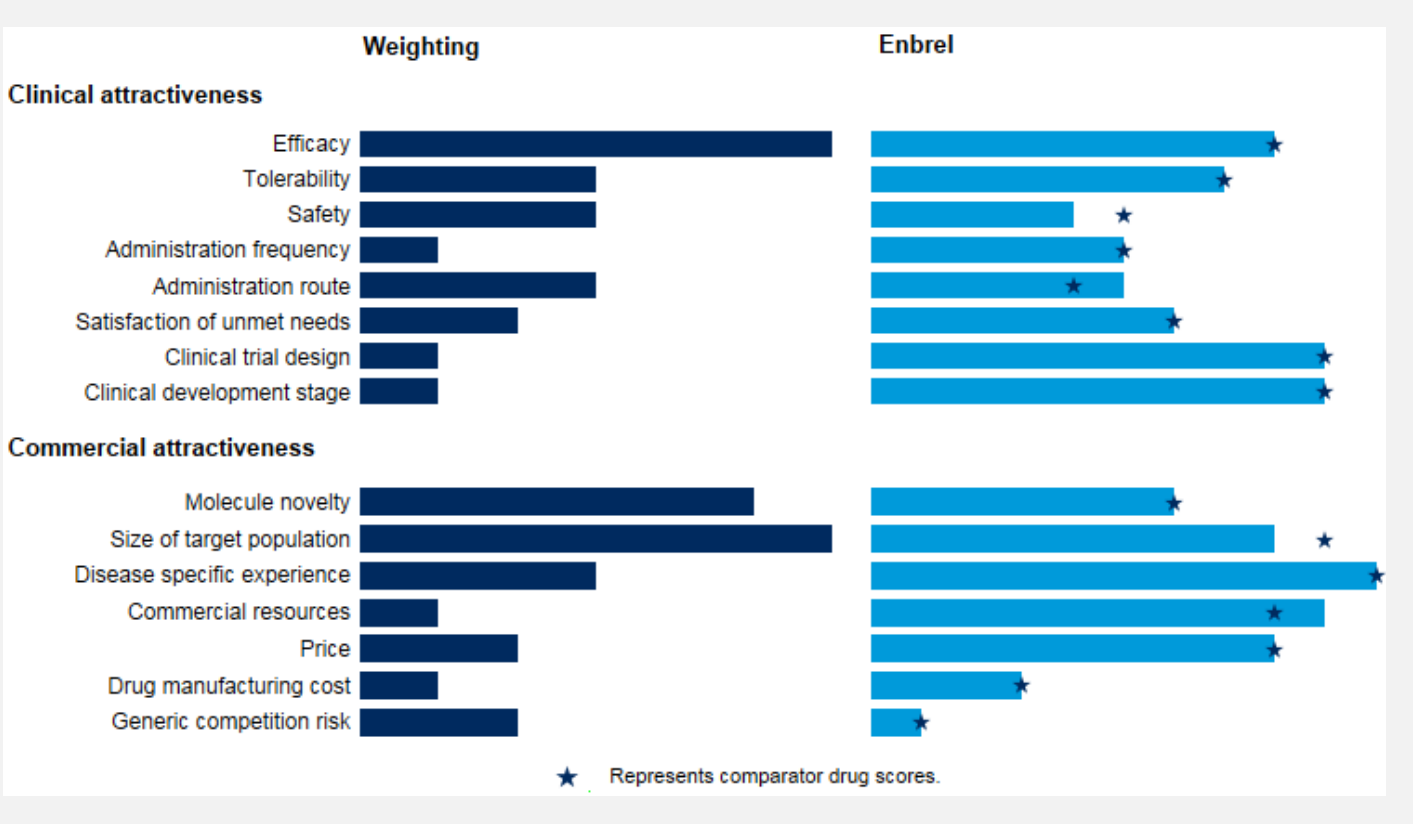
The figures below depict Datamonitor Healthcare's assessment of Enbrel's clinical and commercial attractiveness as a therapy for axSpA in relation to other marketed and pipeline therapies. Datamonitor Healthcare has assigned Enbrel as the comparator therapy for axSpA.

Figure 20: **Datamonitor Healthcare's drug assessment summary of Enbrel in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 21: **Datamonitor Healthcare's drug assessment summary of Enbrel in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Enbrel for axial spondyloarthritis:

REGULATORY

- Enbrel gained US approval for the treatment of adult patients with active AS in July 2003 (Amgen, 2003).
- In the EU, Enbrel was first granted approval in January 2004 for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy (EMA, 2004).
- In July 2014, the EMA expanded Enbrel's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to NSAIDs (EMA, 2014).
- Datamonitor Healthcare does not forecast Enbrel to launch in Japan as no evidence of the drug's clinical development in Japanese axSpA patients has been found.

COMPETITION

- Datamonitor Healthcare does not assume a launch for biosimilar etanercept in the US at this time. In August 2016, the US Food and Drug Administration (FDA) approved Sandoz's biosimilar etanercept, Erelzi/GP2015, for all of Enbrel's indications (FDA, 2016; Novartis, 2016). However, the launch of biosimilar etanercept in the US is dependent on successful litigation relating to multiple patents held by Amgen for Enbrel, with expiry dates of 2028 and 2029 (United States Securities and Exchange Commission, 2015). Datamonitor Healthcare will provide a forecast for Enbrel which includes US biosimilar etanercept competition once there is greater clarity regarding the success of intellectual property challenges against Enbrel.

- In January 2016, the first biosimilar etanercept, Benepali (Biogen/Merck & Co/Samsung Bioepis), was approved by the EMA. Benepali launched in the UK in February 2016, and in France, Germany, Italy, and Spain in April 2016 (Pharmaprojects, 2016; Biogen, 2016). Datamonitor Healthcare forecasts further biosimilar competition from Sandoz's Erelzi/GP2015, which was approved by the EMA in June 2017 (Novartis, 2017).

- Datamonitor Healthcare does not forecast a biosimilar etanercept to launch in Japan for axSpA, as the originator brand is not licensed for this indication in Japan. However, Datamonitor Healthcare's primary research reveals there is high off-label use of Enbrel in Japan (see Datamonitor Healthcare's Treatment: Axial Spondyloarthritis).

- In Europe, Datamonitor Healthcare expects the overall price of biosimilar etanercept to decrease by 30% over the forecast period, as additional biosimilar etanercept entrants launch.

- Over the 10-year forecast period, Datamonitor Healthcare assumes the price of Enbrel will decrease by approximately 30% in Europe, in order to maintain a constant price differential from the average price of biosimilar etanercept.

- In Europe, Datamonitor Healthcare forecasts Enbrel to lose up to 55% of its patient share to biosimilar etanercept. Datamonitor Healthcare expects rheumatologists' initial caution with biosimilars to translate into relatively slow uptake of biosimilar etanercept, with use limited primarily to new patients. In the long term, growing confidence in biosimilars driven by increasing familiarity and post-marketing data, in conjunction with further expected decreases in the cost of biosimilar etanercept, will lead to greater erosion of Enbrel's patient share to biosimilar etanercept.

"I think if the drug were really a biosimilar and done in a way they could save cost [...] that would shake things up, that would make these drugs much more available to people who do not necessarily get it [...] there are some patients who cannot afford their medicine [...] and that just makes me infuriated."

US key opinion leader

- While biosimilar etanercept is not forecast to launch in the US, Datamonitor Healthcare assumes the price of Enbrel will decrease by approximately 10% following the launch of biosimilar adalimumab in Q1 2023, in order to remain competitive in the marketplace.

- In the US, the absence of a biosimilar etanercept entrant over the forecast period will result in Enbrel losing some patient share to biosimilar adalimumab, which is forecast to launch from 2023. Enbrel is expected to lose only up to 10% patient share to biosimilar adalimumab. Similarly, in Japan, biosimilar adalimumab is forecast to erode up to 20% of Enbrel's patient share, which is currently used off-label in axSpA. Greater erosion is not anticipated; Datamonitor Healthcare's primary research indicates that physicians are reluctant to switch patients from a branded biologic to a biosimilar of the non-reference brand.

- The availability of cheaper etanercept biosimilars and Enbrel's price reduction is expected to lessen prescribing of conventional disease-modifying antirheumatic drugs (DMARDs). Discussions with key opinion leaders highlight that, despite a lack of evidence

promoting the use of conventional DMARDs such as methotrexate and sulfasalazine, their use is heavily driven by their lower cost and often mandated by insurance providers.

"Yes, in axial disease I think it [use of traditional DMARDs] may be driven by – just maybe kind of mandated by – either insurance or payers. I think it is a pretty futile effort in most circumstances, and the data supports that. I mean, for axial disease if you have a patient with ankylosing spondylitis, I think you are just wasting your time if you put them on methotrexate or sulfasalazine. I think the payers are just hoping that something is going to happen favorably, or they are just trying to make it harder to – they have been delaying it for three months and they have saved money."

Anonymous key opinion leader

- Methotrexate and sulfasalazine are forecast to lose up to 5% patient share to Enbrel and up to 10% patient share to biosimilar etanercept across the US and five major EU markets (France, Germany, Italy, Spain, and the UK). Loss of patient share will be greatest in second and later lines of therapy.
- In the US and five major EU markets, Enbrel is expected to face competition from first-in-class IL-17A inhibitor Cosentyx. Datamonitor Healthcare forecasts Cosentyx to take up to 15% of patient share from Enbrel. Loss of patient share will be greatest at the third and later lines of therapy. Anti-TNF biologics – either the reference brands or their biosimilar versions – are anticipated to remain the preferred biologic agents at early lines based on their proven efficacy and preferential formulary placement.
- Enbrel is expected to further lose up to 3.5% patient share to Cosentyx in the US and five major EU markets in response to Cosentyx's indication expansion for non-radiographic axSpA, which is expected to be granted in Q4 2019. Loss of patient share will be greatest in the third and later lines of therapy.
- Enbrel is forecast to face minimal competition from the second-to-market IL-17 inhibitor Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical). Taltz is forecast to take up to 5% of Enbrel's patient share across the US and five major EU markets. Loss of patient share will be greatest in the third and later lines of therapy.
- Once approved, Cosentyx and Taltz are expected to curtail the off-label use of Enbrel in Japan, and will have a stronger impact on Enbrel's patient share in Japan compared to the other markets: Cosentyx and Taltz are expected to take up to 25% and up to 15% of Enbrel's patient share, respectively, across all lines of therapy.

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Enbrel for axial spondyloarthritis:

REGULATORY

- Enbrel gained US approval for the treatment of adult patients with active AS in July 2003 (Amgen, 2003).
- In the EU, Enbrel was first granted approval in January 2004 for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy (EMA, 2004).

- In July 2014, the EMA expanded Enbrel's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to NSAIDs (EMA, 2014).

- Datamonitor Healthcare does not forecast Enbrel to launch in Japan as no evidence of the drug's clinical development in Japanese axSpA patients has been found.

COMPETITION

- Datamonitor Healthcare does not assume a launch for biosimilar etanercept in the US at this time. In August 2016, the US Food and Drug Administration (FDA) approved Sandoz's biosimilar etanercept, Erelzi/GP2015, for all of Enbrel's indications (FDA, 2016; Novartis, 2016). However, the launch of biosimilar etanercept in the US is dependent on successful litigation relating to multiple patents held by Amgen for Enbrel, with expiry dates of 2028 and 2029 (United States Securities and Exchange Commission, 2015). Datamonitor Healthcare will provide a forecast for Enbrel which includes US biosimilar etanercept competition once there is greater clarity regarding the success of intellectual property challenges against Enbrel.

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- Datamonitor Healthcare does not forecast a biosimilar etanercept to launch in Japan for axSpA, as the originator brand is not licensed for this indication in Japan. However, Datamonitor Healthcare's primary research reveals there is high off-label use of Enbrel in Japan (see Datamonitor Healthcare's Treatment: Axial Spondyloarthritis).

- In Europe, Datamonitor Healthcare expects the overall price of biosimilar etanercept to decrease by 30% over the forecast period, as additional biosimilar etanercept entrants launch.

- Over the 10-year forecast period, Datamonitor Healthcare assumes the price of Enbrel will decrease by approximately 30% in Europe, in order to maintain a constant price differential from the average price of biosimilar etanercept.

- In Europe, Datamonitor Healthcare forecasts Enbrel to lose up to 55% of its patient share to biosimilar etanercept. Datamonitor Healthcare expects rheumatologists' initial caution with biosimilars to translate into relatively slow uptake of biosimilar etanercept, with use limited primarily to new patients. In the long term, growing confidence in biosimilars driven by increasing familiarity and post-marketing data, in conjunction with further expected decreases in the cost of biosimilar etanercept, will lead to greater erosion of Enbrel's patient share to biosimilar etanercept.

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- The availability of cheaper etanercept biosimilars and Enbrel's price reduction is expected to lessen prescribing of conventional disease-modifying antirheumatic drugs (DMARDs). Discussions with key opinion leaders highlight that, despite a lack of evidence promoting the use of conventional DMARDs such as methotrexate and sulfasalazine, their use is heavily driven by their lower cost and often mandated by insurance providers.

"Yes, in axial disease I think it [use of traditional DMARDs] may be driven by – just maybe kind of mandated by – either insurance or payers. I think it is a pretty futile effort in most circumstances, and the data supports that. I mean, for axial disease if you have a patient with ankylosing spondylitis, I think you are just wasting your time if you put them on methotrexate or sulfasalazine. I think the payers are just hoping that something is going to happen favorably, or they are just trying to make it harder to – they have been delaying it for three months and they have saved money."

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- Enbrel is expected to further lose up to 3.5% patient share to Cosentyx in the US and five major EU markets in response to Cosentyx's indication expansion for non-radiographic axSpA, which is expected to be granted in Q4 2019. Loss of patient share will be greatest in the third and later lines of therapy.

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DOSING

- Datamonitor Healthcare has assumed dosing of 50mg once weekly, as described in Enbrel's prescribing information (EMA, 2017; FDA, 2017).

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PRICING

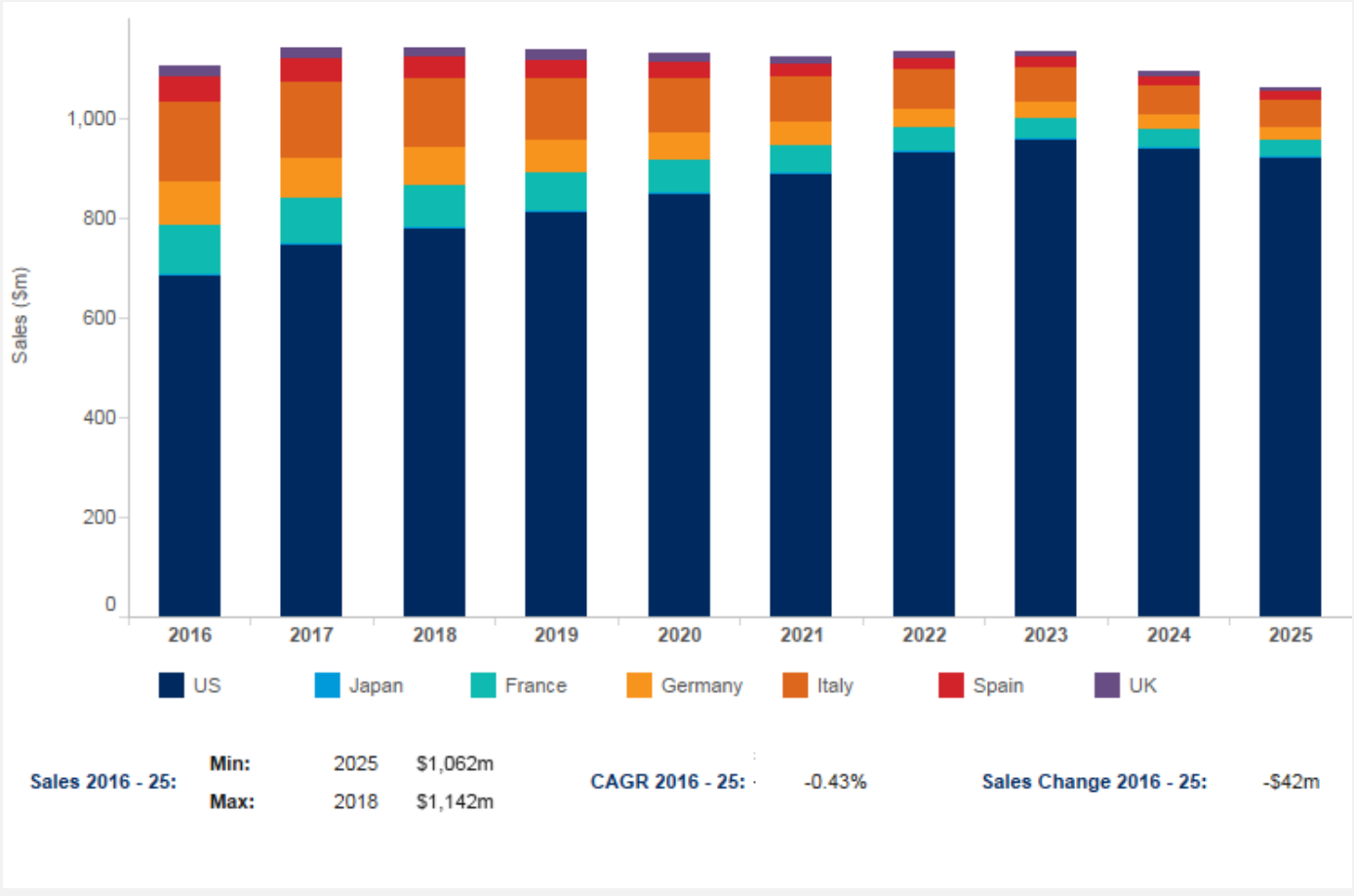
- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for each country. Historical prices are used to trend forward prices over the forecast period. Based on discussions with US payers, Datamonitor Healthcare assumes that Enbrel's net price in the US is 40% lower than the list price due to discounts and rebates.

- Please view the accompanying datapack for a full table of drug costs per patient per year.

ENBREL FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Enbrel in axial spondyloarthritis, by country, over 2016–25.

Figure 22: **Enbrel sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Sales 2016 - 25:	**Min:**	2025	$1,062m	**CAGR 2016 - 25:**	-0.43%	**Sales Change 2016 - 25:**	-$42m
	Max:	2018	$1,142m				

Source: Datamonitor Healthcare

Table 20: **Enbrel sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	685.0	745.5	779.8	813.4	848.9	887.9	931.9	959.3	940.3	920.9
Japan	1.5	1.5	1.5	1.4	1.3	1.1	1.0	0.8	0.7	0.6
France	96.4	91.2	83.9	75.0	65.1	54.9	46.4	40.0	35.5	32.7
Germany	88.0	82.3	74.5	65.3	55.8	46.3	38.5	32.6	28.5	26.1
Italy	159.1	150.0	137.5	122.6	106.8	90.6	77.3	67.1	59.9	55.5
Spain	51.0	48.0	43.9	39.1	34.0	28.8	24.6	21.3	19.0	17.6
UK	23.4	22.1	20.4	18.3	16.0	13.7	11.9	10.4	9.4	8.8
Grand total	1,104.4	1,140.6	1,141.5	1,135.1	1,127.9	1,123.4	1,131.6	1,131.6	1,093.5	1,062.2

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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Available from: https://www.novartis.com/news/media-releases/sandoz-receives-approval-europe-erelzir-biosimilar-etanercept-treat-multiple [Accessed 30 January 2018].

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Humira : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Datamonitor Healthcare's proprietary market research reveals that Humira (adalimumab; AbbVie/Eisai) has managed to successfully penetrate the first-line biologic setting in the axial spondyloarthritis (axSpA) market due to its proven efficacy and safety profile, sharing this position with Enbrel (etanercept; Amgen/Pfizer/Takeda). While Humira will face significant competition from Novartis's interleukin (IL)-17A inhibitor Cosentyx (secukinumab), and from cheaper biosimilar versions of adalimumab over the forecast period, Datamonitor Healthcare expects physician familiarity with the brand and its proven efficacy to protect its market position, with Humira expected to remain among the preferred first-line biologics in the axSpA market for the foreseeable future.

DRUG OVERVIEW

Humira is a recombinant human immunoglobulin G1 monoclonal antibody that acts as a tumor necrosis factor (TNF) inhibitor. In the US and EU, Humira is marketed by AbbVie, while in Japan, Abbott partnered with Eisai in 1999 to commercialize and develop the biologic.

Humira is approved for use in several autoimmune indications, namely rheumatoid arthritis, psoriatic arthritis, axSpA, Behçet's syndrome, ulcerative colitis, juvenile idiopathic arthritis, Crohn's disease, hidradenitis suppurativa, non-infectious uveitis, and plaque psoriasis (EMA, 2017).

Table 21: **Humira drug profile**

Molecule	adalimumab
Mechanism of action	TNF-alpha MAb
Originator	Abbott
Marketing company	AbbVie (US, EU); Eisai (Japan)
Formulation	SC injection
Alternative names	n/a

MAb = monoclonal antibody SC = subcutaneous; TNF = tumor necrosis factor

Source: Datamonitor Healthcare; Pharmaprojects

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DEVELOPMENT OVERVIEW

Humira first gained US approval for the treatment of adult patients with active axSpA in July 2006 (Biomedtracker, 2006). Within the EU, Humira was first granted approval in June 2006 for the treatment of adults with severe, active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy (EMA, 2006). Both approvals were based on data from the ATLAS Phase III study (ClinicalTrials.gov identifier: NCT00085644), which showed that a significant percentage of patients with active axSpA treated with Humira achieved the ASAS20 response over 24 weeks in comparison to placebo (Van der Heijde et al., 2006).

In July 2012, the European Medicines Agency (EMA) expanded Humira's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to or are intolerant to non-steroidal anti-inflammatory drugs, based on data from the ABILITY-1 Phase III trial (Biomedtracker, 2018).

In October 2010, Humira gained Japanese approval for the treatment of adult patients with axSpA who have had an inadequate response to conventional therapy, based on data from a single Phase III trial (ClinicalTrials.gov identifier: NCT00667355).

PIVOTAL TRIAL DATA

The Phase III studies that have supported Humira's approvals in axSpA are summarized below.

Table 22: **Humira pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
ATLAS (NCT00085644) (Phase III)	315	Patients with active AS, who had an inadequate response to ≥1 NSAIDs or in whom ≥1 DMARDs had failed	Randomized, double-blind, placebo-controlled	40mg every other week; 24 weeks. After 24 weeks, open-label period, 40mg every other week; 80 weeks	Achieved ASAS20* at week 12: Adalimumab: 58.2% Placebo: 20.6%	Van der Heijde et al., 2006
JapicCTI-080580 (NCT00667355) (Phase III)	41	Patients with active AS who had an inadequate response to or intolerance to ≥1 NSAIDs	Open-label, single group assignment	40mg every other week; 12 weeks	Achieved ASAS20 response at week 12: Adalimumab: 73.2%	Kobayashi et al., 2012
ABILITY-1 (NCT00939003) (Phase III)	185	Patients with axSpA who had responded inadequately or been intolerant to ≥1 NSAIDs	Randomized, double-blind, placebo-controlled with open-label phase	40mg every other week; 12 weeks. After 12 weeks, open-label period, 40mg every other week; 92 weeks	Achieved ASAS40 response at week 12: Adalimumab: 36% Placebo: 15%	Sieper et al., 2013

*ASAS20 response at week 12 (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of BASDAI questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

Table 22: **Humira pivotal trial data in axial spondyloarthritis**

AS = ankylosing spondylitis; ASAS20/40 = Assessment of SpondyloArthritis international Society response criteria 20/40; axSpA = axial spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DMARD = disease-modifying antirheumatic drug; NSAID = non-steroidal anti-inflammatory drug

Source: Source: various (see above)

OTHER LATE-PHASE TRIAL DATA

The table below provides an overview of Humira's Phase III RHAPSODY study in AS.

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Table 23: **Humira late-phase trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
RHAPSODY (NCT00478660) (Phase III)	1,250 (924 patients who were TNF antagonist-naïve, and 326 patients who had received prior anti-TNF therapy)	Adult patients with active AS with failure of ≥1 NSAIDs and failure of ≥1 TNF antagonists (etanercept and infliximab)	Randomized, open-label, single arm	40mg every other week, in addition to their standard antirheumatic therapies; 12 weeks	Achieved BASDAI 50* response at week 12: 40.8% of patients with AS who had received prior anti-TNF therapy and 63.0% of patients who were TNF antagonist-naïve. Achieved ASAS40** at week 12: 53.7% of all patients	Rudwaleit et al., 2009; Rudwaleit et al., 2010

*BASDAI 50 response at week 12 (clinical primary endpoint) defined as an improvement of ≥50% in Bath Ankylosing Spondylitis Disease Activity Index. The BASDAI is a self-assessment tool to determine disease activity using a scale of 0–10 (0 = none and 10 = very severe) to measure fatigue, spinal pain, joint pain, enthesitis, morning stiffness duration, and morning stiffness severity. The final BASDAI score (0–10) provides an assessment of the effectiveness of a particular drug therapy. Scores of 4 or greater suggest suboptimal control of disease, with the patient considered a good candidate for a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies.

**ASAS40 response at week 12 (clinical primary endpoint) defined as an improvement of ≥40% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of BASDAI questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS40 = Assessment of SpondyloArthritis international Society response criteria 40; NSAID = non-steroidal anti-inflammatory drug; TNF = tumor necrosis factor

Source: various (see above)

SWOT ANALYSIS

Figure 23: **Humira for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Successfully penetrated first-line biologic setting with strong efficacy and safety profile • Greater efficacy than Enbrel (etanercept) in patients with IBD or frequently recurrent uveitis • Strong marketing capabilities from AbbVie and Eisai • Excellent reputation among general practitioners and patients • Approved in Japan for adult patients with active AS • Approved in EU for patients with nr-axSpA	• Black box warning for serious infections and malignancies • Slightly inferior safety profile compared to Enbrel • FDA voted against expanding current indication for ax-SpA to include nr-axSpA due to inadequacies in clinical trial design
Opportunities	**Threats**
• Capitalize on increasing use as first-line treatment in AS • Promote uptake in Japan where anti-TNF biologics Cimzia (certolizumab pegol), Enbrel, and Simponi (golimumab) are not approved • Recommended by NICE for AS and nr-axSpA • ACR guidelines recommend treatment with infliximab (Remicade/biosimilars) or Humira for patients with IBD or frequently recurrent uveitis instead of Enbrel • Increasing prevalence of disease across US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK)	• Anticipated launch of adalimumab biosimilars in the EU in 2018 and the US in 2023 • Infliximab biosimilars are available in all major markets • First etanercept biosimilar launched in EU in Q1 2016 • Increasing availability of real-world data for Cosentyx (secukinumab) • Competition in Japan from Remicade

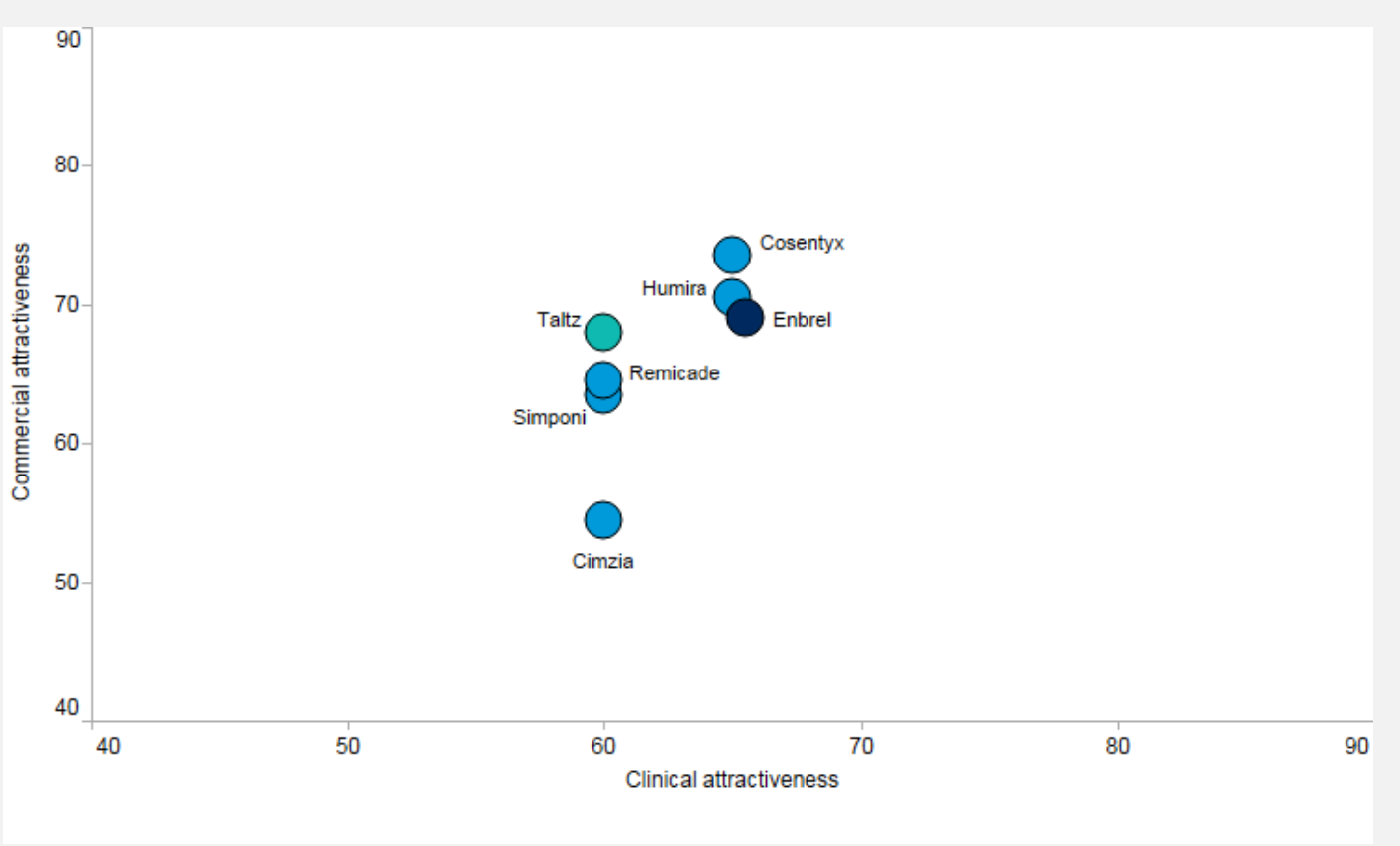
ACR = American College of Rheumatology; AS = ankylosing spondylitis; axSpA = axial spondyloarthritis; FDA = US Food and Drug Administration; IBD = inflammatory bowel disease; NICE = National Institute for Health and Care Excellence; nr-axSpA = non-radiographic axial spondyloarthritis; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

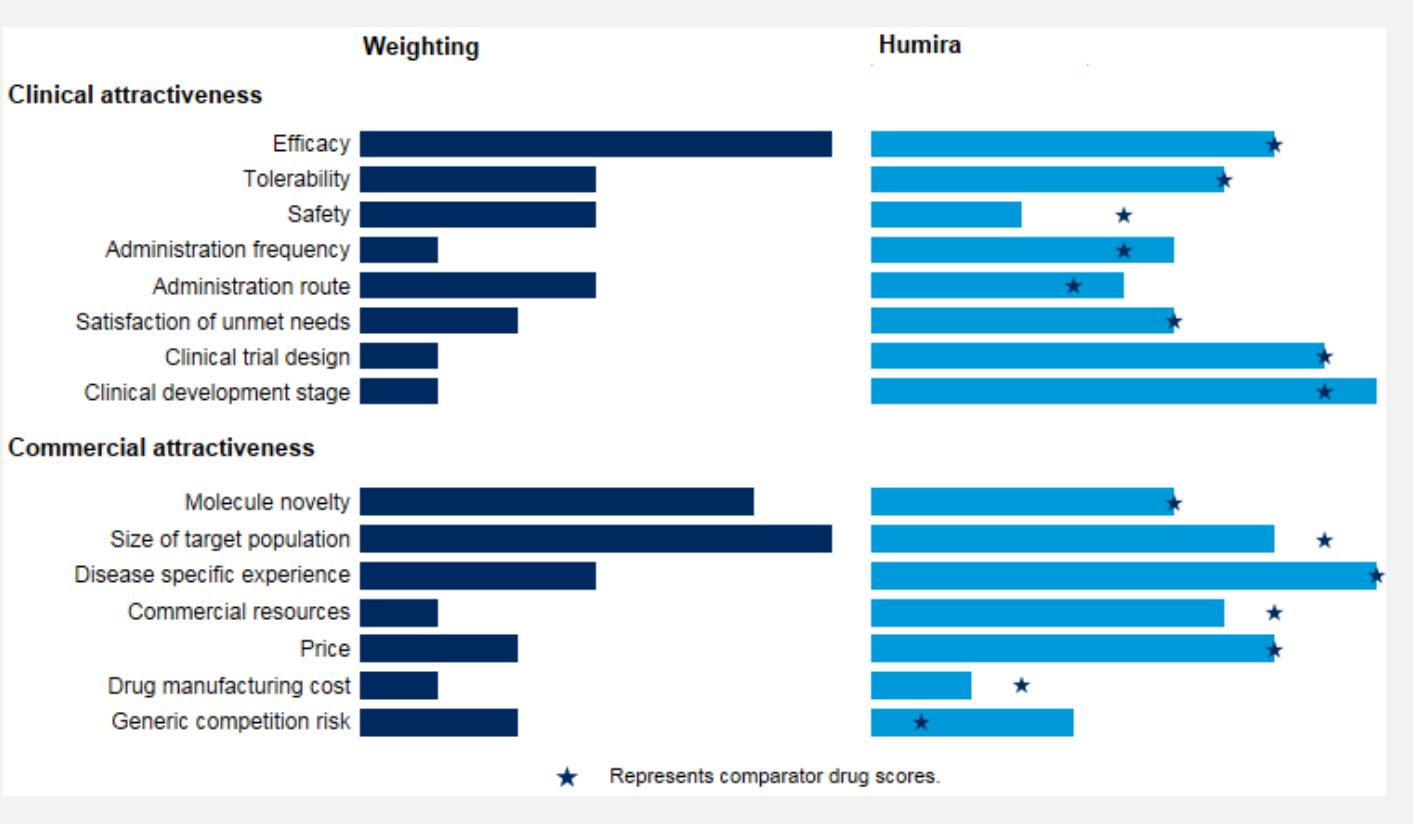
The figures below depict Datamonitor Healthcare's assessment of Humira's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel and all of the other key marketed and pipeline drugs profiled.

Figure 24: **Datamonitor Healthcare's drug assessment summary of Humira in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 25: **Datamonitor Healthcare's drug assessment summary of Humira in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Humira for axial spondyloarthritis:

REGULATORY

- Humira gained US approval for the treatment of adult patients with active axSpA in July 2006 (Biomedtracker, 2018).
- Humira was granted approval in the EU in June 2006 for the treatment of adults with severe, active AS who have had an inadequate response to conventional therapy (EMA, 2006).
- In July 2012, the EMA expanded Humira's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to or are intolerant to non-steroidal anti-inflammatory drugs (Biomedtracker, 2018).

COMPETITION

- Datamonitor Healthcare expects biosimilar adalimumab to be the first biosimilar of a subcutaneous anti-TNF biologic to enter

the US axSpA market, in Q1 2023. In September 2016, the US Food and Drug Administration (FDA) approved Amgen's biosimilar adalimumab, Amjevita, for all of Humira's indications excluding those for which Humira has outstanding orphan exclusivity (FDA, 2016). Further competition comes from Boehringer Ingelheim's biosimilar adalimumab, Cyltezo, which was approved by the FDA in August 2017 (FDA, 2017b). However, the launch of any adalimumab biosimilar in the US is dependent on successful litigation relating to multiple patents held by AbbVie for Humira. In September 2017, AbbVie announced a global resolution of all intellectual property-related litigation with Amgen, which will delay the launch of Amjevita in the US until January 2023 (AbbVie, 2017). While this does not preclude other biosimilar developers from undertaking an at-risk launch, successfully challenging patents held by AbbVie, or designing around patents, and using their own patent estate to support a biosimilar launch, Datamonitor Healthcare believes that a biosimilar adalimumab launch in the US is unlikely prior to 2023.

- Biosimilar adalimumab is expected to reach the Japanese axSpA market in Q1 2020, following the expiry of key patent protection (Medtrack, 2017).

- Datamonitor Healthcare forecasts biosimilar adalimumab to enter the EU axSpA market in Q4 2018, following the expiry of residual patent protection in the five major EU markets (France, Germany, Italy, Spain, and the UK) (Medtrack, 2016). Amgen won EMA approval for its biosimilar adalimumab, Amjevita, in March 2017 (Amgen, 2017). Datamonitor Healthcare forecasts further biosimilar competition in Europe from Samsung Bioepis' biosimilar adalimumab candidate, Imraldi/SB5, which was approved by the EMA in August 2017 (Biogen, 2017).

- In the US, Datamonitor Healthcare forecasts biosimilar adalimumab to be priced at 20% below the annual cost of Humira. The first biosimilar approved in the US, Zarxio (filgrastim; Sandoz/Novartis), was priced at a 15% discount to its reference product, Neupogen (filgrastim; Amgen/Kyowa Hakko Kirin/Roche). Datamonitor Healthcare assumes a marginally greater discount for biosimilar adalimumab; this is based on the generally greater competition in autoimmune indications compared to neutropenia and, in particular, the fact that several adalimumab biosimilars are under development in the US (Biomedtracker, 2018).

- In Japan, Datamonitor Healthcare forecasts biosimilar adalimumab to be priced at a 30% discount to the annual cost of Humira, based on Japanese pricing regulations which state that biosimilar therapies will be initially priced at 70% of the reference product's price (The Japan Times, 2015).

- Based on biosimilar pricing policies and trends in Europe, Datamonitor Healthcare forecasts biosimilar adalimumab to be priced up to 25% below the annual cost of Humira in the five major EU markets. In France and Italy, biosimilars are required to launch at a price that is 25–35% and 20% less than the originator drug, respectively. While Germany, Spain, and the UK have free pharmaceutical pricing, biosimilars will need to have a cost advantage over the originator in order to achieve penetration (Foxon et al., 2015).

- Datamonitor Healthcare expects the price of biosimilar adalimumab in all markets to decrease by 30% over the forecast period, as additional biosimilar adalimumab entrants launch.

- Following the launch of biosimilar adalimumab, Datamonitor Healthcare assumes the price of Humira will decrease by approximately 30% across all markets, in order to maintain a constant price differential from the average price of biosimilar adalimumab.

- Datamonitor Healthcare forecasts Humira to lose up to 55% of its patient share to biosimilar adalimumab over the forecast period, across all markets. Datamonitor Healthcare expects rheumatologists' initial caution with biosimilars to translate into relatively slow uptake of biosimilar adalimumab, with use primarily limited to new patients. In the long term, growing confidence in biosimilars driven by increasing familiarity as well as post-marketing data, alongside expected decreases in biosimilar adalimumab's cost, will lead to greater erosion of Humira's patient share to biosimilar adalimumab.

"I think if the drug were really a biosimilar and done in a way they could save cost [...] that would shake things up, that would make these drugs much more available to people who do not necessarily get it [...] there are some patients who cannot afford their medicine [...] and that just makes me infuriated."

US key opinion leader

- The availability of a cheaper adalimumab biosimilars and Humira's anticipated price reduction is expected to lessen prescribing of the conventional disease-modifying antirheumatic drugs (DMARDs) methotrexate and sulfasalazine. Discussions with key opinion leaders highlight that, despite a lack of evidence promoting the use of traditional DMARDs, this is heavily influenced by their lower cost and often mandated by insurance providers.

"Yes, in axial disease I think it [use of traditional DMARDs] may be driven by – just maybe kind of mandated by – either insurance or payers. I think it is a pretty futile effort in most circumstances, and the data supports that, I mean, for axial disease if you have a patient with ankylosing spondylitis, I think you are just wasting your time if you put them on methotrexate or sulfasalazine. I think the payers are just hoping that something is going to happen favorably, or they are just trying to make it harder to – they have been delaying it for three months and they have saved money."

Anonymous key opinion leader

- Conventional DMARDs are forecast to lose up to 5% patient share to Humira and up to 10% patient share to biosimilar adalimumab across the US, Japan, and five major EU markets, with loss of patient share greatest in second and later lines of therapy.

- Humira is forecast to face competition from the first-in-class IL-17A inhibitor Cosentyx. Humira is set to lose up to 15% of its patient share to Cosentyx across all markets. Loss of patient share will be greatest in the third and later lines of therapy. Anti-TNF biologics – either the reference brands or their biosimilar versions – are anticipated to remain the preferred biologic agents at earlier lines based on their proven efficacy and preferential formulary placement.

- Humira is expected to further lose up to 3.5% patient share to Cosentyx in response to Cosentyx's indication expansion for non-radiographic axSpA, which is expected to be granted in Q4 2019. Loss of patient share will be greatest in the third and later lines of therapy.

- Humira is forecast to face minimal competition from the second-to-market IL-17A inhibitor, Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical). Humira is set to lose up to 5% of patient share to Taltz. Loss of patient share will be greatest in the third and later lines of therapy.

DOSING

- Datamonitor Healthcare has assumed dosing of 40mg every other week, as described in Humira's prescribing information (EMA, 2017; FDA, 2017a).

PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for each country. Historical prices are used to trend forward prices over the forecast period. Based on discussions with US payers, Datamonitor Healthcare assumes that

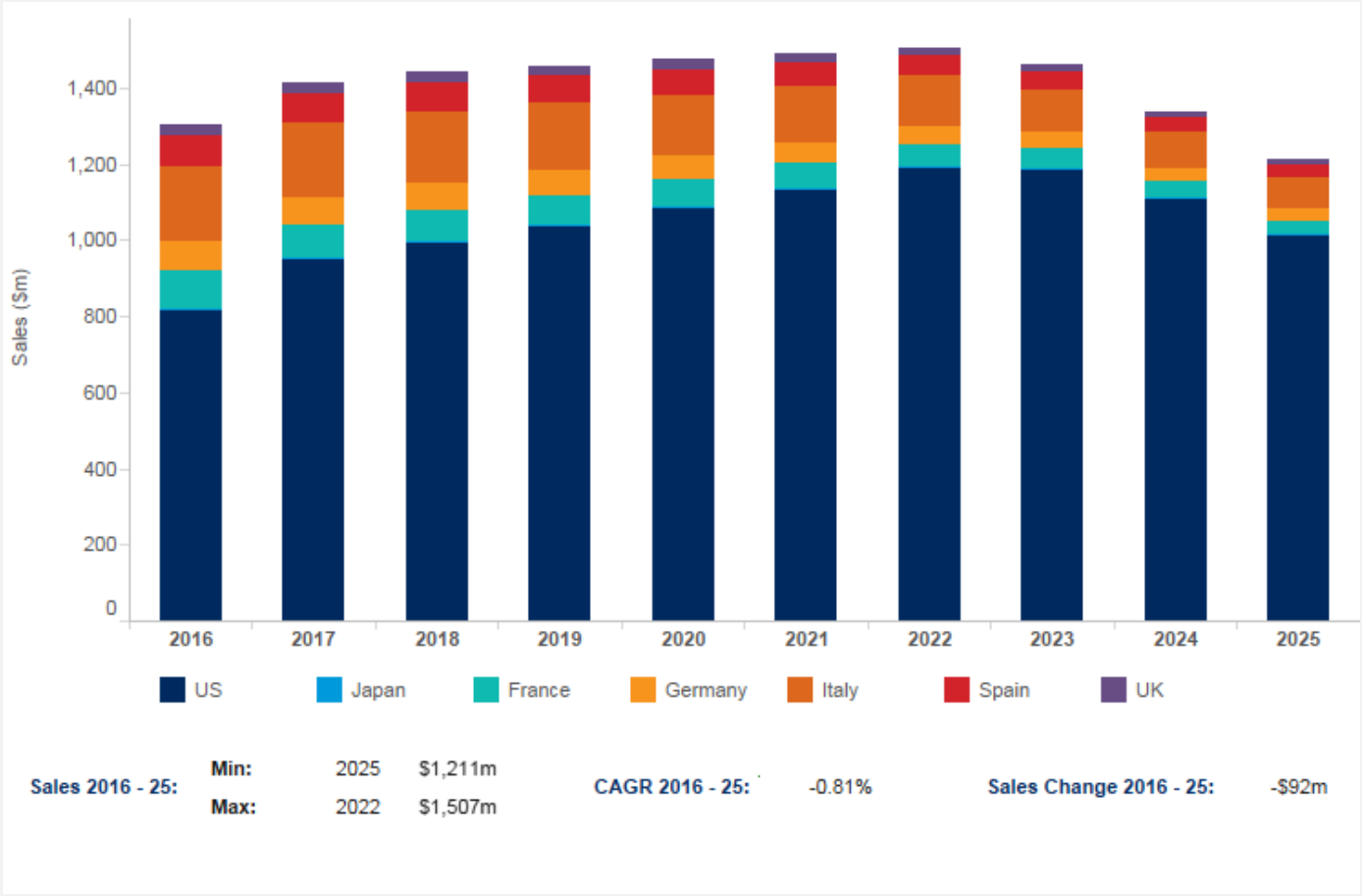
Humira's net price in the US is 40% lower than the list price due to discounts and rebates.

- Please view the accompanying datapack for a full table of drug costs per patient per year.

HUMIRA FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Humira in axial spondyloarthritis, by country, over 2016–25.

Figure 26: **Humira sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 24: **Humira sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	815.7	951.6	995.6	1,038.5	1,084.0	1,133.8	1,190.1	1,187.7	1,109.7	1,014.8
Japan	2.5	2.5	2.4	2.3	2.2	2.0	1.8	1.6	1.3	1.1
France	103.7	84.8	82.7	78.2	72.6	66.0	58.5	50.2	42.2	35.9
Germany	75.4	74.1	71.9	67.2	62.2	56.6	50.3	43.2	36.5	31.1
Italy	197.0	194.3	184.1	173.7	161.6	147.6	131.6	113.6	96.1	82.2
Spain	79.3	78.2	76.0	71.5	66.2	60.2	53.5	46.0	38.8	33.1
UK	30.1	29.8	29.1	27.4	25.5	23.3	20.9	18.1	15.4	13.3
Grand total	1,303.8	1,415.4	1,441.8	1,459.0	1,474.4	1,489.5	1,506.7	1,460.4	1,339.9	1,211.5

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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Published on 18 May 2018

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Published on 18 May 2018

Remicade : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Despite being favored by certain niche patient subgroups, Remicade's (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) intravenous (IV) administration is a major drawback for the brand given that all of the other anti-tumor necrosis factor (TNF) biologics are administered subcutaneously. Furthermore, as a chimeric antibody, Remicade's immunogenicity can lead to patients exhibiting an anti-drug antibody response, translating to blunted efficacy and side effects including susceptibility to infectious diseases, contributing to physicians' preference for competitor anti-TNF biologics. These factors have negatively impacted Remicade's commercial attractiveness and have kept sales lower than for other drugs in its class. With significant competition from infliximab biosimilars, Datamonitor Healthcare expects the use of Remicade in axial spondyloarthritis (axSpA) to decline further in the foreseeable future.

DRUG OVERVIEW

Remicade is a chimeric, humanized monoclonal antibody targeting TNF-alpha, with a long history of use in a number of immune-mediated inflammatory diseases, including Crohn's disease, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), Behçet's syndrome, and ulcerative colitis (EMA, 2017; FDA, 2017a). Remicade has also been granted orphan drug status for Kawasaki disease in Japan (Mitsubishi Tanabe Pharma, 2015).

Table 25: **Remicade drug profile**

Molecule	infliximab
Mechanism of action	Chimeric TNF-alpha MAb
Originator	Janssen Biotech (formerly Centocor Ortho Biotech; a subsidiary of Johnson & Johnson)
Marketing company	Johnson & Johnson (US); Merck & Co (EU, ex-US); Mitsubishi Tanabe (Japan)
Formulation	IV infusion
Alternative names	n/a
IV = intravenous; MAb = monoclonal antibody; TNF = tumor necrosis factor	

Source: Datamonitor Healthcare; Pharmaprojects

DEVELOPMENT OVERVIEW

Remicade gained EU approval in May 2003 for the treatment of adults with severe, active AS who had responded inadequately to conventional therapy (EMA, 2004). The US Food and Drug Administration (FDA) approved Remicade for the treatment of adult patients with active AS in December 2004 (FDA, 2004). Both approvals were based on data from the ASSERT Phase III trial (ClinicalTrials.gov identifier: NCT01128504), which showed that a significant percentage of patients with active AS treated with Remicade achieved the ASAS20 response over 24 weeks in comparison to placebo (Van der Heijde et al., 2005).

In April 2010, Remicade gained Japanese approval for the treatment of adult patients with AS who have not responded sufficiently to conventional treatments (PMDA, 2010).

PIVOTAL TRIAL DATA

The Phase III study that supported approvals of Remicade in axSpA is summarized below.

Table 26: **Remicade pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
ASSERT (NCT01128504) (Phase III)	279	Patients with AS	Randomized, double-blind, placebo-controlled	5mg/kg infliximab infused at weeks 0, 2, 6, 12, and 18; 96 weeks	Achieved ASAS20* at week 24: Infliximab: 61.2% Placebo: 19.2%	Van der Heijde et al., 2005

*ASAS20 response (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis international Society response criteria 20

Source: see above

SWOT ANALYSIS

Figure 27: **Remicade for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Johnson & Johnson/Merck & Co/Mitsubishi Tanabe have strong marketing capabilities and knowledge of multiple autoimmune indications • Approved in Japan for adult patients with active AS • Greater efficacy than Enbrel (etanercept) in patients with IBD or frequently recurrent uveitis	• Black box warning for serious infections and malignancies • Higher cost of treatment for overweight patients • IV route of administration inconvenient for most patients • Development of anti-drug antibodies can lead to blunted efficacy and more side effects
Opportunities	**Threats**
• Minimize biosimilar erosion through exclusive contracts with payers • Promote for subset of patients who favor IV formulation and physician interaction • Recommended by NICE for AS • ACR guidelines recommend treatment with infliximab (Remicade/biosimilars) or Humira (adalimumab) for patients with IBD or frequently recurrent uveitis instead of Enbrel • Capitalize on the increased reimbursement Medicare offers for IV drugs in the US • Increasing prevalence of disease across US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK)	• Infliximab biosimilars are available in all major markets • First etanercept biosimilar launched in EU in Q1 2016 • Anticipated arrival of adalimumab biosimilars in the US and in the EU will intensify pricing competition • Increasing availability of real-world data for Cosentyx (secukinumab) • Threat from Simponi Aria (golimumab), the IV formulation of Simponi, which was approved in the US in October 2017 • Competition in Japan from Humira • NICE recommends infliximab only if treatment is started with least expensive infliximab product, which is likely to be a biosimilar

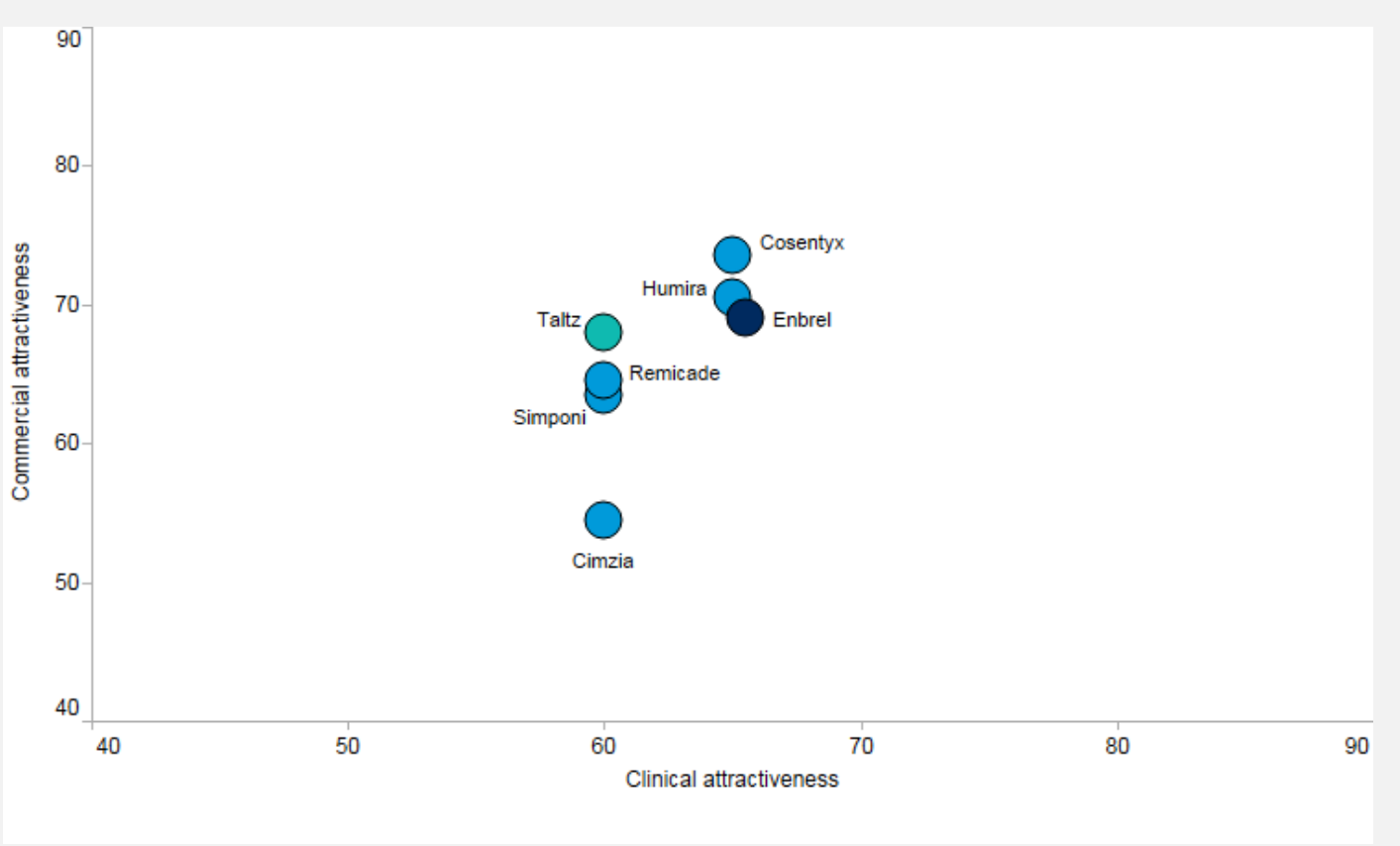
ACR = American College of Rheumatology; AS = ankylosing spondylitis; FDA = US Food and Drug Administration; IBD = inflammatory bowel disease; IV = intravenous; NICE = National Institute for Health and Care Excellence; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

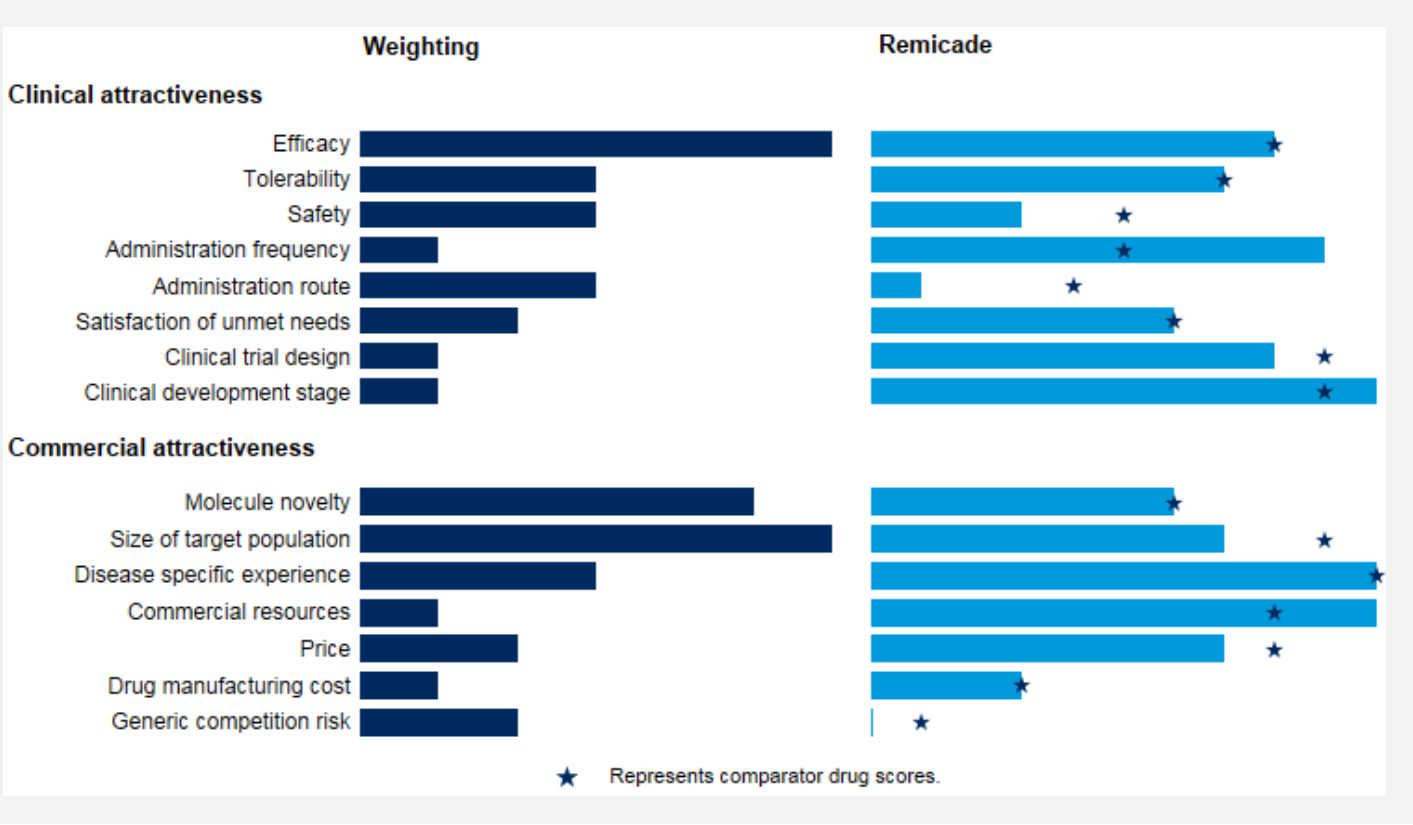
The figures below depict Datamonitor Healthcare's assessment of Remicade's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel (etanercept; Amgen/Pfizer/Takeda) and all of the other key marketed and pipeline drugs profiled.

Figure 28: **Datamonitor Healthcare's drug assessment summary of Remicade in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 29: **Datamonitor Healthcare's drug assessment summary of Remicade in axial spondyloarthritis**



Source: Datamonitor Healthcare

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PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Remicade for axial spondyloarthritis:

REGULATORY

- Remicade gained EU approval in May 2003 for the treatment of adults with severe, active AS who had responded inadequately to conventional therapy (EMA, 2004).
- The FDA approved Remicade for the treatment of adult patients with active AS in December 2004 (FDA, 2004).
- In April 2010, Remicade gained Japanese approval for the treatment of adult patients with AS who have not responded sufficiently to conventional treatments (PMDA, 2010).

COMPETITION

- Despite being favored by certain niche patient subgroups, Remicade's IV administration is a major drawback for the brand, given that all of the other anti-TNF biologics are administered subcutaneously. Furthermore, as a chimeric antibody, Remicade's immunogenicity can lead to patients exhibiting an anti-drug antibody response that translates to blunted efficacy and side effects including susceptibility to infectious diseases, which contributes to physicians' preference for competitor anti-TNF biologics. Combined with significant competition from infliximab biosimilars, Datamonitor Healthcare expects sales of Remicade to decline further in the foreseeable future.

"Infliximab has logistical impedances like the fact that it is IV and needs to be infused."

Anonymous key opinion leader

"Those three [Enbrel, Humira, and Remicade] have been around the longest but we tend not to go to infliximab unless needed... no incentive for me to infuse someone."

Anonymous key opinion leader

- Celltrion/Pfizer's infliximab biosimilar Inflectra was the first anti-TNF biosimilar to enter the US axSpA market in Q4 2016. In April 2016, the FDA approved Inflectra for use in all indications for which Remicade is licensed (FDA, 2016). Johnson & Johnson (the originator and marketing company of Remicade in the US) and Pfizer are still in ongoing patent dispute proceedings over a patent covering Remicade's cell culture media (US6284471); however, Pfizer launched Inflectra at-risk in November 2016 (Johnson & Johnson, 2016; Pfizer, 2016). Datamonitor Healthcare forecasts further biosimilar competition in the US from Samsung Bioepis' biosimilar infliximab (marketed as Renflexis by Merck & Co and Flixabi by Biogen) and Pfizer's Ixifi, which won regulatory approvals in April and December 2017, respectively (FDA, 2017b; Pfizer, 2017).

- Celltrion's infliximab biosimilar was also the first anti-TNF biosimilar to launch in Japan and Europe. It launched in Japan in Q2 2016 and in the five major EU markets (France, Germany, Italy, Spain, and the UK) in Q1 2015 (Hospira, 2015; Nippon Kayaku, 2015). Datamonitor Healthcare forecasts further biosimilar competition in Europe from Samsung Bioepis' Flixabi, which won regulatory approval in Europe in May 2016 (Biogen, 2016).

- Datamonitor Healthcare expects the price of biosimilar infliximab in all markets to decrease by 30% over the forecast period, as additional biosimilar infliximab entrants launch.

- Over the 10-year forecast period, Datamonitor Healthcare assumes the price of Remicade will decrease by approximately 30% across all markets, in order to maintain a constant price differential from the average price of biosimilar infliximab.

- Datamonitor Healthcare forecasts Remicade to lose up to 55% of its patient share to biosimilar infliximab over the forecast period, across all markets. Datamonitor Healthcare expects rheumatologists' initial caution with biosimilars to translate into relatively slow uptake of biosimilar infliximab, with use limited primarily to new patients. In the long term, growing confidence in biosimilars driven by increasing familiarity and post-marketing data, in conjunction with expected decreases in biosimilar infliximab's cost, will lead to greater erosion of Remicade's patient share to biosimilar infliximab.

- Datamonitor Healthcare forecasts Remicade to face competition from Simponi Aria, the IV formulation of Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), which was approved in the US in Q4 2017. Based on discussions with key opinion leaders, Datamonitor Healthcare expects uptake of Simponi Aria to be restricted by physician familiarity with Remicade, and the fact that cheaper infliximab biosimilars are available. Datamonitor Healthcare forecasts Simponi Aria to erode up to 15% patient share from Remicade and its biosimilar versions across all lines of therapy. Patient share is expected to come mainly

from patients that require a weight-specific dosage and an IV drug with a lower risk of infection, and a lower potential for generation of autoantibodies in comparison to Remicade.

"So, I actually like Simponi Aria, and the patients do too for many reasons [...] so there [are] a lot of advantages to it when you compare it to Remicade, the other intravenous option: it is a shorter infusion [and] it is often less frequent so those are both advantages in some ways. It does have a lower risk of allergic reaction and infusion reaction compared to Remicade [...] it is a good option for the Remicade [patient] who develops a hypersensitivity to the drug."

US key opinion leader

- Datamonitor Healthcare does not forecast any other novel brands to impact Remicade's patient share in the US and five major EU markets. This is based on the limited use of Remicade in these markets as a result of its inconvenient IV formulation.

- With a limited number of biologics licensed for axSpA in Japan, namely Remicade and Humira (adalimumab; AbbVie/Eisai), Remicade has higher usage in Japan compared to the US and five major EU markets. First-in-class interleukin (IL)-17A inhibitor Cosentyx (secukinumab; Novartis), which is expected to launch in Japan in Q1 2019, is forecast to pose some competition to Remicade as it provides a viable option for TNF-refractory patients. Exclusively in Japan, Datamonitor Healthcare forecasts Cosentyx to directly impact Remicade's patient share, with Cosentyx expected to take up to 5% of patient share from Remicade and its biosimilar versions at second and later lines of therapy. Remicade is also forecast to lose up to 3% of its second and later line patient share to Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical), following its anticipated launch in Q4 2019.

DOSING

- Datamonitor Healthcare assumes that the dosage of Remicade is 5mg/kg at 0, two, and six weeks, and then every six weeks, as described in the drug's prescribing information (EMA, 2017; FDA, 2017a). Datamonitor Healthcare assumes that the average weight of an axSpA patient is 75kg.

PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product, and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for Remicade in each country.

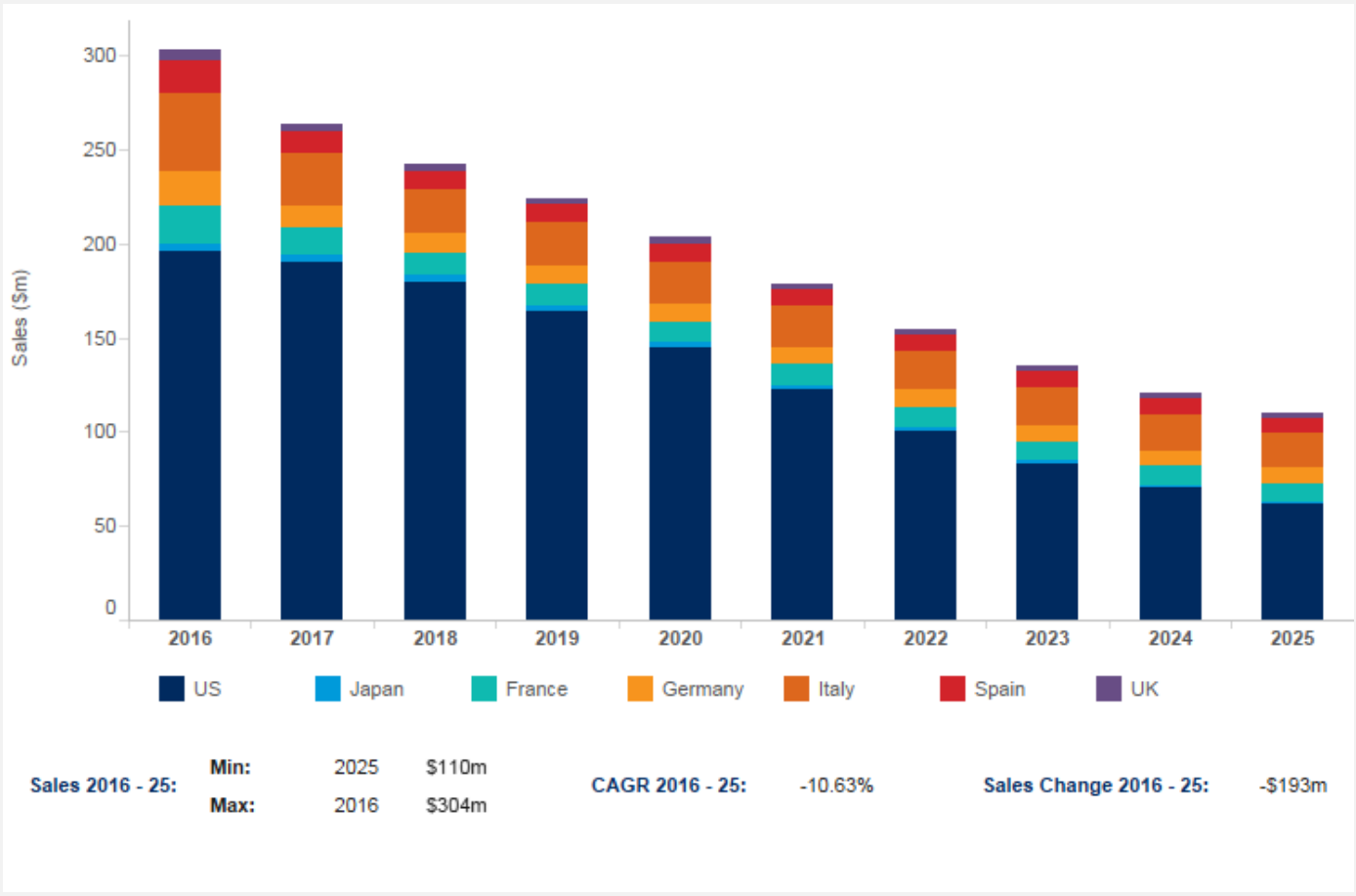
- Historical prices are used to trend forward prices over the forecast period. Based on discussions with US payers, Datamonitor Healthcare assumes that Remicade's net price in the US is 30% lower than the list price due to discounts and rebates in the US.

- Please view the accompanying datapack for a full table of drug costs per patient per year.

REMICADE FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Remicade in axial spondyloarthritis, by country, over 2016–25.

Figure 30: **Remicade sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 27: **Remicade sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	196.2	190.5	179.8	163.9	144.7	122.7	100.6	83.0	70.3	61.8
Japan	3.7	3.6	3.4	3.1	2.7	2.2	1.9	1.6	1.4	1.2
France	20.8	14.1	11.9	11.7	11.4	11.0	10.7	10.4	10.0	9.7
Germany	18.1	12.2	10.3	10.0	9.7	9.4	9.1	8.7	8.4	8.1
Italy	41.3	27.9	23.5	22.9	22.2	21.5	20.8	20.1	19.4	18.7
Spain	17.7	12.0	10.1	9.8	9.6	9.3	9.0	8.7	8.4	8.1
UK	5.7	3.9	3.3	3.2	3.1	3.1	3.0	2.9	2.8	2.8
Grand total	303.6	264.1	242.3	224.5	203.4	179.2	155.0	135.4	120.8	110.4

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis and Rheumatism, 52(2), 582–591.

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Simponi : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Despite being marketed by Johnson & Johnson, Merck & Co, and Mitsubishi Tanabe – companies with extensive experience in axial spondyloarthritis (axSpA) and other autoimmune indications – Simponi (golimumab) is currently being prescribed at a lower rate than Enbrel (etanercept; Amgen/Pfizer/Takeda), Humira (adalimumab; AbbVie/Eisai), and Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe). This is mainly due to its late market entry in 2009 and its lack of differentiation from the other tumor necrosis factor (TNF) inhibitors in terms of efficacy or safety, which has made it difficult for the brand to capture significant market share. With competition from cheaper biosimilars and Novartis's interleukin (IL)-17A inhibitor Cosentyx (secukinumab), an agent with a novel mechanism of action, Datamonitor Healthcare expects Simponi's uptake to remain low.

DRUG OVERVIEW

Simponi is a second-generation TNF inhibitor following Johnson & Johnson's Remicade. It is a fully human monoclonal antibody that inhibits the TNF-alpha receptor and is indicated for the treatment of psoriatic arthritis (PsA), rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, ulcerative colitis, and axSpA (EMA, 2017; FDA, 2017a). In the US, both the subcutaneous and intravenous (IV) formulations of Simponi are licensed for use in RA, PsA, and ankylosing spondylitis (AS). Simponi IV is marketed under the brand name Simponi Aria.

Table 28: **Simponi drug profile**

Molecule	golimumab
Mechanism of action	TNF-alpha MAb
Originator	Janssen Biotech (formerly Centocor Ortho Biotech; a subsidiary of Johnson & Johnson)
Marketing company	Johnson & Johnson (US); Merck & Co (EU, Japan); Mitsubishi Tanabe (Japan)
Formulation	SC injection
Alternative names	CNTO 148
MAb = monoclonal antibody; SC = subcutaneous; TNF = tumor necrosis factor	

Source: Datamonitor Healthcare; Medtrack; Pharmaprojects

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DEVELOPMENT OVERVIEW

Simponi gained US approval for the treatment of adult patients with active AS in April 2009 (FDA, 2009). Within the EU, Simponi was granted approval in October 2009 for the treatment of adults with severe, active AS who had responded inadequately to conventional therapy (EMA, 2009). Both approvals were based on data from the GO-RAISE Phase III trial (ClinicalTrials.gov identifier: NCT00265083), which showed that a significant percentage of patients with active AS treated with Simponi achieved the ASAS20 response over 14 weeks in comparison to placebo (Inman et al., 2008).

In June 2015, the European Medicines Agency (EMA) expanded Simponi's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to non-steroidal anti-inflammatory drugs (Johnson & Johnson, 2015). This expansion was based upon positive data from the GO-AHEAD Phase III clinical trial (EMA, 2015).

In October 2017, Simponi Aria was approved for the treatment of active AS in the US (Johnson & Johnson, 2017). The approval was based on positive data from the Phase III GO-ALIVE study (ClinicalTrials.gov identifier: NCT02186873).

PIVOTAL TRIAL DATA

The Phase III studies that supported approvals for Simponi and Simponi Aria in axSpA are summarized in the tables below.

Table 29: **Simponi pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	References
GO-RAISE (NCT00265083) (Phase III)	356	Adult patients with AS with an inadequate response to current or previous NSAIDs or DMARDs	Randomized, double-blind, placebo-controlled	50mg or 100mg golimumab administered every four weeks; five years	Achieved ASAS20* response at week 14: Golimumab 50mg: 59.4% Golimumab 100mg: 60.0% Placebo: 21.8%	Inman et al., 2008
GO-AHEAD (NCT01453725) (Phase III)	197	Adult patients with active nr-axSpA	Randomized, double-blind, placebo-controlled	50mg golimumab administered at weeks 0, 4, 8, and 12; 16 weeks. After 16 weeks, open-label period, 50mg administered every four weeks; 28 weeks	Achieved ASAS20* response at week 16: Golimumab: 71.1% Placebo: 40.0%	Sieper et al., 2015

*ASAS20 response (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis international Society response criteria 20; DMARD = disease-modifying antirheumatic drug; nr-axSpA = non-radiographic axial spondyloarthritis; NSAID = non-steroidal anti-inflammatory drug

Source: various (see above)

Table 30: **Simponi Aria pivotal trial data in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Dosing tested and duration	Results	Reference
GO-ALIVE (NCT02186873) (Phase III)	208	Adult patients with active AS	Randomized, double-blind, placebo-controlled	IV infusions of golimumab 2mg/kg at weeks 0, 4, and thereafter every eight weeks; 16 weeks	Achieved ASAS20* response at week 16: Golimumab: 73.3% Placebo: 26.2%	Johnson & Johnson, 2016

*ASAS20 response (clinical primary endpoint) is defined as an improvement of ≥20% and ≥1 unit on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.

AS = ankylosing spondylitis; ASAS20 = Assessment of SpondyloArthritis international Society 20; IV = intravenous

Source: see above

SWOT ANALYSIS

Figure 31: **Simponi for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Johnson & Johnson/Merck & Co/Mitsubishi Tanabe have strong marketing capabilities and knowledge of multiple autoimmune indications • Dosing regimen is favored by some patients • Indication expansion: has been approved for use in nr-axSpA patients in the EU • Available in both SC and IV (Simponi Aria) formulations in the US	• Black box warning for serious infections and malignancies • Low uptake as other anti-TNFs launched first • Once-monthly dosing regimen can result in blunted efficacy • Not approved in Japan
Opportunities	**Threats**
• Boost Johnson & Johnson's franchise as Remicade (infliximab) loses patient share due to launch of biosimilars • Promote use of Simponi Aria in patients with severe symptoms who need immediate relief • Capitalize on the increased reimbursement that Medicare offers for IV drugs in the US to boost Simponi Aria's uptake • Potential for future filing in Japan • US and EU patent protection until 2024 • Recommended by NICE for AS • Increasing prevalence of disease across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK)	• Increasing availability of biosimilars of leading anti-TNF brands will intensify pricing competition • Threat from Novartis's Cosentyx (secukinumab), which is primarily used in patients refractory to TNF inhibition • Anticipated competition from Taltz (ixekizumab)

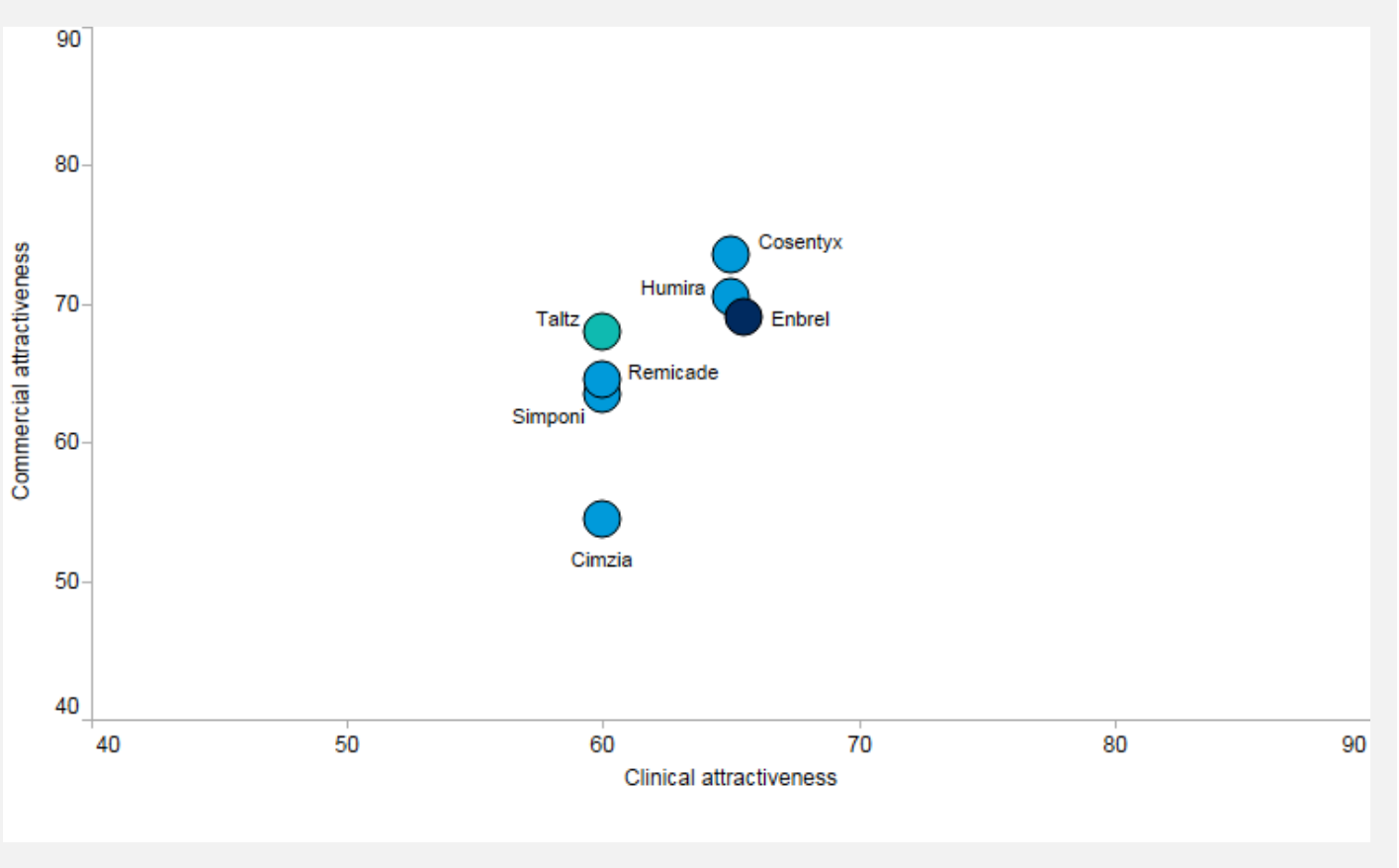
AS = ankylosing spondylitis; FDA = US Food and Drug Administration; IV = intravenous; NICE = National Institute for Health and Care Excellence; nr-axSpA = non-radiographic axial spondyloarthritis; SC = subcutaneous; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

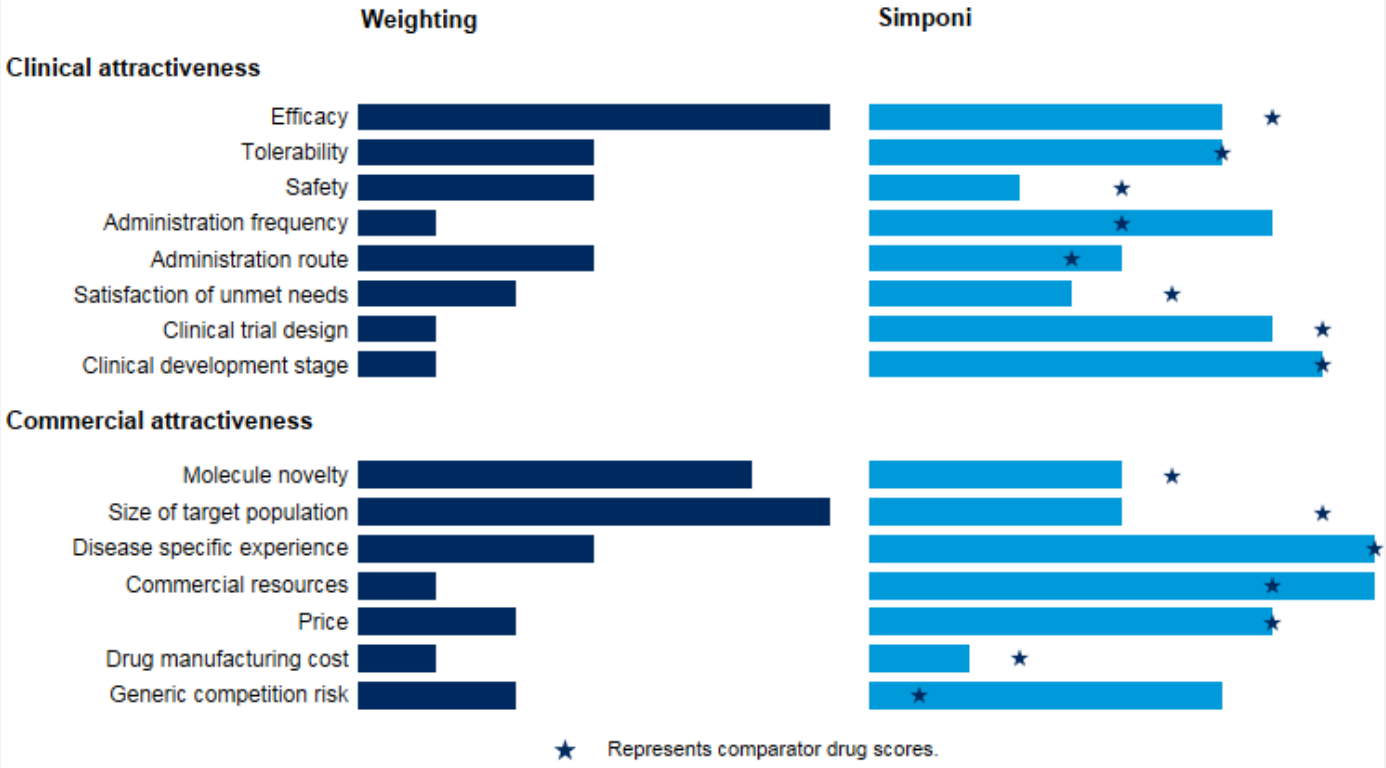
The figures below depict Datamonitor Healthcare's assessment of Simponi's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel and all of the other key marketed and pipeline drugs profiled.

Figure 32: **Datamonitor Healthcare's drug assessment summary of Simponi in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 33: **Datamonitor Healthcare's drug assessment summary of Simponi in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

Datamonitor Healthcare makes the following assumptions in its forecast of Simponi for axial spondyloarthritis:

REGULATORY

- Simponi gained US approval for the treatment of adult patients with active AS in April 2009 (FDA, 2009).
- Simponi was granted approval in the EU in October 2009 for the treatment of adults with severe, active AS who had responded inadequately to conventional therapy (EMA, 2009).
- In June 2015, the EMA expanded Simponi's approved indication to include the treatment of adults with severe nr-axSpA who have had an inadequate response to non-steroidal anti-inflammatory drugs (Johnson & Johnson, 2015).
- Simponi Aria received US approval for the treatment of active AS in October 2017 (Johnson & Johnson, 2017). The approval was based on positive data from the Phase III GO-ALIVE study (ClinicalTrials.gov identifier: NCT02186873). Simponi Aria became available for prescription for axSpA immediately upon approval since it had already been available in the US due to its prior approval in RA.

- Based on Simponi Aria's development history in RA, Datamonitor Healthcare does not expect the IV drug to launch in the EU over the 10-year forecast period. While the IV formulation of Simponi received US approval for the treatment of RA in July 2013, it has failed to enter the EU RA market. Janssen filed Simponi Aria for EU approval in RA in November 2011, but withdrew the Marketing Authorization Application (MAA) in January 2013 as the additional manufacturing data required by the EMA were unavailable within the timeline requested. In June 2013, Janssen resubmitted an MAA for IV Simponi, but this was again withdrawn in May 2014 following an assessment report indicating that additional clinical data were required to further evaluate the risk-to-benefit profile of the IV formulation (Biomedtracker, 2014). No additional clinical trials have been initiated following this last withdrawal. Datamonitor Healthcare therefore believes Janssen will no longer pursue the development of Simponi Aria for approval in the EU.

- Datamonitor Healthcare does not forecast Simponi or Simponi Aria to launch in Japan for axSpA, as no evidence of clinical development of the drugs in Japanese axSpA patients has been found.

COMPETITION

- Due to its late market entry in 2009 and its lack of differentiation from the other TNF inhibitors in terms of efficacy or safety, Simponi has not managed to capture significant patient share. Simponi competes mainly with Cimzia (certolizumab pegol; UCB/Astellas) for patients with active axSpA who have failed or responded inadequately to first-line anti-TNF biologics and patients with co-morbidities. Key opinion leaders emphasize that of the two anti-TNF agents, Cimzia is the preferred TNF inhibitor for women of childbearing age and pregnant women due to data showing Cimzia has the lowest level of placental transfer to the fetus in comparison to other anti-TNF agents (Mahadevan et al., 2013; UCB, 2018).

"Cimzia has kind of a unique niche in the pregnant state, so if it is a young woman and she is contemplating pregnancy, and if I had my way I might start her on Cimzia [...] if I am deciding between Cimzia and Simponi in that patient I might lean toward Cimzia [...] I have been a bit disappointed with Simponi as far as its apparent wear off before the four-week interval for injections, and before the eight-week interval for infusion, the drug just does not seem to last as long as the clinical trials really pointed it to do. So, disappointing a little bit in that way, and many of my Simponi patients take it every three weeks instead of every four, which is just an additional cost and I will usually lean on Cimzia for that reason."

US key opinion leader

- Datamonitor Healthcare believes that the increasing availability of cheaper anti-TNF biosimilars and the emergence of biologics with novel mechanisms of action are likely to further restrict Simponi's uptake, with its sales prospects not expected to reach those of the leading anti-TNF brands by 2025.

- Simponi is forecast to face strong competition from the first-in-class IL-17A inhibitor Cosentyx, which is primarily prescribed to patients following the failure of at least one TNF inhibitor. Datamonitor Healthcare expects Simponi to lose up to 35% of its patient share to Cosentyx across the US and five major EU markets (France, Germany, Italy, Spain, and the UK). Loss of patient share will be greatest in the second and later lines of therapy.

"In the case of inadequate response to the first biologic, so the first TNF inhibitor, we have the choice between a second TNF or secukinumab [Cosentyx], which is the only one that is launched currently in spondyloarthritis, which is an anti-IL-17. Especially when we have primary failure with an anti-TNF, we prefer an anti-IL17 [...]"

EU key opinion leader

- Datamonitor Healthcare expects Simponi to lose up to another 10% of its patient share across the US and five major EU markets to Cosentyx as a result of the latter's indication expansion for nr-axSpA in Q4 2019. Loss of patient share will be greatest in the second and later lines of therapy in patients who are refractory to TNF inhibition, or in cases where anti-TNF therapy is not suitable due to a history of malignancy, or concerns about the side effect profiles of anti-TNFs.

- Simponi is forecast to face competition from the second-to-market IL-17A inhibitor, Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical), which is expected to be primarily used in TNF-experienced patients. Simponi is set to lose up to 15% of patient share across the US and five major EU markets to Taltz. Loss of patient share will be greatest in the second and later lines of therapy.

- Based on discussions with key opinion leaders, Datamonitor Healthcare expects uptake of Simponi Aria in the US to be restricted by physician familiarity with Remicade, and the fact that cheaper infliximab biosimilars are available. Datamonitor Healthcare forecasts Simponi Aria to erode up to 15% patient share from Remicade and biosimilar infliximab across all lines of therapy. Discussions with key opinion leaders highlight that Simponi Aria's patient share is expected to come mainly from patients who require a weight-specific dosage and an IV drug with a lower risk of infection and a lower potential for generation of autoantibodies in comparison to Remicade.

"So, I like it, I actually like Simponi Aria, and the patients do too for many reasons. It does have the advantage of being IV [...] the other advantage like I said is if the person needs a weight-based drug [...] and for my non-compliant patients it is also very nice, a patient who you are not guaranteed is going to get done what they need to have. So, then you can know that checking in with a nurse once every two months at least, and they are getting their blood checked, so there is a lot of advantages to it when you compare it to Remicade, the other intravenous option: it is a shorter infusion [and] it is often less frequent so those are both advantages in some ways. It does have a lower risk of allergic reaction and infusion reaction compared to Remicade [...] it is a good option for the Remicade [patient] who develops a hypersensitivity to the drug."

US key opinion leader

- Simponi is forecast to lose just 10% of its patient share to Simponi Aria, from second and later lines of therapy, primarily in patients aged 65 years and older who are covered by Medicare and are inadequate responders to Remicade (the other IV option for axSpA), or else in patients who consider the IV formulation an advantage.

- Datamonitor Healthcare's primary research revealed that there is some off-label use of Simponi in Japan. Datamonitor Healthcare forecasts that Cosentyx and Taltz, once approved in Japan, will curtail this off-label use; they are expected to take up to 30% and up to 20% of patient share from Simponi, respectively, across all lines of therapy.

DOSING

- Datamonitor Healthcare assumes dosing of 50mg of Simponi once monthly, as described in the drug's prescribing information (EMA, 2017; FDA, 2017a).

- Datamonitor Healthcare assumes that the dosage of Simponi Aria is 2mg/kg at weeks 0 and four, and then every eight weeks, as described in the drug's prescribing information (FDA, 2017b). Datamonitor Healthcare assumes that the average weight of an axSpA patient is 75kg.

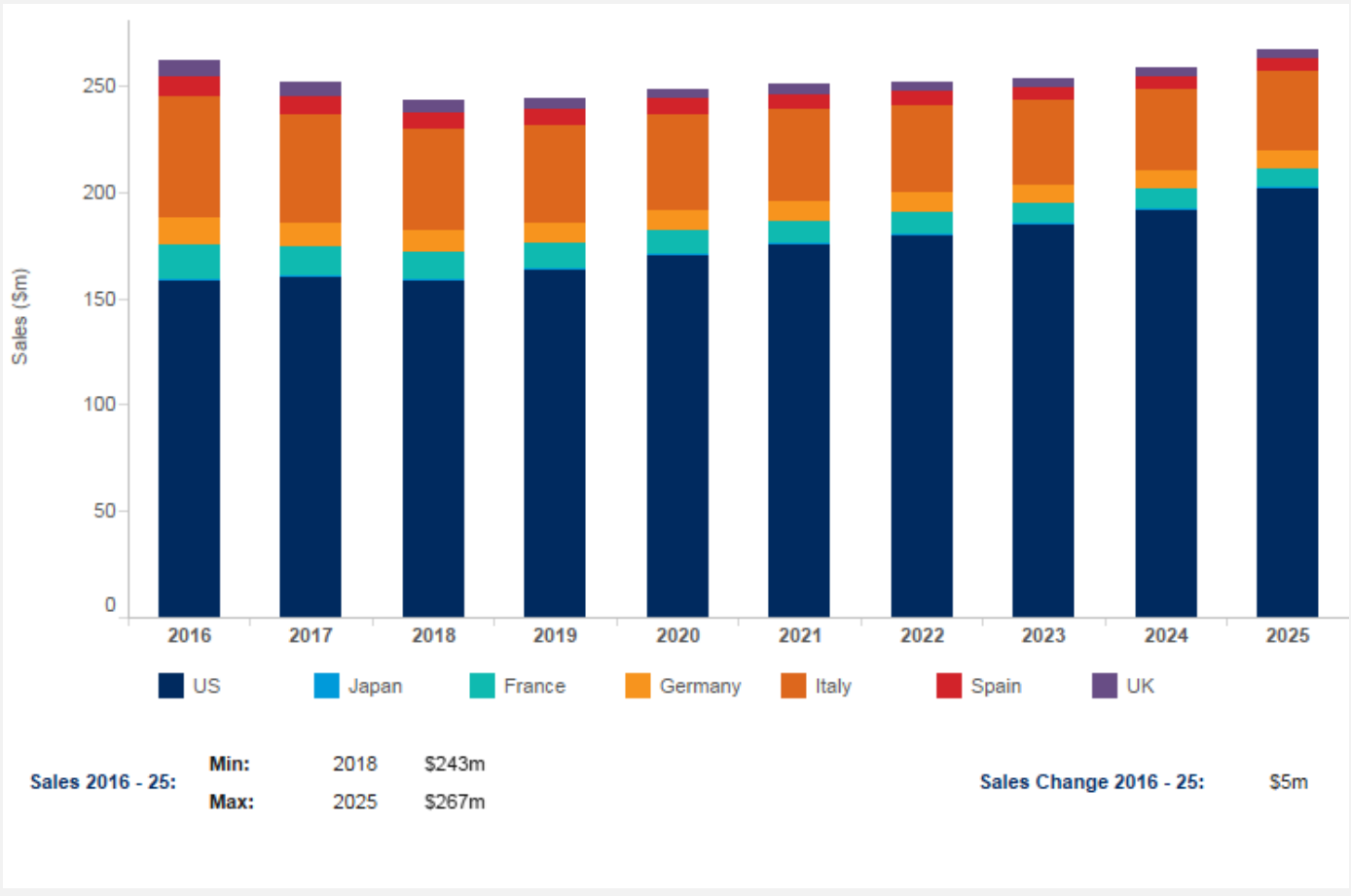
PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for Simponi and Simponi Aria in each country. Historical prices are used to trend forward prices over the forecast period.
- Please view the accompanying datapack for a full table of drug costs per patient per year.

SIMPONI FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Simponi and Simponi Aria in axial spondyloarthritis, by country, over 2016–25.

Figure 34: **Simponi and Simponi Aria sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 31: **Simponi and Simponi Aria sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	Formulation	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	SC	158.2	160.3	158.1	160.6	164.8	166.8	167.6	167.9	171.0	177.1
US	IV (Simponi Aria)	-	<0.1	0.8	2.8	5.4	8.6	12.6	17.0	21.1	24.6
Japan	SC	0.6	0.6	0.6	0.6	0.6	0.5	0.4	0.4	0.3	.3
France	SC	16.4	13.3	12.2	11.6	11.2	10.6	10.0	9.4	9.0	8.7
Germany	SC	12.4	11.0	10.2	9.8	9.6	9.3	9.0	8.6	8.4	8.3
Italy	SC	57.0	51.1	47.5	46.0	45.0	43.2	41.4	39.7	38.6	38
Spain	SC	10.0	8.7	7.9	7.6	7.4	7.1	6.7	6.4	6.2	6.1
UK	SC	7.7	6.8	5.8	5.1	4.8	4.6	4.4	4.3	4.2	4.2
Grand total		262.4	251.9	243.2	244.2	248.7	250.6	252.1	253.7	258.7	267.4

Note: totals may not sum due to rounding.

IV = intravenous; SC = subcutaneous

Table 31: **Simponi and Simponi Aria sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Source: Datamonitor Healthcare

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Taltz : Axial spondyloarthritis (axSpA)

PRODUCT PROFILE

ANALYST OUTLOOK

Taltz (ixekizumab; Eli Lilly/Torii Pharmaceutical) is forecast to face several barriers upon launch in axial spondyloarthritis (axSpA), despite its positive clinical performance to date and the need for novel therapies suitable for tumor necrosis factor (TNF)-refractory patients or patients with contraindications to TNF inhibition. While Taltz demonstrated efficacy in biologic-naïve patients in the Phase III COAST-V study, it will struggle to penetrate the first-line biologic setting. The growing availability of real-world data for the first-in-class interleukin (IL)-17A inhibitor Cosentyx (secukinumab; Novartis), coupled with the increasing presence of biosimilars of well-established anti- TNF brands, will negatively impact Taltz's commercial prospects. Datamonitor Healthcare believes that in order to capture significant market share, Taltz will have to demonstrate a superior clinical profile to that of key marketed biologics, and/or launch at a lower cost.

DRUG OVERVIEW

Taltz is a humanized, immunoglobulin G subclass 4 monoclonal antibody that neutralizes IL-17A. It gained approval from the US Food and Drug Administration for the treatment of adults with moderate to severe plaque psoriasis in March 2016, followed by EU and Japanese approvals in April 2016 (FDA, 2016; EMA, 2016; Torii, 2016). Taltz is also approved for the treatment of psoriatic arthritis in the US, Japan, and EU (EMA, 2018; Eli Lilly, 2016; Eli Lilly, 2017).

Table 32: **Taltz drug profile**

Molecule	ixekizumab
Phase of development	Phase III (US/Japan/EU)
Mechanism of action	IL-17A MAb
Originator	Eli Lilly
Marketing company	Eli Lilly (US/EU); Torii Pharmaceuticals (Japan)
Formulation	Subcutaneous
Alternative names	LY2439821, Torutsu (Japan)

IL = interleukin; MAb = monoclonal antibody

Source: Datamonitor Healthcare; Pharmaprojects

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DEVELOPMENT OVERVIEW

Taltz's pivotal Phase III clinical trials are evaluating its efficacy and safety in different patient subpopulations, including anti-TNFα-naïve participants with active ankylosing spondylitis (AS) (ClinicalTrials.gov identifier: NCT02696785), anti-TNFα-experienced participants with active AS (ClinicalTrials.gov identifier: NCT02696798), and anti-TNFα-naïve participants with non-radiographic axial spondyloarthritis (nr-axSpA) (ClinicalTrials.gov identifier: NCT02757352).

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Table 33: **Taltz Phase III trials in axial spondyloarthritis**

Trial	Sample size	Target patients	Study design	Treatment arms	Primary endpoints	Start date/primary completion date
COAST-V (NCT02696785) (Phase III)	320	Adult patients with active AS who are anti-TNFα-naïve	Randomized, double-blind, placebo-controlled	Arm 1: Starting dose of 80mg or 160mg given at week 0, followed by 80mg every two weeks to week 14; 52 weeks Arm 2: Starting dose of 80mg or 160mg given at week 0, followed by 80mg every four weeks to week 14; 52 weeks Arm 3: 40mg adalimumab (Humira) given every two weeks up to week 14, then 80mg given every two weeks or every four weeks to week 52	ASAS40* response at 16 weeks**	May 2016/ December 2017
COAST-W (NCT02696798) (Phase III)	300	Adult patients with active AS who are TNFα inhibitor-experienced	Randomized, double-blind, placebo-controlled	Arm 1: Starting dose of 80mg or 160mg given at week 0, followed by 80mg every two weeks; 52 weeks Arm 2: Starting dose of 80mg or 160mg given at week 0, followed by 80mg every four weeks; 52 weeks	ASAS40* response at week 16	April 2016/May 2018

Table 33: **Taltz Phase III trials in axial spondyloarthritis**

COAST-X (NCT02757352) (Phase III)	300	Adult patients with nr-axSpA who are anti-TNFα-naïve	Randomized, double-blind, placebo-controlled	Arm 1: Ixekizumab (dose unspecified) given every two weeks; 52 weeks Arm 2: Ixekizumab (dose unspecified) given every four weeks; 52 weeks	ASAS40* response at week 16	August 2016/June 2018

*ASAS40 response at week 16 (clinical primary endpoint) is defined as achieving an improvement of ≥40% and ≥2 units on a 0–10 numerical rating scale (NRS) in ≥3 of the following: patient's global assessment of disease activity, pain assessment (total spinal pain NRS score), function (represented by Bath Ankylosing Spondylitis Functional Index), inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index questions 5 and 6 relating to morning stiffness), and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining area.
**Taltz demonstrated statistical improvement in the signs and symptoms of AS measured by ASAS40 compared to placebo (Eli Lilly, 2018).

AS = ankylosing spondylitis; ASAS40 = Assessment of SpondyloArthritis international Society response criteria 40; nr-axSpA = non-radiographic axial spondyloarthritis; TNF = tumor necrosis factor

Source: Trialtrove; ClinicalTrials.gov

SWOT ANALYSIS

Figure 35: **Taltz for axial spondyloarthritis – SWOT analysis**

Strengths	Weaknesses
• Comprehensive Phase III development program, assessing Taltz in TNF-naïve and TNF-experienced patients, and nr-axSpA • Met primary and all key secondary endpoints in Phase III COAST-V study in biologic-naïve patients • COAST-V study includes established anti-TNF biologic Humira (adalimumab) as active control arm • Has a marketing partner in Japan (Torii Pharmaceutical) in comparison to competitor Cosentyx (secukinumab), which is marketed solely by Novartis	• Clinical data are not yet available in TNF-refractory patients, where there remains significant unmet need • No clear efficacy advantage over first-in-class IL-17A inhibitor Cosentyx; potential to be perceived as a me-too drug • Marketed by Eli Lilly, which has less marketing experience in immunology compared to its competitors
Opportunities	**Threats**
• Leverage a discounted price at a time when drug costs are heavily influencing prescribing decisions • Leverage physician familiarity with the drug in PsA to drive prescribing in axSpA	• Physician and patient familiarity with established anti-TNF biologics • Growing availability of real-world data for first-to-market IL-17A inhibitor Cosentyx • Increasing availability of lower-cost anti-TNF biosimilars, which are likely to be used early in the treatment algorithm

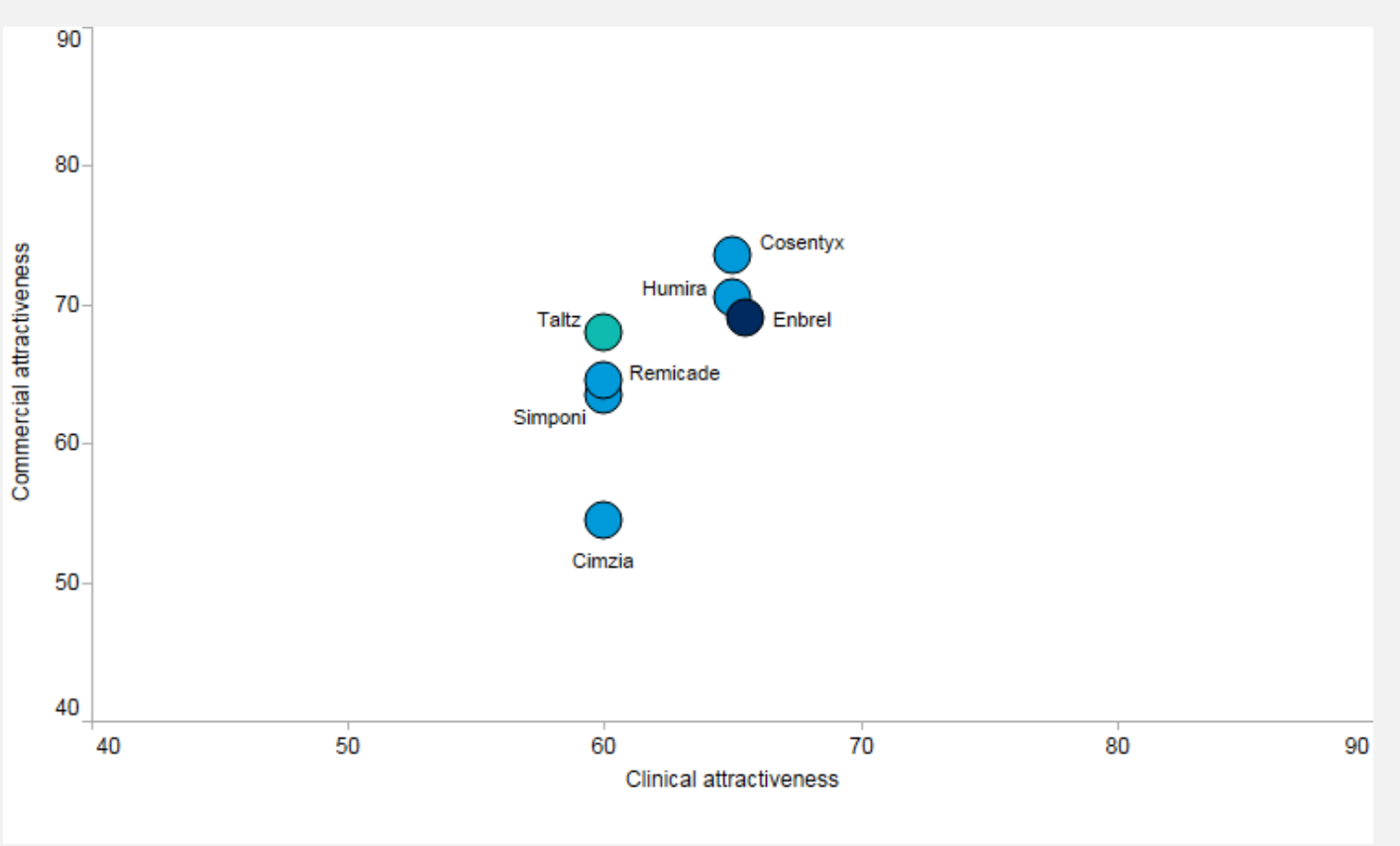
axSpA = axial spondyloarthritis; IL = interleukin; nr-axSpA = non radiographic axial spondyloarthritis; PsA = psoriatic arthritis; TNF = tumor necrosis factor

Source: Datamonitor Healthcare

CLINICAL AND COMMERCIAL ATTRACTIVENESS

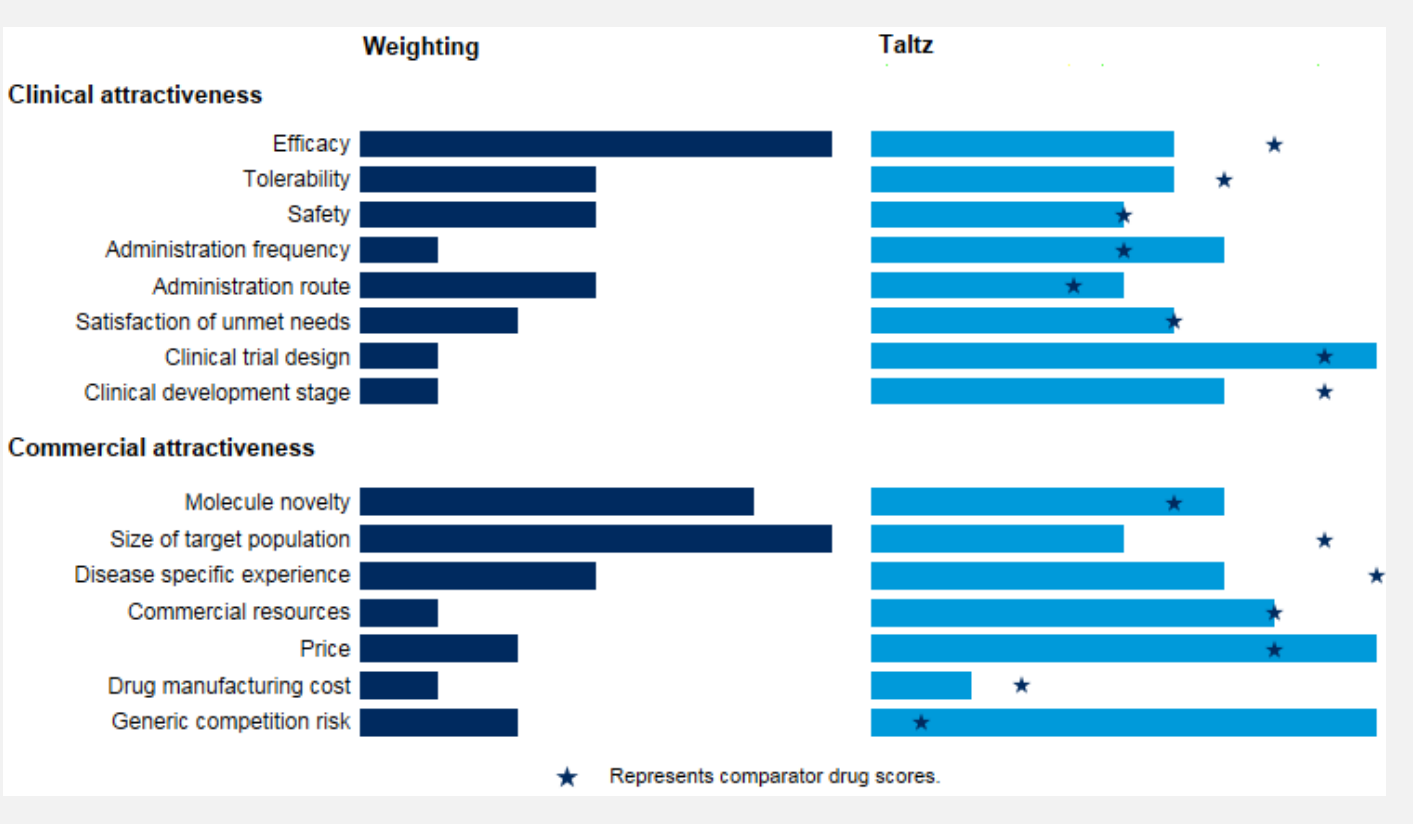
The figures below depict Datamonitor Healthcare's assessment of Taltz's clinical and commercial attractiveness as a therapy for axSpA in relation to the comparator drug Enbrel (etanercept; Amgen/Pfizer/Takeda) and all of the other key marketed and pipeline drugs profiled.

Figure 36: **Datamonitor Healthcare's drug assessment summary of Taltz in axial spondyloarthritis**



Source: Datamonitor Healthcare

Figure 37: **Datamonitor Healthcare's drug assessment summary of Taltz in axial spondyloarthritis**



Source: Datamonitor Healthcare

PATIENT BASED FORECAST

FORECAST ASSUMPTIONS

REGULATORY

- Datamonitor Healthcare forecasts Taltz to launch in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) in Q4 2019. Eli Lilly indicated that it plans to file for approval of Taltz with US, Japanese, and EU regulatory agencies by Q4 2018. Assuming a positive decision from regulators, Datamonitor Healthcare anticipates that Taltz will become available for use in axSpA immediately upon approval, in Q4 2019, as a result of its prior approvals for psoriasis and psoriatic arthritis. Datamonitor Healthcare expects Taltz to launch simultaneously for AS and nr-axSpA.

COMPETITION

- Taltz is expected to be primarily relegated to later lines of therapy. The increasing availability of anti-TNF biosimilars, which are marketed at a lower cost than the reference brands, will prevent Taltz from penetrating the first-line biologic setting, despite having demonstrated positive efficacy in biologic-naïve patients (Eli Lilly, 2018). Taltz's lack of differentiation from the first-in-class IL-17A inhibitor Cosentyx will also negatively impact its commercial prospects. Key opinion leaders stress that in order to capture significant market share, Taltz will have to launch at a lower cost compared to Cosentyx.

"Taltz [...] is pretty much a second Cosentyx [...] It seems like kind of a me-too that just got to the race a little bit late, not that that disadvantages it necessarily, I mean it is only a little bit – it is like Enbrel [etanercept; Amgen/Pfizer/Takeda] and Remicade [infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe] came out pretty close to each other way back then, although [with] different formulations: IV [intravenous] and subcutaneous but Taltz, it is going to probably end up just coming down to cost and insurance coverage, it is going to be one of those factors rather than any particular efficacy issue [...] if one of these drugs were to undercut the market by 30% all the insurance companies would go with it, and guess what happens? Physicians are compelled to use it a little sooner and they get a better comfort level, and they will use it more, so it is like you can expand yourself into a market much more quickly by undercutting it."

Anonymous key opinion leader

"I would have preferred to see Cosentyx as a comparator [to Taltz]. I think it isn't quite as good as Cosentyx... but it is too early to say that, it's hard to decide that now. We will have to see whether there are any specific advantages or disadvantages."

EU key opinion leader

"We don't really understand the difference [with Taltz], being [another] IL-17. It's like a second Cosentyx. The problem could be that it wasn't compared to Cosentyx for non-inferiority."

French national payer

- With the same mechanism of action as Cosentyx, Taltz is also expected to show the same potential correlation with inflammatory bowel disease (IBD) that was displayed by patients treated with Cosentyx during clinical trials in plaque psoriasis (FDA, 2017).

"I think that I do have some concerns about IL-17 in particular with regards to inflammatory bowel disease, because when studied in IBD people flared, and so you are looking at a population of patients with more subclinical gut inflammation than other disease states like psoriasis, so I do worry that if you block IL-17 in someone with even subclinical gut inflammation you may unmask IBD. So, that is a theoretical concern [...] there is some basic science data that was presented at the ACR [American College of Rheumatology meeting] last year [2015] that suggested potentially [that] if you blocked IL-17 there was actually more bowel inflammation, so I think we need longer-term studies to really know beyond the clinical response what the outcomes are going to be with these drugs."

US key opinion leader

- Datamonitor Healthcare expects Taltz to take up to 13% patient share from Cosentyx in the US and five major EU markets, at the second and later lines of therapy.

- Datamonitor Healthcare forecasts Taltz to compete with TNF inhibitors Cimzia (certolizumab pegol; UCB/Astellas) and Simponi (golimumab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe); Cimzia is expected to lose up to 10% and Simponi up to 15% patient share to Taltz across the US and five major EU markets. As Taltz is expected to be primarily used in the post-TNF setting, Cimzia and Simponi are anticipated to lose patient share at the second and later lines of therapy, which are primarily comprised of patients who failed to respond to a previous anti-TNF, or who experienced a secondary loss of response to an anti-TNF agent.

- In the US and Europe, Datamonitor Healthcare expects the market leaders Enbrel and Humira (adalimumab; AbbVie/Eisai) to face minimal competition from Taltz. Taltz is expected to erode just 2% of patient share from Enbrel and Humira at the first and second lines, and up to 5% of their patient share at the third and later lines of therapy. Enbrel and Humira are likely to retain their status as the preferred biologics at early lines, hence erosion at first and second lines will be lower.

- Datamonitor Healthcare expects conventional disease-modifying antirheumatic drugs, such as methotrexate and sulfasalazine,

to face minimal competition from Taltz, which is expected to erode just 1.5% of patient share across all markets, from third and later lines of therapy.

- With a limited number of biologics licensed for axSpA in Japan, namely Remicade (infliximab; Johnson & Johnson/Merck & Co/Mitsubishi Tanabe) and Humira, off-label use of other TNF inhibitors including Enbrel and Simponi is high. Taltz's arrival in the Japanese axSpA market is expected to curtail this off-label use, absorbing 15% and 20% of patient share from Enbrel and Simponi, respectively, across all lines of therapy.

- Exclusively in Japan, Datamonitor Healthcare forecasts Taltz to directly impact Remicade's patient share, as a result of the scarcity of approved biologics in axSpA. Taltz is expected to take up to 3% of second-line and beyond patient share from Remicade and biosimilar infliximab.

- In Japan, Taltz is forecast to take only 2% of patient share from Humira at the first and second line of therapy, and up to 8% of its patient share at the third and later lines of therapy.

DOSING

- Datamonitor Healthcare assumes dosing of 80mg every four weeks. This is based on the dosing schedules assessed in Taltz's Phase III program, and is in line with the dosing licensed for psoriatic arthritis.

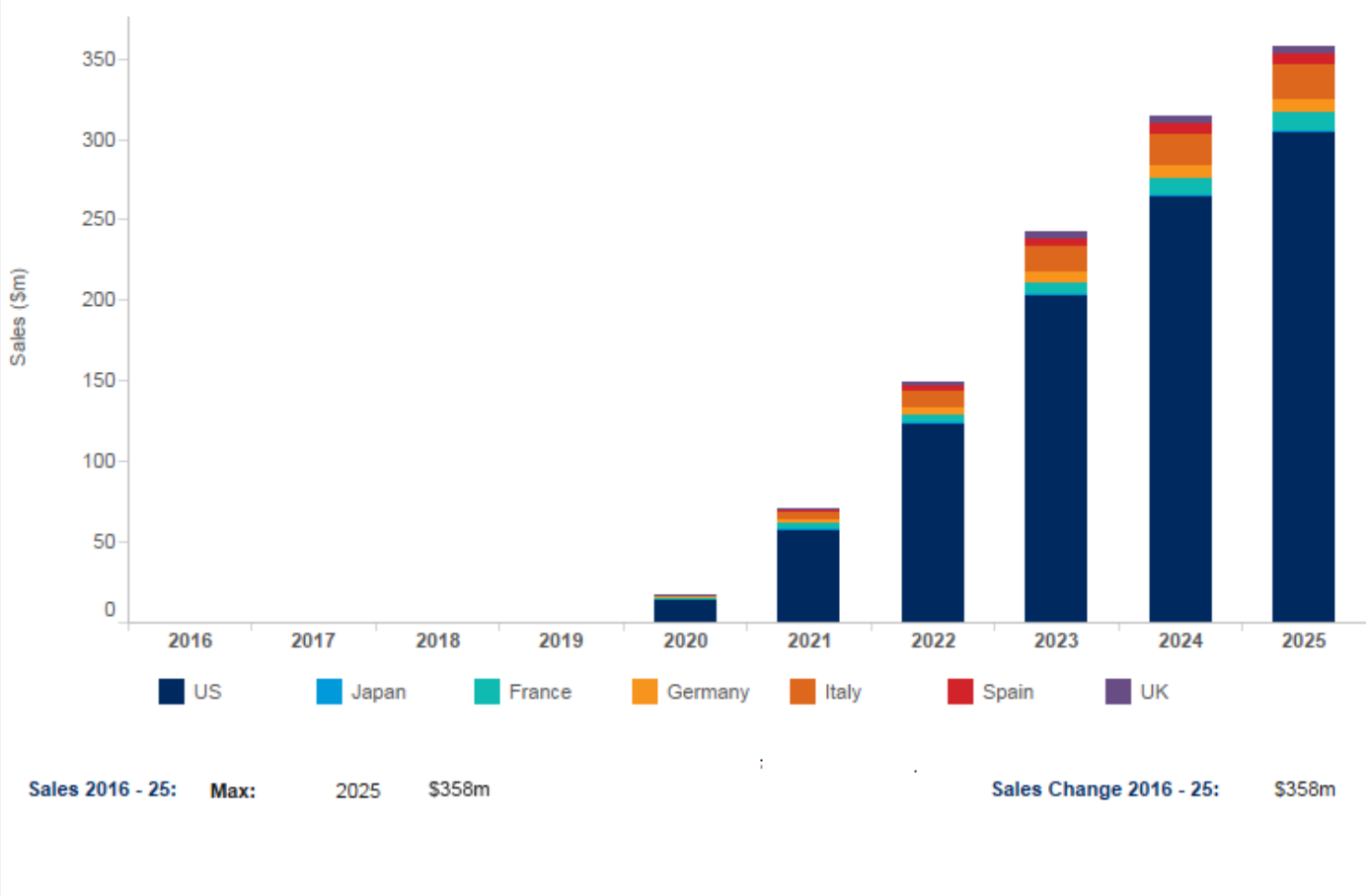
PRICING

- Datamonitor Healthcare uses national formularies to gather pricing information per product and applies backing-out formulas to adjust formulary prices in order to obtain estimates of ex-factory wholesale prices for each country. Four years of historical prices are used to trend forward prices over the forecast period. In Japan, where prices for Taltz were not available in national formularies, Datamonitor Healthcare estimated Taltz's annual treatment cost based on the average annual cost per patient of available IL inhibitors, namely Stelara (ustekinumab; Johnson & Johnson/Mitsubishi Tanabe) and Cosentyx. Please view the accompanying datapack for a full table of drug costs per patient per year.

TALTZ FORECAST, 2016–25

The figure and table below show Datamonitor Healthcare's forecast of Taltz in axial spondyloarthritis, by country, over 2016–25.

Figure 38: **Taltz sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country, 2016–25**



Source: Datamonitor Healthcare

Table 34: **Taltz sales for axial spondyloarthritis across the US, Japan, and five major EU markets, by country ($m), 2016–25**

Country	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
US	-	-	-	<0.1	14.3	58.5	123.8	203.1	265.5	304.9
Japan	-	-	-	<0.1	0.0	0.1	0.1	0.2	0.3	0.4
France	-	-	-	<0.1	0.7	2.6	5.1	7.8	9.8	11.1
Germany	-	-	-	<0.1	0.5	2.1	4.2	6.4	7.7	8.3
Italy	-	-	-	<0.1	1.1	4.7	10.0	16.0	19.8	21.5
Spain	-	-	-	<0.1	0.4	1.5	3.2	4.9	6.0	6.4
UK	-	-	-	<0.1	0.3	1.1	2.4	4.0	4.9	5.4
Grand total	-	-	-	<0.1	17.3	70.7	148.9	242.4	314.1	357.8

Note: totals may not sum due to rounding.

Source: Datamonitor Healthcare

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