Innovation in biopharma: a new way of assessing companies' potential for growth

Ernst & Young GmbH and Innoplexus AG

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> “Autoimmune diseases offer tremendous opportunities for the pharma market, as there are numerous unmet needs. With the combined expertise and insights of EY and Innoplexus, we identified the top performers and investigated their recipes for success.”
>
> Klaus Ort, EY Europe West Industry Market Leader of HS&W (Life Sciences & Healthcare)

> “Autoimmune diseases are chronic and difficult to treat. We aim to recognize the patterns of what works versus not from available data, helping to identify the innovative companies with higher probability of success.”
>
> Gunjan Bhardwaj, Founder and CEO, Partex NV and Innoplexus AG

Executive summary

Innovation in biopharma: a new way of assessing companies’ potential for growth

EY and Innoplexus have jointly developed an innovative and thorough approach to systematically identify the growth potential of biopharma companies that are active in a specific therapeutic area or medical technology field. We do this by anticipating the company’s genuine innovation potential and commercial competency, leveraging the proprietary artificial intelligence (AI)-based Clinical Trial Prediction (CTP) engine to crunch massive volumes of data from the ever-growing number of clinical trials and predict the success probability of clinical assets.

This approach offers unique, ready-to-use growth forecasts for various stakeholders which are updated at regular intervals based on latest innovations and developments. The method can be used as a living go-to tool across multiple use cases, from competitive landscaping and strategic decisions (e.g., portfolio optimization) to investment decisions (including target scouting and due diligence for M&As, in/out-licensing and partnerships).

This growth potential index ranks companies based on their clinical pipeline in the autoimmune space, as well as their commercialization capabilities. The factors taken into consideration include the novelty of the intervention (e.g., first in class in its mechanism, orphan drug designation, fast track designation and breakthrough therapy designation), the number of approved indications, consolidated expert opinions in the literature, commercial launches of blockbuster drugs, an individual drug’s advertising spend versus its sale performance, and the number of products being marketed in the portfolio.

Autoimmune diseases are the first focus area to which we have applied this approach, as they are of high investment and innovation interest with numerous treatment innovations, difficult to treat with (often unsatisfactory) existing drugs, and challenging to develop new therapeutics for. Without proper treatment, autoimmune diseases reduce people’s productivity, which often carries economic costs.

More than 1,000 trials, covering around 100 autoimmune diseases and 400 pharmaceutical companies, were chosen to be included in the index analysis. The clinical innovation aspect is calculated based on clinical pipeline parameters and the estimated probability of success – the likelihood that trials will meet their primary endpoints. Machine learning algorithms are employed to estimate the success probability of a clinical asset, and these algorithms have been shown to achieve more than 85% accuracy in hundreds of clinical trial projects.

The scores from the clinical and commercial aspects for each company are aggregated and ranked within their size categories (small, medium and large). In Chapter 5 of this report, you can find the list of the top 15 small, top 15 medium-sized, and top 20 large biopharma companies with the leading growth potential in the autoimmune space.

The methodology used for this index is applicable to other therapeutic areas and medical technologies. In future collaborations, EY and Innoplexus plan to expand the scope of the approach to other important diseases and technologies.

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The Autoimmune Index and what it does

The index demonstrates our ability to identify the growth potential of biopharma companies in the key therapeutic area of autoimmune diseases. We do this by assessing a company's genuine innovation potential (e.g., by predicting the probability of clinical trial success for novel, first-in-class therapies, etc.) and factoring in its commercial competency.

Drug development can be lucrative but is time-consuming, expensive and risky. It takes 10–15 years and costs approximately US$1.5–2b to bring a new drug to market (Harrer et al., 2019). Knowing which firms have the highest potential for growth can give pharmaceutical companies and investors an advantage. This is especially critical in the rapidly developing field of autoimmune illnesses.

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For instance, companies with a track record of innovative research and development (R&D), a focus on developing novel first-in-class or best-in-class drugs, and experience of launching successful blockbuster drugs, are classified as having higher growth potential.

Artificial intelligence to predict clinical success probability

The index combines industry knowledge and expertise with advanced technology, using an artificial intelligence (AI)-based Clinical Trial Prediction (CTP) engine which predicts the success probability of clinical assets with over 85% precision, based on a training data set of 80,000 annotated clinical trial read-outs.

As the number of trials grows each year, an automated strategy based on AI that can crunch massive volumes of data has become increasingly important. (Figure 1.1).

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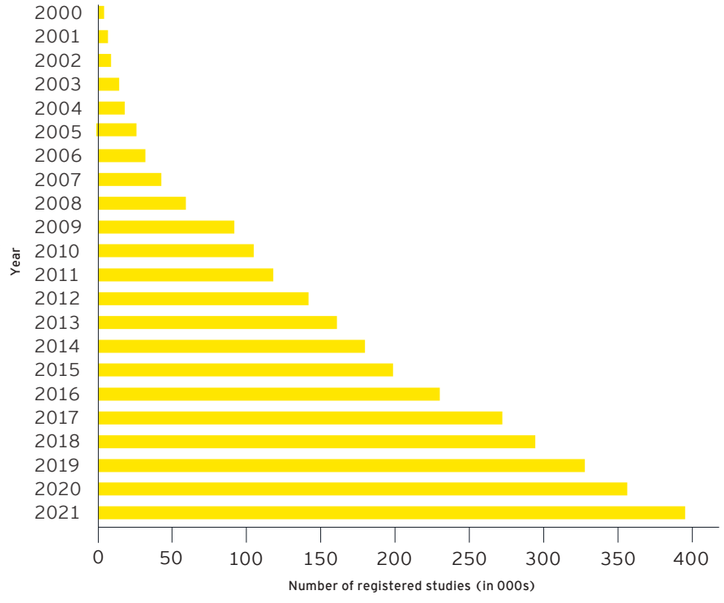
Figure 1.1: Increase in number of clinical trials (2000–2021)



Source: Statista, data extracted as of March 2022

Clinical trials have an average failure rate of 50–60%, and more than half of all trials (57%) show limited efficacy. Most trials (86%) do not meet participant recruitment targets on time, and participant dropout rates are in the region of 15–40%. Trials are often underpowered and have poor statistical endpoints (Fogel, 2018).

The CTP engine applies advanced AI and machine learning techniques as it draws on publicly available trial data and real-world events. It continuously crawls, aggregates and analyzes information, considering more than 350 parameters for each trial protocol including indication, drug, trial design, targeted patient population, and information on the drug company funding the trial.

The AI- and advanced analytics-enabled engine is fully automated and calculates predictions for ongoing trials in real time, continuously accounting for new information that may impact the probability of a trial meeting its endpoints. Its automated approach minimizes bias to provide an independent and impartial result.

It provides an innovative perspective on the growth potential of biopharma companies, to identify new commercial and clinical opportunities. It can also be used to scout relevant targets for licensing and partnerships, optimize investment portfolio and growth strategies, and mitigate operational and financial risks. This information can benefit all investors and pharmaceutical companies, regardless of size.

Companies are categorized within the index according to their revenue size or total number of clinical trials in the pipeline (as at February 2022) (Table 1.1).

Table 1.1: Top 15 pharma companies by revenue and pipeline as of 2021

Rank	Company	2021 pharma revenue (US$b)*	Number of drugs in pipeline (as of February 2022)
1	Pfizer	79.6	178
2	AbbVie	56.2	54
3	Johnson & Johnson **	52.1	53
4	Roche	49.2	145
5	Bristol Myers Squibb	46.4	122
6	Merck Sharp & Dohme	42.7	106
7	Novartis	42.0	150
8	Sanofi	37.7	91
9	AstraZeneca	37.4	177
10	GlaxoSmithKline	33.1	75
11	Takeda **	29.3	40
12	Eli Lilly	28.3	70
13	Gilead Sciences	27.3	66
14	Amgen	26.0	40
15	Novo Nordisk	21.4	29

Source: FDA, Company reports and websites.

** Non-USD currencies are converted to USD using spot exchange rates on 31 December 2021.*

*** Pharma revenue for Johnson & Johnson as per annual report for fiscal year ended 2 January 2022 and for Takeda as per annual report for fiscal year ended 31 March 2022.*

50–60%

Clinical trials have an average failure rate of 50–60% and more than half of all trials (57%) show limited efficacy.

Why autoimmune diseases?

The global incidence and prevalence of autoimmune diseases are steadily increasing, yet current treatments prove to be ineffective, provide sub-optimal relief and fail to address the underlying causes.

Autoimmune conditions result from the human body's immune system attacking its own organs, tissues and cells. They lead to pain, disability and poor quality of life, often requiring long-term health care, including drug therapy.

Collectively, autoimmune diseases affect approximately 5–10% of the USA's and 4% of the world's population (Autoimmune Registry, 2022; Hood, 2018) and are becoming more prevalent. Treating them is estimated to cost more than US$100b a year in the US (American Autoimmune Related Diseases Association and National Coalition of Autoimmune Patient Groups, 2011; Harris, 2015).

Autoimmune diseases can make patients more susceptible to other conditions, such as cancers and heart diseases, resulting in complicated treatment regimes with changes in side effects from drug-drug interactions. Autoimmune diseases reduce people's productivity, and this carries economic costs, as individuals are unable to work for intermittent to prolonged periods of time or must take on caring responsibilities.

Autoimmune diseases have been highlighted as prominent comorbidities associated with COVID-19 that can limit treatment options and prolong the disease. In particular, rheumatoid arthritis, psoriasis, type 1 diabetes, systemic lupus erythematosus (SLE) and a few others can cause problems with treatment and recovery.

Rheumatology patients and those with SLE are more susceptible to pneumonia, which is a severe manifestation of COVID-19 infection. Acute respiratory distress syndrome (ARDS), which can result from COVID-19, has also been observed in people with autoimmune diseases such as SLE.

The cytokine storm caused by the body's immune response to COVID-19 infection pushes the patient into an immunological overdrive, causing inflammatory molecules such as tumor necrosis factor (TNF) and interferons to be overexpressed and reduce the effect of immunosuppressive medications. This makes patients sicker, deteriorating the immune system further and causing more complications during treatment.

Treatment gaps and solutions

Autoimmune conditions are difficult to treat, and existing drugs are often unsatisfactory. They often have adverse effects, and medication regimens (such as regular injections) can reduce the quality of life and make treatment compliance difficult, especially in the long term.

The development of new therapeutics for autoimmune diseases is a challenging field involving numerous novel mechanisms of action being studied by scientists and pharmaceutical companies worldwide (see 'Emerging treatments from R&D', p16).

Many therapies relieve symptoms through anti-inflammatory action or by suppressing the immune response. In both cases, the therapies do not address the underlying cause of the autoimmunity, and can cause undesirable side effects, e.g., increased susceptibility to infection (Rose, 2017).

US$100b

Autoimmune diseases affect approximately 5–10% of the US's and 4% of the world's population. Treating them is estimated to cost more than US$100b a year in the US.

Treatments for autoimmune diseases within the pharma market

This chapter gives an overview of the current global market for autoimmune diseases (including the increase in therapies and advances in treatment revenues from pharmaceuticals), as well as the future outlook for the market and any gaps, and how R&D is closing these gaps to boost the market (including novel drugs, emerging treatments and biosimilars).

Overview of pharma market and recent trends

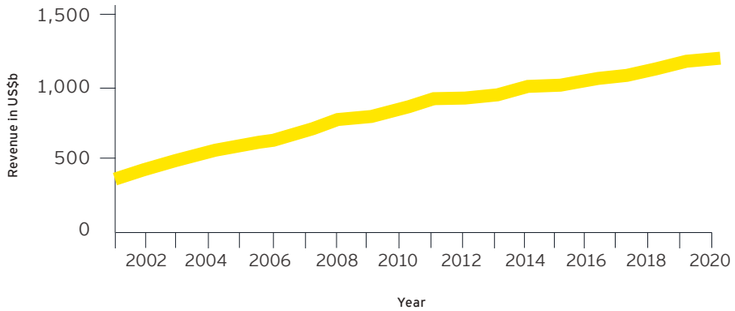
The global pharma market was estimated at US$1.3t at the end of the 2020 calendar year and grew at a compound annual growth rate (CAGR) of approximately 7% over 2001–2020 (Figure 3.1). This shows strong, steady growth.

This growth is driven primarily by:

- Growing, aging populations, rising income and emerging medical conditions
- Innovative treatment for previously unmet medical needs in several therapeutic areas
- Increase in the prevalence and incidence of medical conditions, aided by better diagnostics to identify people in need of care

R&D plays an important role in the quest for innovative treatment, despite declining R&D success rates and spending productivity. The growing market and the discovery of new disease areas has kept the industry investing in R&D; global R&D spending increased at a CAGR of around 4.5%, to approximately US$198b, from 2010 to 2020.

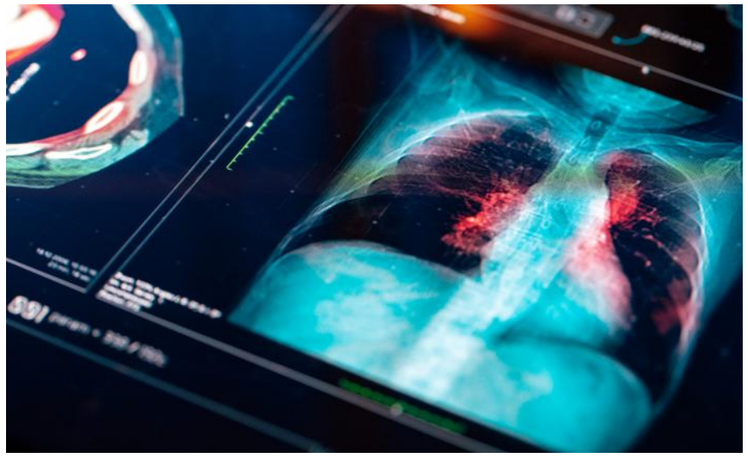
Figure 3.1: Global pharma market size (2001–2020)



Source: Statista, data extracted as of December 2020

7%
CAGR of the global pharma market from 2001–2020

4.5%
CAGR of R&D expenditure in pharma from 2010–2020



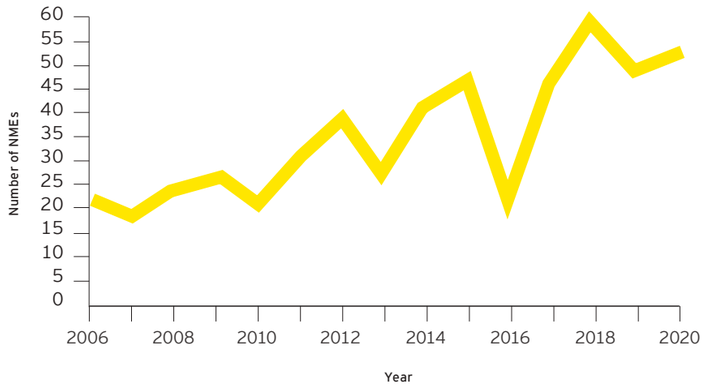
Increase in therapeutic areas

The entire pharma market has grown as a result of expansion in a variety of therapeutic areas. The majority of this growth is attributable to oncology, diabetes, dermatology and multiple sclerosis medications, as well as anticoagulants. Drug launches, rises in illness incidence, and improved diagnosis have all helped to boost the market.

Backed by robust investment in R&D and more projects in the clinical pipeline, 53 new molecular entities (NMEs) were approved by the U.S. Food and Drug Administration (FDA) in 2020 (Figure 3.2).

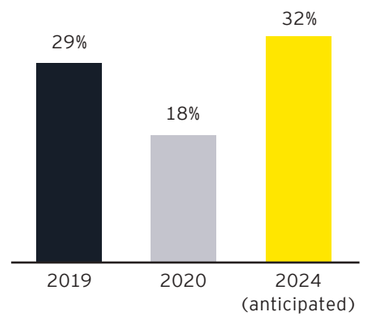
However, there was a large patent cliff between 2010 and 2014, when major drugs such as Lipitor (atorvastatin) and Nexium (esomeprazole) went off patent, which made a major dent in the overall pharmaceutical market.

Figure 3.2: Approvals of new molecular entities by FDA (2006–2020)



Source: FDA, data extracted as of January 2021

Figure 3.3: Biologics as a proportion of the global pharma market



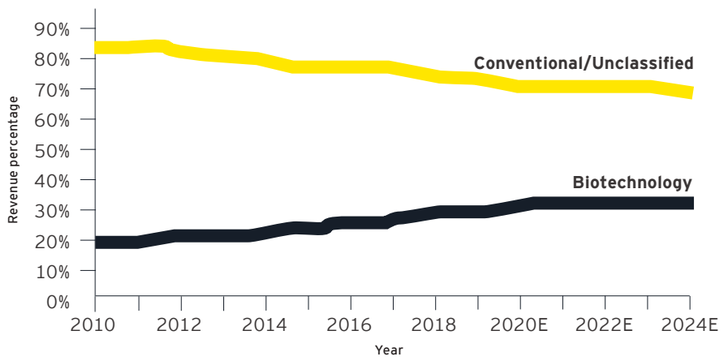
Source: Evaluate Pharma, 2021

Table 3.1: Top 10 drugs by revenue as of 2020

No.	Drug	2020 sales (US$m)	Disease	Therapeutic area	Company
1	Humira	19,832	Rheumatoid arthritis	**Autoimmune**	AbbVie
2	Keytruda	14,380	Several cancers	Oncology	Merck Sharp & Dohme
3	Revlimid	12,106	Multiple myeloma, mantle cell lymphoma	Oncology	BMS
4	Eliquis	9,168	Blood clots	Hematology	BMS, Pfizer
5	Biktarvy	7,259	HIV	Infectious	Gilead Sciences
6	Opdivo	6,992	Several cancers	Oncology	BMS
7	Xarelto	6,749	Blood clots, coronary artery disease, peripheral artery disease	Cardiology	Bayer, Johnson & Johnson
8	Rituxan	6,700	Rheumatoid arthritis, non-Hodgkin lymphoma, chronic lymphocytic leukemia	**Autoimmune**	Roche
9	Stelara	6,438	Plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis	**Autoimmune**	Johnson & Johnson
10	Prevnar	5,850	Pneumococcal pneumonia	Infectious	Pfizer

Source: Blankenship, 2021 and Company reports

Figure 3.4: Revenue from biological and conventional treatments within global pharma market (2010–2024E)



Source: Evaluate Pharma, 2019

Advances in treatment

Innovative treatments, backed by serious expenditure on R&D, have led to phenomenal growth in the pharma market.

Previously unmet needs were met with blockbuster drugs such as pembrolizumab (Keytruda, launched 2014), adalimumab (Humira, 2002), lenalidomide (Revlimid, 2005), bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy, 2018), rivaroxaban (Xarelto, 2008) and rituximab (Rituxan, 1997).

The increase in the proportion of biologics – which are highly attractive for autoimmune indications – in the overall global pharma market also accounted for the overall growth and increase in R&D expenditure. Biological drugs contributed around 10% of the global pharma market in 2010, and this rose to 18% in 2018. This proportion is anticipated to reach 32% in 2024.

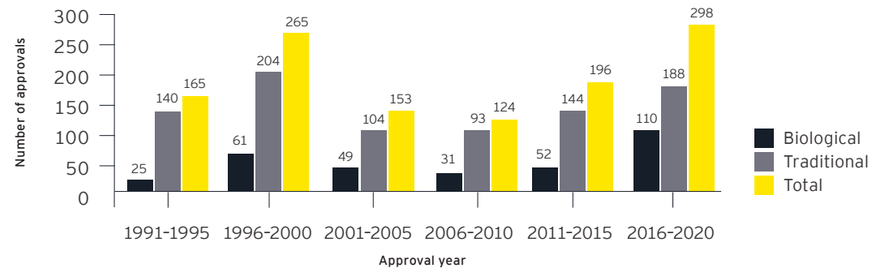
A consistent, marked rise in revenue from biologics boosted overall growth in the pharma market.

Why are more biologics getting approved?

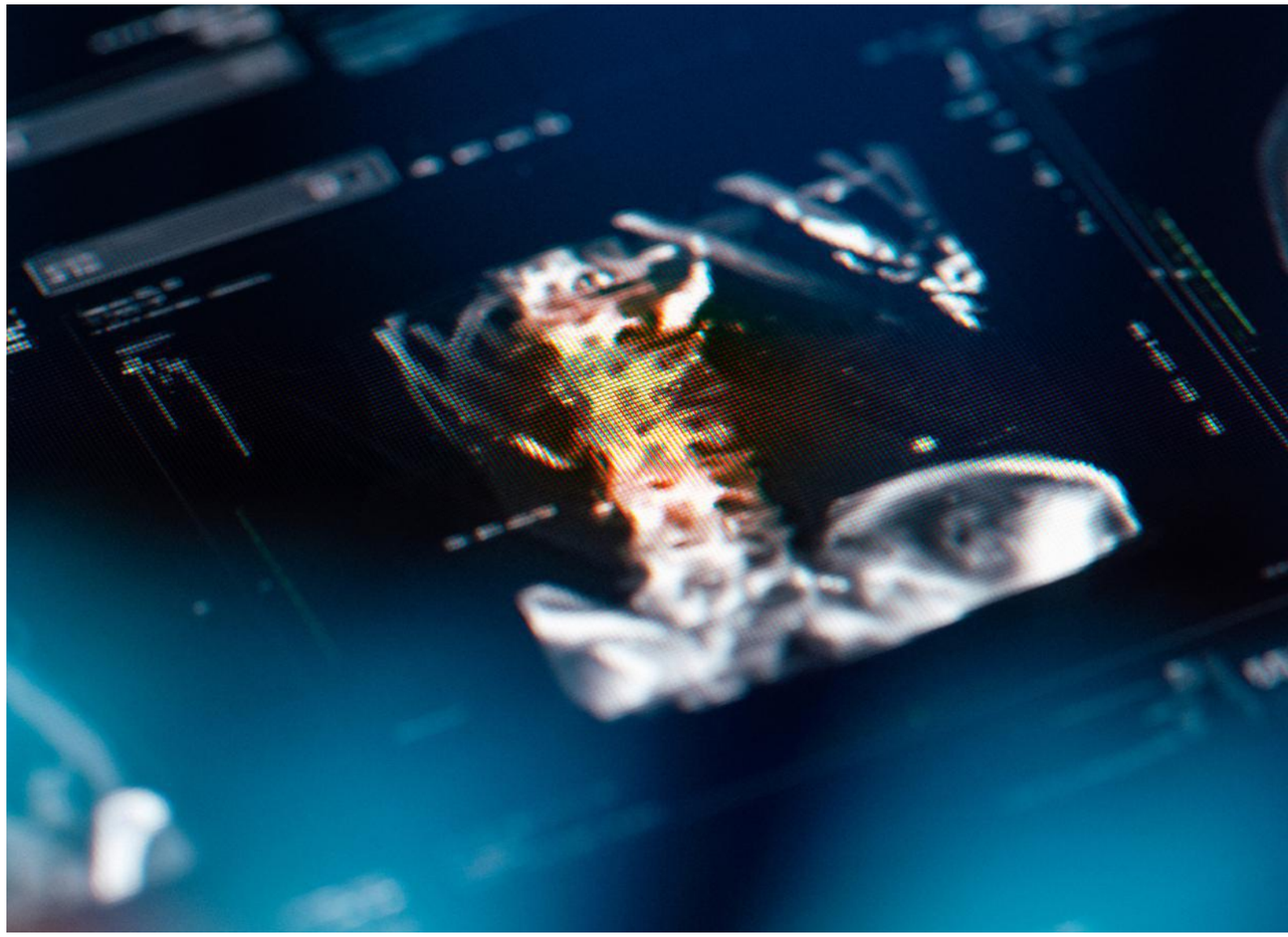
More biological NMEs have been approved since 2010 because of:

- Increased clarity on regulatory pathways for FDA approvals
- The fact that most of the targets in chemical synthesis/traditional drugs have been exploited and exhausted
- More targeted therapies

Figure 3.5: Share of biologics approvals by FDA



Source: FDA



The autoimmune market now

Biological therapies are driving the market for treatment for autoimmune conditions and new treatments are emerging.

Johnson & Johnson's Remicade (infliximab) has lost patent protection, which has led companies to develop biosimilars themselves or acquire or merge with other companies to enter the market. Examples of biosimilars are Amgen's Amgevita, a biosimilar of adalimumab, and Novartis's Sandoz approval of Erelzi, an etanercept biosimilar.

Merck Sharp & Dohme (MSD) and Pfizer set up a partnership to enter the biosimilar market. MSD marketed Benepali (an etanercept biosimilar) and Flixabi (an infliximab biosimilar) worldwide with Samsung Bioepis. Pfizer took over US company Hospira, which markets Inflectra (an infliximab biosimilar).

The top 20 autoimmune treatment companies generated around US$103b in 2021 (Table 3.2), while the global market for autoimmune conditions is pegged at US$110b.

While approvals for autoimmune treatments have recently fallen, new molecular entities for autoimmune conditions are nonetheless entering the market; those becoming available since 2010 are shown in Table 3.3. The decline in approvals has led to the market becoming more concentrated, with the top 20 companies cornering 65% of the market and the top 10 taking 56%.

Table 3.2: Top 20 pharma companies by immunology revenue in 2021

Position	Company	2021 immunology revenue (US$m)*
1	AbbVie	25,284
2	Johnson & Johnson**	16,750
3	Roche	9,148
4	Amgen	6,714
5	Sanofi	6,269
6	Novartis	5,777
7	CSL**	4,460
8	Pfizer	4,431
9	Takeda**	3,895***
10	Eli Lilly	3,361
11	Bristol Myers Squibb	3,306
12	Incyte Corporation	2,698
13	Grifols	2,640****
14	UCB	2,089
15	Horizon Therapeutics	1,979
16	Astellas Pharma**	1,521
17	AstraZeneca	1,266
18	Merck Sharp & Dohme	1,124
19	GlaxoSmithKline	1,002

Source: Company reports and websites

** Non-USD currencies are converted to USD using spot exchange rates on 31 December 2021.*

*** Immunology revenue for Johnson & Johnson as per annual report for fiscal year ended 2 January 2022, Takeda for fiscal year ended 31 March 2022, CSL for fiscal year ended 30 June 2021, and Astellas Pharma for fiscal year ended 31 March 2022.*

**** For Takeda, sales from PDT Immunology therapeutic area are not included.*

***** Immunology revenue for Grifols is as per Evaluate Pharma.*

US$103b

The amount generated by the top 20 autoimmune treatment companies in 2021. The global market for autoimmune conditions is pegged at US$110b.

Table 3.3: New molecular entities for autoimmune conditions (2015 to early 2021)

Disease	Drug	Active ingredient	Molecule type	Target	Approval year
Vitiligo	Cosentyx	Secukinumab	Biologic	IL17A	2015
Diabetes type 1	Tresiba	Insulin degludec	Biologic	INSR	2015
Immune thrombocytopenic purpura	Ninlaro	Ixazomib	Small molecule	CYP3A4	2015
Psoriasis	Taltz	Ixekizumab	Biologic	IL17A	2016
Multiple sclerosis	Zinbryta	Daclizumab	Biologic	IL2RA	2016
Sjögren's syndrome	Xiidra	Lifitegrast	Small molecule	ITGAL	2016
Diabetes type 1	Adlyxin	Lixisenatide	Small molecule	GLP1R	2016
Psoriasis	Siliq	Brodalumab	Biologic	IL17RA	2017
Multiple sclerosis	Ocrevus	Ocrelizumab	Biologic	MS4A1	2017
Rheumatoid arthritis	Kevzara	Sarilumab	Biologic	IL6R	2017
Psoriasis	Tremfya	Guselkumab	Biologic	IL23A	2017
Diabetes type 1	Ozempic	Semaglutide	Small molecule	GLP1R	2017
Diabetes type 1	Steglatro	Ertugliflozin	Small molecule	SLC5A2	2017
Psoriasis	Ilumya	Tildrakizumab	Biologic	IL23A	2018
Immune thrombocytopenic purpura	Tavalisse	Fostamatinib	Small molecule	SYK	2018
Systemic lupus erythematosus	Olumiant	Baricitinib	Small molecule	JAK1	2018
Myasthenia gravis	Ultomiris	Ravulizumab	Biologic	C5	2018
Multiple sclerosis	Mayzent	Siponimod	Small molecule	S1PR5	2019
Psoriasis	Skyrizi	Risankizumab	Biosimilar	IL23A	2019
Rheumatoid arthritis	Rinvoq	Upadacitinib	Small molecule	JAK1	2019
Neuromyelitis optica spectrum disorder	Enspryng	Satralizumab	Biologic	IL6 receptor antagonists	2020
Neuromyelitis optica spectrum disorder	Uplizna	Inebilizumab	Biologic	Antibody-dependent cell cytotoxicity	2020
Relapsing multiple sclerosis	Zeposia	Ozanimod	Small molecule	S1P receptor modulators	2020
Thyroid eye disease	Tepezza	Teprotumumab	Biologic	Signal pathway inhibitors	2020
Lupus nephritis	Lupkynis	Voclosporin	Small molecule	Calcineurin inhibitor	2021

Source: Statista, FDA

Emerging treatments from R&D

A major shift has been observed recently in the entire autoimmune drug discovery paradigm – large, complex molecules have started attracting more attention vis-à-vis biological agents.

Innovation continues in biological drugs, however. The advent of genetic analysis biomarkers has allowed them to be tailored to become more cost-effective (American Autoimmune Related Diseases Association, 2015).

Emerging treatments for several autoimmune conditions are detailed below.

Systemic lupus erythematosus
Interferons have been identified as important proteins in research into drugs to treat lupus. Interferons are signaling proteins and any presence of pathogens triggers their production and release. Patients with lupus produce too many interferons, and this drew attention to these proteins for research purposes.

Ustekinumab, which has already been approved for psoriasis, psoriatic arthritis and Crohn's disease, is being evaluated for lupus in phase 3 of clinical trials. Ustekinumab blocks the IL12/23 pathway, which is linked to the pathogenesis of lupus.

Voclosporin, a calcineurin inhibitor that blocks T cells, has recently received FDA approval for lupus nephritis.

Biomarkers could enable clinicians to recognize the development of disease in advance, leading to earlier treatment. Research to identify biomarkers is under way.

Type 1 diabetes
Teplizumab, an anti-CD3 monoclonal antibody, has been found to delay the onset of type 1 diabetes for an average of two years in adults and children who are at high risk of developing the condition. This is a further step in the quest to find a cure with immune therapies and beta cell therapies.

A Biologics License Application (BLA) for teplizumab has been submitted to the FDA for approval; research on this was funded by the Juvenile Diabetes Research Foundation (JDRF, 2020).

Progress in medication development includes new immunotherapies, including drugs that inhibit SGLT 1 (sotagliflozin) and SGLT 2 (dapagliflozin). Their mechanism of actions affects glucose absorption in the kidney, thereby enabling glycemic control in a novel way.

Researchers are making efforts to transplant pancreatic islets containing healthy beta cells into patients with diabetes. This could reduce or even eliminate the need for insulin therapy for life.

Rheumatoid arthritis
With future treatments becoming more targeted and selective to improve efficacy and reduce negative effects, Janus kinase (JAK) inhibitors are emerging as potentially competent candidates in the treatment of rheumatoid arthritis (Managed Healthcare Executive, 2018).

Biosimilars in autoimmune diseases

Biologics are effective in the treatment of autoimmune inflammatory conditions such as rheumatoid arthritis and inflammatory bowel diseases. Biosimilars, the therapeutic equivalents of original biological therapies, have growing potential. There are no clinically meaningful differences in efficacy or safety between biologics and biosimilars. Biosimilars can increase patient access to biological treatment options at a lower cost than biologics. While there is concern that cost savings could come at the expense of efficacy, patients need to understand biosimilars to obtain the maximum benefit from them and avoid nocebo effects.

Approximately 33 biosimilars have been approved to date by the FDA, with Yusimry (adalimumab), the seventh biosimilar to Humira, being the most recently approved, in December 2021.

Most biosimilars approved for autoimmune diseases are equivalent to the major blockbusters etanercept, adalimumab, infliximab and rituximab. Several more are in the clinical development pipeline (Isaacs et al., 2016; Kim et al., 2020).

The future autoimmune market

The size of the global autoimmune disease therapeutics market is projected to reach US$119.4b by 2027, from US$98.2b in 2020, at a CAGR of 2.4% from 2021 to 2027 (Market Reports World, 2022).

The market for autoimmune diseases grew at a CAGR of approximately 10% from 2014 to 2018 on the back of approvals for medications in autoimmune conditions in general and continued growth from blockbuster drug Humira, which has not only been approved for rheumatoid arthritis, but also for many other indications.

Approvals of biologics also drove momentum between 2014 and 2018, although patent expiries pulled this back. A few important drugs lost patent protection, which led the generic drugs to grasp a larger slice of the market.

Looking ahead and closing gaps in the market

A significant amount of R&D is taking place to address the rise in autoimmune conditions, and in needs that remain unmet. Existing treatments often have adverse effects and can carry risks, some of them significant.

New types of therapies and maintenance strategies can help to meet needs and improve adherence to medication regimens, which patients can struggle with.

New types of clinical trial designs could also lead to treatments being developed more quickly and in a more cost-effective manner.

Different approaches, their modes of action and how they feed into future trends are shown in Figure 3.6.

Figure 3.6: Future trends and what drives them

	Future trends
Disease related	▸ **Use of biomarkers for patient stratification and targeted treatment** ▸ Novel biomarker identified – **S100A11 (calgizzarin)** shown to have association with several autoimmune diseases ▸ It is dependent on NETosis ▸ It augments the inflammatory response by inducing pro-inflammatory cytokines in neutrophils
Trial design related	▸ **Basket trials** – Gradual adoption in clinical trial design of rare autoimmune disease, e.g., study of TNT009 in patients with complement-mediated disorders ▸ Drivers for this type of trial are less expensive, time-intensive and can include subtype of diseases ▸ **Adaptive trial design** – In rheumatology, this can be applied to early-stage trials ▸ **Bayesian Markov model** – Multistate version of this model to compare treatments in autoimmune diseases like immune thrombocytopenic purpura
Treatment related	▸ **Peptide analog** – To disrupt the formation of the MHC autoantigen – T cell receptor complex ▸ **Tolerizing therapies:** ▸ **Attenuated activated T cells** – To suppress the disease-causing T cells ▸ **Desensitization** – Uses disease-specific autoantigen peptides or antigens like oral collagen type II ▸ **Anti-PD1 therapy** – Selectively ablates the dysfunctional cells and restores balance of immune system ▸ **Gene therapy** – Strong anti-inflammatory properties and the ability to induce regeneration, e.g., MSCs ▸ **mRNA vaccination** – This approach could transform the treatment of autoimmune diseases

Source: EY analysis, Company reports and websites

Upcoming significant drugs

Many innovative drugs are in the clinical pipeline, and these are discussed in the Autoimmune Index (Chapter 5). A few that are projected to perform particularly well and gain significant commercial market share in coming years are listed below.

ARGX-113 (Efgartigimod)

This drug has had positive results in phase 3 trials in myasthenia gravis (June 2021) and has received orphan drug status for this condition. Efgartigimod has a projected revenue of US$1.9b by 2024. The FDA accepted BLA filing for efgartigimod for the treatment of generalized myasthenia gravis in March 2021 and approved it in December.

Filgotinib

This has been developed in a collaboration between Galapagos NV and Gilead Sciences. It is being tested for several diseases including ulcerative colitis, Crohn's disease and psoriasis. Filgotinib has recently been approved and is now marketed as Jyseleca in the European Union, UK and Japan for the treatment of rheumatoid arthritis. Its revenue is projected to be US$1.4b by 2024.

Upadacitinib

This has been developed by AbbVie. It received FDA approval in 2019 for the treatment of rheumatoid arthritis. Upadacitinib is approved by the European Commission for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Currently, it is being tested in ankylosing spondylitis, hidradenitis suppurativa, psoriatic arthritis and Crohn's disease. It is showing promise as a treatment for ankylosing spondylitis. Upadacitinib has a projected revenue of US$2.6b by 2024.

Lirentelimab

This drug has been developed by Allakos. Currently, it is being tested for eosinophilic esophagitis. It was given orphan drug designation for eosinophilic gastritis, eosinophilic gastroenteritis and eosinophilic esophagitis in October 2020. It is estimated that it will generate revenue of over US$1b a year by 2028.

Avacopan

Avacopan is a first-in-class small molecule that binds to C5a, preventing it from binding to its receptor. ChemoCentryx amended the approval application for avacopan and it was approved in October 2021. Analysts are forecasting peak sales in the early 2030s that will exceed US$1b.

Lenabasum

Corbus Pharmaceuticals is developing lenabasum for systemic sclerosis, dermatomyositis and systemic lupus erythematosus. Lenabasum was granted orphan drug designation for the treatment of dermatomyositis and systemic sclerosis from the FDA and the European Medicines Agency in March 2021. Analysts estimate that lenabasum could generate peak sales of up to US$2b if it wins approvals in treating all three conditions.

HZN-825

Horizon Therapeutics is developing HZN-825 for systemic sclerosis. Currently, the drug is in phase 2b of clinical trials. HZN-825 is an oral selective LPAR1 antagonist with early signals of benefit in diffuse cutaneous systemic sclerosis. It is estimated that the drug could generate peak sales of over US$1b.

Index methodology

Building the Autoimmune Index

The Autoimmune Index rates companies based on two factors:

- The clinical innovation of all the drugs in their pipeline
- Their commercial competency

Together they help in building the index (Steps A, B and C). Apart from this, other key factors in creating the Autoimmune Index involve assessing just how innovative a company is in the autoimmune space. To do this, we first look at how new and original its ongoing clinical trials are.

Clinical innovation of drugs

- A.1) This is the first step to identify ongoing trials at overall and phase 2/phase 3 level. This is an important step toward identifying the right drugs to build the index.
- (A.2) This step involves the identification of unique drugs that are present in the clinical pipeline of the sponsor.
- (A.3) Once all unique drugs are identified, blockbuster drugs (drugs with present or expected sales of greater than US$1b) will be further identified.

In addition to evaluating the innovation potential of companies, we need to evaluate their commercial capabilities (B). We need to use three key performance indicators to evaluate this. The performance indicators are as follows:

- (B.1) Overall sales volumes
- (B.2) An individual drug's sales volume in relation to its advertising spend
- (B.3) The company's sales volume in autoimmune diseases and the number of marketed drugs per company

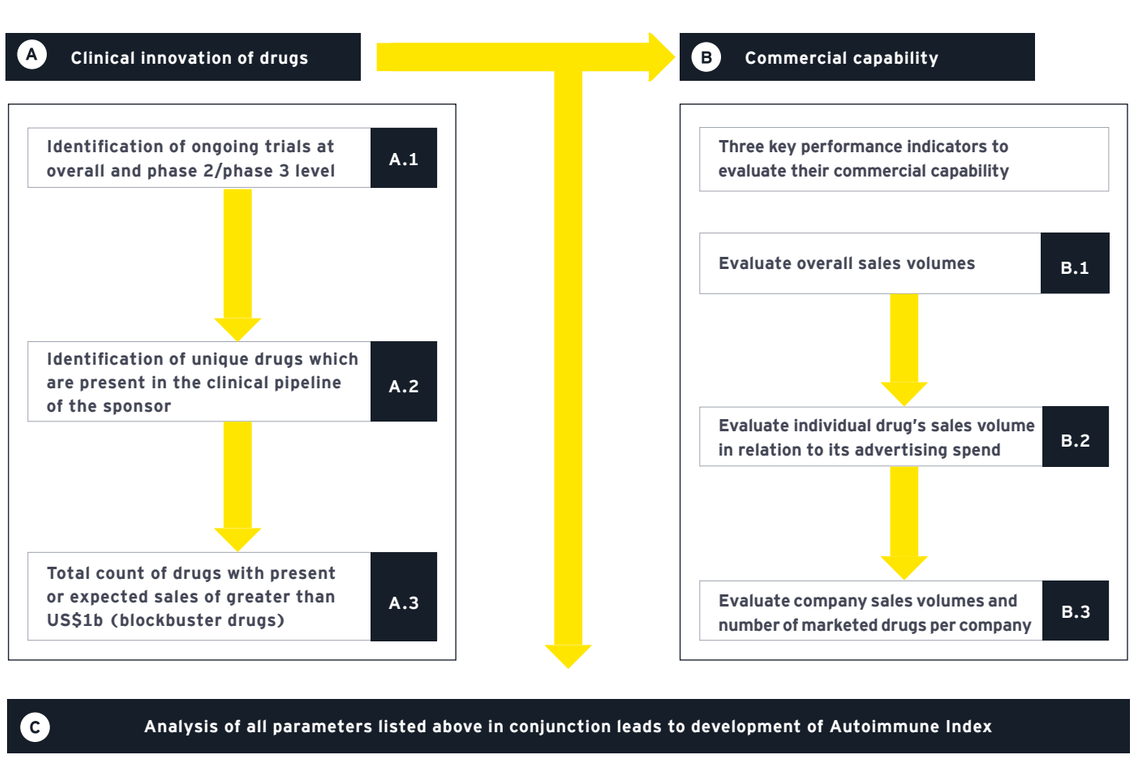
The detailed methodology of the Autoimmune Index is set out below.

Trial populations

More than 1,000 trials, covering around 100 autoimmune diseases, were chosen based on the following factors:

- The trial is ongoing.
- The recency of completed trials.
- It is an interventional trial.

Figure 4.1: Building the Autoimmune Index



Innovation parameters

The innovativeness of a trial is assessed based on the following factors. These parameters are listed in order of their contribution, as follows:

Novelty of drug
Molecules that are active against a therapeutic target, have a unique mechanism of action for that disease and received special regulatory approval for the development of that molecule.

First-in-class drug
Mechanism of action explored for the first time by this drug for the disease.

Literature score
This is based on number of scientific articles sourced from peer-reviewed journals about the drug-disease combination, their recency and publication impact factor.

Orphan drug/fast-track/ breakthrough designation
European Medicines Agency and FDA designation status for that disease and/or drug.

Prior drug approval
If the drug is approved for any other disease.

Disease has approved drug
If the disease already has any approved drug.

Drug addresses unmet need
Whether the drug addresses any unmet need in autoimmune disease.

The clinical innovation aspect is calculated based on the parameters above and the probability of success – the likelihood that trials will meet their primary clinical trial objectives. For example, a highly innovative drug with a medium probability of success would be scored as having a medium level of innovativeness in the clinical innovation aspect.

Listed companies are divided by market capitalization.	Unlisted companies are categorized by total number of clinical trials conducted so far.
Large pharmaceutical companies:	**Large pharmaceutical companies:**
>US$20b	**>200 trials**
Medium-sized pharmaceutical companies:	**Medium-sized pharmaceutical companies:**
US$1-20b	**30–200 trials**
Small pharmaceutical/ biotech companies:	**Small pharmaceutical/ biotech companies:**
<US$1b	**<30 trials**

Biopharma company categories

When we assess the innovativeness of the clinical pipeline of a company in the autoimmune space, we categorize pharmaceutical sponsors in three broad categories:

- Large pharmaceutical companies
- Medium-sized pharmaceutical companies
- Small pharmaceutical/biotech companies

Calculating probability of success

By leveraging advanced AI and machine learning techniques based on publicly available trial data and real-world events that are continuously crawled, aggregated and analyzed, the AI-enabled engine calculates predictions for ongoing trials in real time.

It identifies which features predominantly contribute to the success or failure of the trial and finds optimal values for these features to increase the probability of success. The engine continuously takes account of new information that may affect the probability of a trial meeting its endpoints.

The engine leverages more than 350 features for each trial protocol, such as clinical indication, drug, trial design, targeted patient population and sponsor-related information.

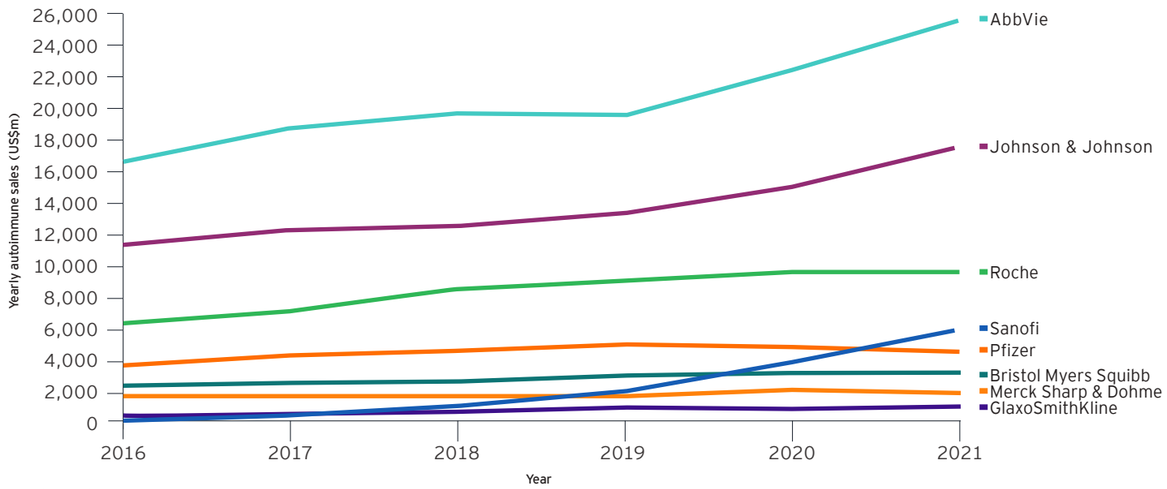
Predicting success through machine learning

To determine the probability of success of a clinical trial and the factors that contribute to its success or failure, machine learning algorithms are employed which have been shown to achieve more than 85% accuracy. This result is then fed to another machine learning-based interpretation algorithm, which identifies the factors that contribute to that trial's success or failure.

Table 4.1: Company category by size

Listed companies	
Size	**Market capitalization**
Small	<US$1b
Medium	US$1b–US$20b
Large	>US$20b
Unlisted companies	
Size	**Total number of clinical trials**
Small	<30
Medium	30–200
Large	>200

Figure 4.2: Yearly sales of top 10 large pharma companies by immunology segment (2016–2021)



Source: Company reports and websites

Table 4.2: Top 6 drugs in autoimmune diseases by ad spend in 2020

Company	Top advertised drug	Drug ad spend 2020 (in US$m)	Drug sales 2020 (in US$m)*	Drug sales/ ad spend ratio 2020
AbbVie	Humira	499.9	19,832.0	39.7
	Skyrizi	202.3	1,590.0	7.9
	Rinvoq	175.5	731.0	4.2
Amgen	Otezla	150.4	2,195.0	14.6
Sanofi	Dupixent	409.8	4,340.6	10.6
Pfizer	Xeljanz	232.7	2,437.0	10.5

Source: Kantar Media, Company reports and websites

** Non-USD currencies are converted to USD using spot exchange rates on 31 December 2021.*

Commercial capabilities of large pharma companies

The commercial capabilities necessary to successfully commercialize a pharmaceutical product are not easy to put in place, but can determine whether even the most innovative compounds will become a commercial success. Practically, only large pharma companies have the necessary scale and experience for launch and commercialization, which medium-sized and small companies don't often achieve.

Therefore, in evaluating commercial capabilities, we focused on the comparisons among large pharma companies that have a commercial track record and footprint.

To determine the biggest players, first the top 10 large pharma companies by aggregated sales in the autoimmune space were identified. Figure 4.2 shows the top large pharma players in autoimmune diseases, with sales ranging from US$1b to approximately US$25.3b in the autoimmune space in the past year.

For these leading players, we have looked at the performance indicators for their advertising effectiveness. To determine advertising effectiveness, the ratio between sales achieved and advertising spend on individual drugs has been used as an indicator.

Table 4.3: Top 10 large pharma companies in autoimmune diseases: annual sales and major marketed autoimmune drugs in 2020

Company	Immunology segment revenue 2020 (US$b)*	Number of major marketed autoimmune drugs 2020	Major marketed autoimmune drugs 2020
AbbVie	22.15	3	Humira, Skyrizi, Rinvoq
Johnson & Johnson**	15.05	4	Remicade, Simponi/Simponi Aria, Stelara,Tremfya
Roche	9.30	6	Actemra/RoActemra, Xolair, Esbriet, CellCept, MabThera/Rituxan, Pulmozyme
Amgen	7.19	2	Enbrel, Otezla
Novartis	4.86	2	Cosentyx, Ilaris
Sanofi	4.60	2	Dupixent, Kevzara
Pfizer	4.56	3	Xeljanz, Enbrel, Inflectra/Remsima
Takeda**	3.56***	1	Entyvio
Bristol Myers Squibb	3.16	1	Orencia
Eli Lilly	2.46	2	Taltz, Olumiant

*Source: FDA, Company reports and websites. * Non-USD currencies are converted to USD using spot exchange rates on 31 December 2021. ** Immunology segment revenue for Johnson & Johnson as per annual report for fiscal year ended 2 January 2022 and Takeda for fiscal year ended 31 March 2022. *** For Takeda, sales from PDT Immunology therapeutic area are not included.*

With regard to commercial effectiveness, large pharma companies with a bigger portfolio of marketed products in autoimmune diseases tend to achieve higher advertising effectiveness. AbbVie, Amgen, Sanofi and Pfizer are among the top performers here (Table 4.2).

Taking these two indicators together (Tables 4.2 and 4.3), AbbVie, Johnson & Johnson, Roche, Amgen, Novartis, Sanofi and Pfizer achieved the highest commercial effectiveness in autoimmune diseases.

Detailed methodology

Training data generation

To develop a supervised machine learning algorithm, training data is required so the algorithm can learn to make data-driven decisions on unseen data. For all the autoimmune diseases, trial data was gathered from multiple clinical trials registries (e.g., clinicaltrials.gov), and those trials were assigned a pass or fail label (the dependent variable).

This data is not available in a single public source, so it was derived from:

- Biomedical and life sciences literature
- Press releases
- Clinical trial results
- FDA reviews and labels
- Terminated and withdrawn trials

> “The top 10 players recorded sales ranging from US$1b to approximately US$25.3b in the autoimmune space in the past year.

Feature engineering and aggregation

There are four classes of features. Each has an independent module to generate features at trial level. Look-ahead bias is taken into account while forming each of them. The features are based on the following:

- **Trial information and study design:** Trial data is extracted using an information retrieval system. This is then parsed and cleaned to retrieve trial information (e.g., enrolment, phase), and features related to study design (e.g., endpoint) are normalized and bucketed at a broader level.
- **Author and drug company reputation:** All authors and companies are extracted from the trial data and normalized using a proprietary named-entity normalization algorithm. Normalized authors are then fed to another proprietary key opinion leader (KOL) scoring algorithm, which returns a score for each author. For company reputation, we examined features such as the number of trials conducted by that company before the start date of the trial and the number of approved drugs it had produced.
- **History:** To generate history-based features based on the trial’s drugs and diseases, we parsed different drugs and diseases from the trials. Once parsed, we normalized them using drug- and disease-based ontologies. These are used to retrieve past information on the number of publications, grants, patents, clinical trials, etc.
- **Drug and disease:** Data from different public sources for drugs and diseases is crawled and normalized using our proprietary ontology. Features such as the biological and pharmacological properties of the drug, the number of pathways and the number of targets are generated on a drug and disease level. These are then aggregated at trial level.

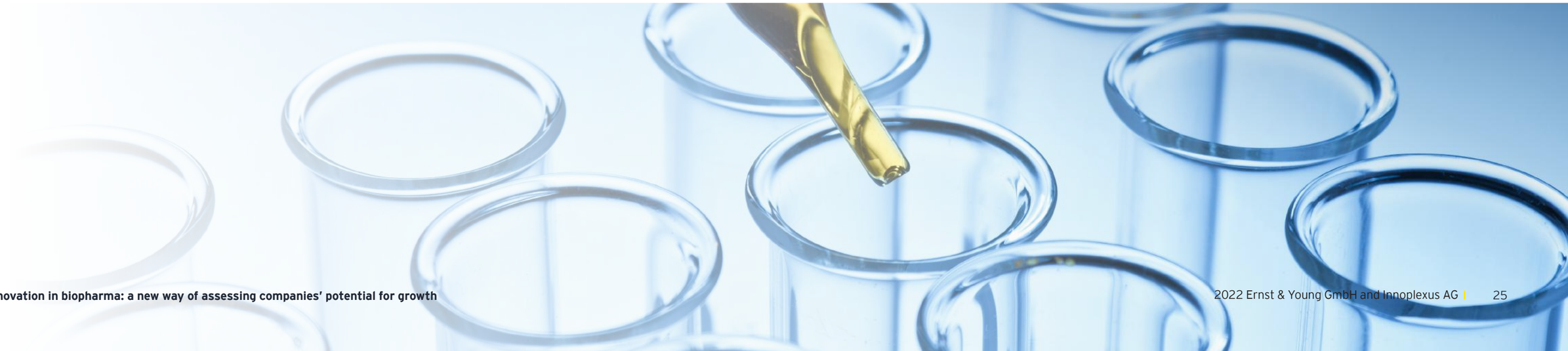
Model building, evaluation and prediction

After the data from various sources has been merged, it is ready to be fed to a machine learning algorithm that can learn from it, derive insights and use it for predicting the probability of success of any trial. The following steps are followed for model building and evaluation:

- **Look-ahead bias removal:** For this, an intermediate version (i.e., a trial that does not have a status of “completed”, “withdrawn” or “terminated”) is used, so the algorithm does not learn from studies with these results.
- **Sample weights:** Each trial in the training data is assigned a weighting based on our indication similarity algorithm, which uses disease hierarchical ontology. Different autoimmune diseases have different weightings.
- **Model building and evaluation:** After the above steps, training data is fed to classification algorithms and we train a different model for each autoimmune disease. For model evaluation, we use 15% of all the data and achieve an accuracy of more than 85%.

Post-modeling analysis and insights

This involves interpreting results generated from the previous steps. A commonly used machine learning model interpretation technique is used for this. The overall summary plot shows the importance of each feature and its effects and assesses the degree to which each feature contributes to the final prediction.



CHAPTER 5

The Autoimmune Index

The Autoimmune Index scoring model was run on some 1,000 trials involving 400 pharmaceutical companies. Scores for each company were aggregated.

The companies are ranked within their size category.

Abbreviations used in the Index

BLA
Biologics license application

EMA
European Medicines Agency

FDA
US Food and Drug Administration

FSGS
Focal segmental glomerulosclerosis

MaB
Monoclonal antibody

MoA
Mechanism of action

MS
Multiple sclerosis

NME
New medical entity

PNH
Paroxysmal nocturnal hemoglobinuria

PsA
Psoriatic arthritis

RA
Rheumatoid arthritis

SLE
Systemic lupus erythematosus

UC
Ulcerative colitis

5.1. Index of small pharmaceutical/biotech companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 5	Abivax	**ABX464:** Three phase 2 trials (two in rheumatoid arthritis [Phase 2a completed] and one in Crohn's disease [Phase 2b pivotal study planned]) **MoA:** Rev gene product inhibitors (promote the production of miR-124 in immune cells) **Importance:** Oral, first in class, small molecule; demonstrated safety and profound anti-inflammatory activity in moderate-to-severe UC and possibly Crohn's disease due to disease similarity
Top 5	Corbus Pharmaceuticals	**Lenabasum:** One phase 2 trial in SLE was completed as of July 2022* **MoA:** Selective agonist to cannabinoid receptor type 2 **Designation:** FDA orphan drug for dermatomyositis, systemic sclerosis **Importance:** First in class, novel, oral, small molecule – demonstrated acceptable safety and tolerability profiles in clinical studies. Company has potential annual market of US$2b due to unique MoA targeting the endocannabinoid system for rare inflammatory and fibrotic diseases
Top 5	Kadmon, a Sanofi company**	**Belumosudil:** Two phase 2 ongoing trials for systemic sclerosis/scleroderma **MoA:** Rho-associated coiled-coil kinase 2 (ROCK2; ROCK-II) inhibitor **Designation:** Orphan drug designation (FDA) for the treatment of systemic sclerosis **Importance**: Belumosudil is orally administered, helps to resolve immune dysregulation by downregulating pro-inflammatory Th17 cells and increasing regulatory T (Treg) cells. FDA approved belumosudil for chronic graft-versus-host disease. Currently, no FDA-approved targeted therapies for systemic sclerosis
Top 5	Provention Bio	**Teplizumab:** One phase 3 and phase 2 trial for type 1 diabetes **PRV-015:** One phase 2 trial for celiac disease **MoA:** Teplizumab – CD3 antigen inhibitors; PRV-015 – IL-15 inhibitor **Designation:** Teplizumab – breakthrough therapy designation (FDA); PRIME designation (EMA) for the treatment of clinical type 1 diabetes **Importance:** Teplizumab – BLA submitted, shown to not only delay the destruction of beta cells but also restore insulin production in dysfunctional beta cells; PRV-015 is monoclonal antibody treat gluten-free-diet celiac disease
Top 5	Rigel Pharmaceuticals	**Fostamatinib:** Phase 3 trial currently ongoing for warm autoimmune hemolytic anemia* **MoA:** Tyrosine kinase inhibitor **Designation:** Orphan drug designation and fast-track designation by FDA for warm antibody AIHA **Importance:** There are no approved therapies for wAIHA. A study showed that it markedly improved the hemoglobin levels in patients with wAIHA. FDA approved fostamatinib for the treatment of adult patients with chronic immune thrombocytopenia
6–15	Caelum Biosciences	**CAEL-101:** Two phase 3 trials for CAEL-101 for AL amyloidosis; one phase 2 trial in active but not yet recruiting stage* **MoA:** Serum amyloid A protein inhibitors **Designation:** CAEL-101 has received orphan drug designation from both FDA and EMA as a therapy for patients with AL amyloidosis **Importance:** First-in-class mAb designed to improve organ function by reducing or eliminating amyloid deposits in the tissues and organs of patients with AL amyloidosis

* Data reassessed and updated as of 22 July 2022
** Kadmon Holdings was acquired by Sanofi in September 2021

5.1. Index of small pharmaceutical/biotech companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
6-15	Calliditas Therapeutics	**Nefecon:** Two phase 3 trials in IgA nephropathy* **MoA:** Glucocorticoid receptor agonists; immunosuppressants **Designation:** Calliditas received 2020 SwedenBio Award for development program of Nefecon (based on recent positive topline data of the pivotal phase 3 NefIgArd trial), orphan drug designation and priority review by FDA for IgA nephropathy **Importance:** Novel, oral formulation of a potent active substance budesonide for targeted release, high concentration can be applied locally where needed limiting systemic exposure and side effects
6-15	Chinook Therapeutics US	**BION-1301:** Phase 2 and phase 1 trials for IgA nephropathy: one trial terminated and one in recruiting stage as of July 2022* **Atrasentan:** Phase 2 and 3 trials for IgA nephropathy in recruiting stage as of July 2022* **MoA:** BION-1301: blocks APRIL binding to both the BCMA and TACI receptors, is being evaluated in IgA nephropathy **Atrasentan:** Selective and potent inhibitor of the endothelin A receptor, or ETA **Importance:** 1. BION-1301 is a first-in-class humanized antibody targeting APRIL (TNFSF13) 2. IgA nephropathy is the lead indication for evaluation of atrasentan due to the role of endothelin activation and proteinuria in IgA nephropathy disease progression and high unmet need
6-15	Concert Pharmaceuticals	**Deuruxolitinib:** Two phase 3 trials in alopecia areata. One phase 2/3 trial in alopecia areata and one phase 2 trial in alopecia areata **MoA:** Deuterium-modified form of the JAK ½ inhibitor ruxolitinib **Designation:** Granted breakthrough therapy (FDA) and fast-track designations (FDA) for CTP-543 **Importance:** CTP-543 is deuterium-modified analogue of ruxolitinib and was found to alter its human pharmacokinetics in ways which may enhance its use as a treatment for alopecia areata, oral treatment
6-15	Diamyd Medical	**Diamyd (GAD-Alum):** One phase 2 trial for latent autoimmune diabetes in adults is complete as of July 2022. One phase 3 trial launched in recruiting stage and one phase 1/2 trial for type 1 diabetes* **MoA:** Induction of a Th2 immune response an increase in GAD IgG4 antibodies, immunostimulants. Antigen-specific immunotherapy for the preservation of endogenous insulin production **Designation:** Orphan drug by FDA, patent granted by the Japan Patent Office is valid until 2035 for Intralymphatic administration of Diamyd **Importance:** First in class. Found to be effective in predefined genetic subgroup consists of patients positive for the human leukocyte antigen (HLA) DR3-DQ2 haplotype (found in approximately 50% of patients)
6-15	Harbour Biomed	**HBM9161:** One phase 2/3 trial for immune thrombocytopenic purpura and one phase 1 trial for neuromyelitis optica has been completed as of July 2022* **MoA:** Selectively inhibits the neonatal fragment crystallizable receptor (FcRn) **Designation:** China CDE breakthrough therapy designation for myasthenia gravis (2021) **Importance:** Fully human mAb. Compared with plasmapheresis and IVIg, has potential benefits as a more effective, first-in-class or best-in-class treatment for rare autoimmune diseases, including subcutaneous delivery

* Data reassessed and updated as of 22 July 2022

5.1. Index of small pharmaceutical/biotech companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
6–15	InflaRx	**IFX-1 (vilobelimab):** Two phase 2 trials for granulomatosis with polyangiitis; one terminated, one completed as of July 2022* **MoA:** Complement C5a inhibitors **Importance:** First-in-class monoclonal anti-human complement factor C5a antibody. Vilobelimab holds large potential for treating various inflammatory diseases and certain cancers including hidradenitis suppurativa, ANCA-associated vasculitis and pyoderma gangraenosum
6–15	Kezar Life Sciences	**KZR-616:** Two phase 2 trials for the treatment of polymyositis-dermatomyositis **MoA:** Dual inhibitor of immunoproteasome subunit LMP7/LMP2 **Designation:** Orphan drug designation (FDA) for the treatment of polymyositis and dermatomyositis **Importance:** Offers novel approach to harmonize the immune system via selective immunoproteasome inhibition, has the potential to affect multiple drivers of immune-mediated diseases, KZR-616 is first-in-class small molecule drugs
6–15	Landos Biopharma	**Omilancor (Bt-11):** One phase 2 trial for Crohn's disease. One phase 1 trial for eosinophilic esophagitis which was ongoing in March 2022 has been withdrawn as of July 2022 **NX-13:** One phase 1 trial for UC **MoA:** Omilancor (Bt-11) – binds to and activates LANCL2 and is inflammation mediator inhibitor; NX-13 – NF-kappa B modulator, NLR protein stimulants **Importance:** 1. BT-11 is first in class, oral, gut-restricted, targeting the LANCL2 pathway in immune cells of the gut. No FDA-approved therapeutic for eosinophilic esophagitis 2. Landos Biopharma seeking US$100m IPO to boost AI autoimmune R&D work (AI-based LANCE platform) 3. NX-13 is a first-in-class, orally active, gut-restricted, small molecule 4. In May 2021, Landos Biopharma and LianBio announce collaboration and license agreement to develop and commercialize omilancor and NX-13 in greater China and select Asian markets
6–15	R-Pharm US	**Olokizumab:** Phase 3 trial completed and phase 1 trial in recruiting stage for RA as of July 2022* **RPH-104:** One phase 2 trial for urticaria **MoA:** Olokizumab: IL6 inhibitor; RPH-104: IL-1β/IL-1F2 inhibitor **Importance:** 1. Olokizumab has a unique biologic mode of action: it is a MAb, which targets the interaction between the IL-6/IL-6 receptor complex and gp-130; positive results in phase 3 for RA 2. RPH-104 is a globally patented novel recombinant heterodimer nanoprotein

*** Data reassessed and updated as of 22 July 2022**

5.2. Index of medium-sized pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 5	Argenx	**Argx-113 (efgartigimod):** Five phase 3 trials in primary immune thrombocytopenia; one completed and one withdrawn as of July 2022* **MoA:** Immunomodulators; neonatal Fc receptor antagonists **Designation:** Received orphan drug status for myasthenia gravis **Importance:** First-in-class; anti-FcRn modified by Argenx proprietary ABDEG™ technology to increase its affinity for FcRn beyond that of normal IgG antibodies; according to analysts at SVB Leerink, it could target a market worth US$20–25b in the USA alone by 2030. FDA acceptance of BLA filing for efgartigimod for the treatment of generalized myasthenia gravis
Top 5	Galapagos	**Filgotinib:** Two phase 3 trials in Crohn's disease with Gilead Sciences; one enrolling by invitation and other active but not recruiting* **GLPG3970:** Phase 1 in SLE terminated; phase 2 in primary Sjögren's syndrome terminated* **MoA:** Filgotinib – JAK 1 inhibitors; GLPG3970 – salt-inducible kinase 3 inhibitors **Designation:** Filgotinib is approved and marketed as Jyseleca in the European Union, the UK and Japan for adults with moderately to severely active RA **Importance:** Filgotinib – favorable pharmacokinetics as it is rapidly absorbed after oral administration and has a half-life of six hours: GLPG3970 – dual mode of action on inflammation by stimulating anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines
Top 5	Horizon Therapeutics	**1. VIB4920 (Dazodalibep):** Two phase 2 trials (each in Sjögren's syndrome and RA) **MoA:** CD40L binding fusion protein **Importance:** VIB4920 significantly reduced circulating Ki67+ dividing B cells, class-switched memory B cells, and a plasma cell gene signature after immunization **2. HZN-825:** Phase 2 for systemic sclerosis **MoA:** Lysophosphatidic acid receptor antagonists **Importance:** HZN-825 is an oral selective LPAR1 antagonist with early signals of benefit in diffuse cutaneous systemic sclerosis Horizon Therapeutics acquired Viela Bio, the developer of inebilizumab **3. Inebilizumab:** Phase 3 for myasthenia gravis **MoA:** A-fucosylated anti-CD19 ab **Importance:** Inebilizumab approved for NMOSD and considered to be first-in-class drug **4.** Teprotumumab (Tepezza): phase 1 for systemic sclerosis **MoA:** Insulin-like-growth-factor-1-receptor antibody **Importance:** Tepezza (teprotumumab-trbw) approved by FDA for the treatment of adults with thyroid eye disease

*** Data reassessed and updated as of 22 July 2022**

5.2. Index of medium-sized pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 5	Incyte Corporation	**Baricitinib:** Phase 3 trials in SLE, atopic dermatitis with Eli Lilly; two terminated, one completed and one in recruiting stage* **INCB054707:** Phase 2 trials in hidradenitis suppurativa and non-segmental vitiligo **Ruxolitinib:** Phase 3 trials in vitiligo (approved by FDA on 19 July 2022), phase 2 trial in hidradenitis suppurativa **MoA:** Baricitinib: Jak1/2-Tyk2 inhibitors; INCB054707: JAK 1 inhibitors; Ruxolitinib: JAK 1/2 inhibitors **Designation:** Baricitinib: received fast-track designation from FDA for SLE **Importance:** Baricitinib is the first JAK inhibitor to demonstrate hair regrowth in phase 3 alopecia areata. Approved for moderate to severe active RA in US, EU and Japan Ruxolitinib: FDA approval for primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults, acute graft-versus-host disease for tablet formulation
6–15	Apellis Pharmaceuticals	**Pegcetacoplan:** Two phase 2 trials (one each in glomerulonephritis and PNH) **Designation:** FDA has granted priority review to pegcetacoplan for the treatment of PNH **MoA:** Pegcetacoplan is complement C3 inhibitor and is targeted C3 therapy designed to regulate excessive activation of the complement cascade **Importance:** Positive results from phase 3 trial for PNH
6–15	Arcutis Biotherapeutics	**ARQ-151 (roflumilast cream):** One phase 3 and two phase 2 trials in psoriasis **MoA:** Type 4 cyclic nucleotide phosphodiesterase inhibitors **Importance:** Topical small molecule. Highly potent and selective PDE4 inhibitor, used as topical cream (25–300 times more potent than other FDA-approved PDE4 inhibitors); positive results for phase 3 in psoriasis, potential best in class Tablet formulation of roflumilast FDA approved for chronic obstructive pulmonary disease. Arcutis and AstraZeneca (strategic collaboration) are trying to reformulate the active ingredient into a topical cream for better efficacy in psoriasis
6–15	Arena Pharmaceuticals**	**Etrasimod:** Five trials for UC (phase 2 and 3), one for alopecia areata (phase 2), one for Crohn's disease (phase 2/3), one for eosinophilic esophagitis (phase 2) **MoA:** Next-generation, highly selective S1P receptor modulator **Designation:** Orphan drug designation for etrasimod for the treatment of eosinophilic esophagitis **Importance:** US$24b+ market opportunity across GI3, targeting ~US$48b market with all current indications. Etrasimod is a potential blockbuster drug as per analysts at Seeking Alpha
6–15	Biocryst Pharmaceuticals	**BCX9930:** Three phase 2 trials in PNH patients ongoing* **MoA:** Oral factor D inhibitor **Designations:** Orphan drug and fast-track designation (FDA) for BCX9930 for the treatment of PNH **Importance:** Novel, oral, potent and selective small molecule inhibitor of factor D that can address both intravascular and extravascular hemolysis in PNH patients
6–15	Chemocentryx	**Avacopan:** Two phase 2 trials (each in C3 glomerulopathy and hidradenitis suppurativa) Positive results in phase 2 trial with hidradenitis suppurativa **Designation:** Orphan drug designation for avacopan in the treatment of patients with C3G **MoA:** Avacopan is a first-in-class small molecule that binds to C5a, preventing it from binding to its receptor **Importance:** ChemoCyntryx submitted NDA to the FDA for avacopan in September 2020 and response was expected by October 2021

*** Data reassessed and updated as of 22 July 2022**
**** Arena Pharmaceuticals was acquired by Pfizer in December 2021**

5.2. Index of medium-sized pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
6–15	Ionis Pharmaceuticals	**IONIS-FB-LRx:** One ongoing phase 2 trial for IgA nephropathy **MoA:** Complement factor B inhibitors, generation 2+ ligand conjugated antisense (LICA) drug **Importance:** Genetic association studies have shown that overaction of complement cascade has been associated with the development of IgA nephropathy, which is being targeted by this drug
6–15	Omeros Corporation	**Narsoplimab:** Phase 3 trial for IgA nephropathy. Positive results from phase 2 trial for IgA nephropathy **Designation:** FDA: breakthrough therapy and orphan drug designation for the treatment of IgA nephropathy. EMA: orphan medicinal product for the treatment of primary IgA nephropathy **MoA:** Mannan-binding lectin-associated serine protease-2 (MASP-2) inhibitor **Importance:** Novel, proprietary drug designed to prevent complement-mediated inflammation and endothelial damage while leaving intact the respective functions of the other pathways of innate immunity
6–15	Remegen	**RC18 (telitacicept):** Three ongoing phase 3 trials for SLE, one phase 2 trial for IgA nephropathy, one phase 2 trial each for MS and myasthenia gravis* **MoA:** Novel, potential first-in-class/best-in-class recombinant transmembrane activator, calcium modulator and cyclophilin ligand interactor fusion protein **Designation:** Fast-track designation by FDA for SLE
6–15	Theravance	**TD-1473:** One phase 2 study of Crohn's disease and diabetic gastroparesis is ongoing; phase 2 and phase 2/3 trials of UC and Crohn's disease have been terminated* **MoA:** Pan-JAK inhibitor **Importance:** TD-1473 is orally administered and gut selective – it is designed to act at the site of inflammation in the intestinal wall with limited systemic exposure
6–15	Travere Therapeutics (formerly Retrophin)	(Retrophin was renamed Travere Therapeutics in late 2020) **Re-021 (Sparsentan):** One phase 3 and two phase 2 trials for IgA nephropathy ongoing* **Designation:** FDA and European Commission granted orphan drug designation for FSGS and IgA nephropathy **MoA:** Selectively block the receptors endothelin 1A and angiotensin II type 1 **Importance:** Sparsentan is a first-in-class orally active compound, and could be the first FDA-approved pharmacologic treatment for FSGS

*** Data reassessed and updated as of 22 July 2022**

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	AbbVie	**Risankizumab:** 13 phase 3 trials (nine for psoriasis, two for UC, two for Crohn's disease) and one phase 4 trial (psoriasis)* **MoA:** Interleukin-23 subunit p19 inhibitors **Designation:** FDA orphan drug designation for pediatric Crohn's disease **Importance:** Already approved for plaque psoriasis; AbbVie submitted regulatory filings for risankizumab to the FDA and EMA for psoriatic arthritis. Positive result found in phase 2; awaiting data from pivotal phase 3 trial; has a clearly differentiated profile in comparison with existing anti-TNF and IL-17 **ABBV-154:** Two phase 2 trials, one for RA and and one for polymyalgia rheumatica **MoA:** Glucocorticoid receptor modulators **Importance:** The drug is composed of a steroid moiety conjugated to an anti-TNF antibody for the delivery of the steroid to TNF receptor expressing cells **Elezanumab:** One phase 2 trial for MS completed* **MoA:** RGMA protein inhibitor **Importance:** In lab models, elezanumab was able to promote repair of axons and myelin and protect against damage; elezanumab inhibits a molecule that plays a role in stopping the outgrowth of nerve endings during development **Ravagalimab:** One phase 2 trial for UC completed* **MoA:** ABBV-323 is an antagonist to CD40 **Importance:** Structure of ABBV-323 Fab or ravagalimab revealed a unique method for antagonist activity by stabilizing the proposed functional antiparallel dimer of CD40 receptor via novel contacts to LCDR1 **Upadacitinib:** Four phase 3 trials (one each for Crohn's disease, UC, Takayasu's arteritis and giant cell arteritis); three phase 2 trials, two for SLE and one for non-segmental vitiligo **MoA:** Selective Janus kinase 1 (JAK1) inhibitor **Importance:** RINVOQ is approved by the European Commission for RA, PsA, and ankylosing spondylitis; FDA approval in 2019 for RA. Showing promise as a treatment for ankylosing spondylitis Upadacitinib is used in the treatment of moderate to severe rheumatoid arthritis, active psoriatic arthritis, ankylosing spondylitis, UC and severe atopic dermatitis **Elsubrutinib:** Two phase 2 trials for SLE **MoA:** BTK inhibitor **Importance:** Has the potential to treat immunological and oncological conditions **ALPN-101:** One phase 2 trial for SLE **MoA:** CD28 antigen inhibitors; inducible T-cell co-stimulator protein antagonists **Importance:** First-in-class dual CD28/ICOS antagonist, efficacy in multiple preclinical disease models, a potent inhibitor of both CD28 and ICOS pathways

* Data reassessed and updated as of 22 July 2022

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Astrazeneca	**Benralizumab:** Three phase 3 trials (one each for vasculitis, eosinophilic esophagitis and bullous pemphigoid) **MoA:** IL-5 receptor alpha-directed cytolytic monoclonal antibody **Importance:** Approved for severe asthma and with eosinophilic phenotype, the drug is being tried in clinical trials for eosinophilic esophagitis Also used for COPD and nasal polyposis, and hypereosinophilic syndrome (HES). Clinical trials of monoclonal antibody Fasenra (benralizumab) for the treatment of skin diseases **Ravulizumab:** Three phase 3 trials for PNH; one phase 3 trial for neuromyelitis optica; one phase 2 trial for lupus nephritis; also used for myasthenia gravis **MoA:** First-generation C5 inhibitor **Designation:** Priority review and orphan drug designation for hemolytic uraemic syndrome, PNH **Importance:** First-in-class, humanized monoclonal antibody C5 complement inhibitor. It is approved in the US, Japan and the EU for PNH **Anifrolumab:** Three phase 3 trials in SLE and one phase 3 trial for lupus nephritis* **MoA:** Blocking the activity of all type I interferons including IFN-alpha, IFN-beta and IFN-omega **Designation:** Saphnelo (anifrolumab) approved in the US for moderate to severe SLE. Saphnelo is under regulatory review for SLE in the EU and Japan **Importance:** Saphnelo is a first-in-class type I interferon receptor antibody and the only new medicine in over a decade for patients with SLE **Brazikumab:** Two phase 3 trials in Crohn's disease, two phase 2 trials in UC **MoA:** Brazikumab selectively blocks the IL23 immune signal, preventing intestinal inflammation **Benralizuma:** Three phase 3 trials (each in eosinophilic esophagitis, vasculitis, bullous pemphigoid) Also used in asthma, hematologic diseases, leukocyte disorders, hypereosinophilia **MoA:** Humanized monoclonal antibody benralizumab specifically binds to IL-5Rα **Designation:** Orphan drug designation for Fasenra (benralizumab) for the treatment of eosinophilic oesophagitis. FDA approved for eosinophilic phenotype **Importance:** Astrazeneca thinks benralizumab has the potential to be the best in class
Top 10	Bristol Myers Squibb (BMS)	**Abatacept:** Three phase 3 trials, one each for RA, vasculitis and giant cell arteritis **MoA:** Consists of the extracellular domain of human CTLA-4 linked to a modified Fc portion of human immunoglobulin G1 **Importance:** First in a new class of drugs known as selective co-stimulation modulators and is approved for the treatment of RA **BMS 986165 (deucravacitinib):** Two phase 3 trials for lupus nephritis, two phase 3 trials for PsA, two phase 2 trials for SLE, three phase two trials for UC, two phase 2 trials for Crohn's disease, two phase 3 trials for psoriasis and plaque psoriasis, one phase 2 trial for lupus erythematosus, discoid and lupus erythematosus, subacute cutaneous* **MoA:** TYK2 kinase inhibitors **Additional conditions:** Plaque psoriasis **Importance:** First-in-class and potentially the best-in-class oral drug, with potential for biologic-like efficacy with convenient administration **Branebrutinib:** One phase 2 trial for rheumatoid arthritis and SLE and one phase 2 trial for atopic dermatitis* **MoA:** Agammaglobulinemia tyrosine kinase inhibitor **Importance:** Pharmacological inhibition of BTK is expected to provide an effective strategy for the clinical treatment of autoimmune diseases such as lupus, RA etc **BMS-986256 (afimetoran):** Two trials – phase 2 and phase 1 for SLE **MoA:** Toll-like receptor 7 antagonist

* Data reassessed and updated as of 22 July 2022

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Johnson & Johnson	**Ustekinumab (Stelara):** Seven phase 3 trials (four in Crohn's disease, one in UC, one in dermatomyositis, one in type 1 diabetes), one phase 1 trial in UC **MoA:** Interleukin 12 inhibitors; Interleukin 23 inhibitors **Importance:** First-in-class therapeutic human IgG1 kappa mAb. UK approved breakthrough psoriasis treatment Stelara. FDA approved in 2009 for plaque psoriasis, psoriatic arthritis in combination with methotrexate and alone for Crohn's disease and UC; additional trials ongoing in plaque psoriasis, pouchitis, psoriatic arthritis, hematologic and lymphocytic disorder, leukocyte adhesion deficiency (type 1) **Guselkumab:** One phase 4 trial in psoriasis, one phase 3 trial in CD, one in PsA, three phase 2 trials (one each in glomerulonephritis, giant cell arteritis and systemic sclerosis), one phase 1 trial in celiac disease, additional trials ongoing in psoriasis vulgaris, adenomatous polyposis coli, plaque psoriasis, lupus nephritis* **MoA:** Interleukin-23 subunit p19 inhibitors **Importance:** First-in-class drug already approved by the FDA and the EMA for the treatment of adult patients with moderate to severe plaque psoriasis, showing significant improvements in PsA in a trial **Golimumab:** Two phase 3 trials (psoriatic arthritis and ulcerative colitis) **MoA:** TNF alpha inhibitor **Designation:** Orphan drug designation for sarcoidosis **Importance:** Golimumab is a human IgG1 monoclonal antibody derived from immunizing genetically engineered mice with human TNFα. Already approved for severely active UC in adult patients who have demonstrated corticosteroid dependence or inadequate response to other treatments. Also approved for active ankylosing spondylitis and RA in combination with methotrexate **JNJ-66525433:** One phase 1 trial in UC **Importance:** JNJ-66525433 is a drug used to treat ulcerative colitis, being studied in phase 1 clinical trials **JNJ-67864238:** One phase 2 trial in Crohn's disease **MoA:** Interleukin-23 receptor antagonist **Importance:** First-in-class oral interleukin-23 receptor antagonist for potential treatment of inflammatory bowel disease

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Novartis	**Secukinumab (Cosentyx):** Six phase 3 trials for psoriasis, hidradenitis suppurativa, PsA and Graves' ophthalmopathy, phase 3 for giant cell arteritis (August 21), six phase 2 trials for pyoderma gangrenosum, psoriasis, polymyalgia rheumatica, discoid lupus erythematosus and lichen planus, additional trials ongoing in axial spondyloarthritis, congenital ichthyosis, thyroid eye disease, Graves' orbitopathy, psoriasis vulgaris, lupus nephritis, active peripheral spondyloarthritis (pSpA), COVID-19, autoimmune inflammation, pityriasis rubra pilaris **MoA:** IL17A protein inhibitors **Importance:** Neutralizes circulating IL-17A and drives the body's immune response in psoriasis, ankylosing spondylitis and PsA. FDA has approved Cosentyx for the treatment of moderate to severe plaque psoriasis in pediatric patients, ankylosing spondylitis and active non-radiographic axial spondyloarthritis **LNP 023 (Iptacopan):** Seven phase 3 trials (four for PNH, two for IgA nephropathy, one for glomerulonephritis), two phase 2 trials (each for PNH and glomerulonephritis); additional trials in age-related macular degeneration, atypical hemolytic uremic syndrome, immune thrombocytopenia (ITP), cold agglutinin disease (CAD) **MoA:** Complement factor B inhibitors **Designation:** Breakthrough therapy designation for PNH and rare pediatric disease designation for C3 glomerulopathy; EMA has granted orphan drug designation for iptacopan (LNP023) in IgA nephropathy **Importance:** First-in-class, orally administered, potent and highly selective factor B inhibitor of the alternative complement pathway. Promising interim phase II data in rare renal disease C3 glomerulopathy (C3G) in October 2020 **CFZ 533 (iscalimab):** Six phase 2 trials – two for Sjögren's syndrome, one each for type 1 diabetes, glomerulonephritis, hidradenitis suppurativa and SLE **MoA:** CD40 antigen inhibitor **Importance:** New, fully human MAb preventing CD40 pathway signaling and activation of CD40+ cell types. Iscalimab might prolong the durability of transplanted kidneys as well as potentially improving long-term outcomes for kidney transplant patients **Eltrombopag:** Eight phase 2 trials for immune thrombocytopenic purpura and aplastic anemia, Diamond-Blackfan anemia, solid tumors **MoA:** Small molecule agonist of the c-mpl receptor **Importance:** Eltrombopag is the physiological target of the hormone thrombopoietin. It is marketed for aplastic anaemia, idiopathic thrombocytopenic purpura and thrombocytopenia

*** Data reassessed and updated as of 22 July 2022**

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Pfizer	**PF-06651600 (Ritlecitinib):** One phase 3 long-term study in alopecia areata, four phase 2 trials (one in alopecia areata, one in Crohn's disease, one in vitiligo, one in UC), RA **MoA:** JAK3 inhibitor and TEC kinase family inhibitor **Designation:** Breakthrough therapy designation (FDA) for alopecia areata **Importance:** The company reported positive results from a phase 2 study for this novel JAK3/TEC inhibitor **PF-06755347:** One phase 1 trial for chronic inflammatory demyelinating polyradiculoneuropathy **MoA:** Immunomodulator **Designation:** FDA granted PF-06755347 orphan drug designation for chronic inflammatory demyelinating polyradiculoneuropathy **Importance:** PF-06755347 is a recombinant immunomodulation drug candidate not derived from blood. It was designed to meet or exceed the efficacy of intravenous blood product immune globulin (IVIg) in treating autoimmune diseases **PF-06835375:** One phase 1 trial in RA **MoA:** CXCR5 receptor antagonists **Tofacitinib (Xeljanz):** Marketed as medication to treat RA, PsA, and UC. Ongoing trials in three phase 3 trials (one for psoriasis and two for UC), one phase 2 SLE and three phase 1 (one for SLE and two for sarcoidosis), additional trials in systemic sclerosis, inflammatory bowel disease, psoriatic arthritis, spondylitis, sacroiliitis, juvenile idiopathic arthritis, Down syndrome, alopecia areata, atopic dermatitis/eczema, hidradenitis suppurativa, vitiligo, psoriasis **MoA:** JAK inhibitor **Importance:** Approved for RA, PsA, UC. This therapy has been shown to prevent inflammation caused by cytokine overexpression and proliferation. Tofacitinib was found to be safe and effective in treating active ankylosing spondylitis **PF-06650833:** Two phase 2 trials – one in RA, one in hidradenitis suppurativa **MoA:** Interleukin-1 receptor-associated kinase inhibitors **Importance:** First IRAK4 inhibitor to enter clinical development. NME small molecule with MoA IRAK4 inhibitor + JAK3/TEC inhibitor + JAK inhibitor and is currently being tested in hidradenitis suppurativa (phase 2) and rheumatoid arthritis (phase 2). It is being seen as potential treatment for RA **Brepocitinib (PF-06700841):** Three phase 2 trials – for psoriasis, SLE and Crohn's disease. Cicatricial alopecia, renal impairment, ulcerative colitis, hidradenitis suppurativa **MoA:** JAK1 inhibitor **Importance:** First-in-class topical inhibitor of both TYK2 and JAK1 in phase 2 clinical trials for the potential treatment of psoriasis and AD in topical formulation, and in oral formulation for psoriatic arthritis, Crohn's disease, UC, vitiligo, SLE, alopecia areata, and hidradenitis suppurativa (HS) In January 2021, topical brepocitinib for atopic dermatitis met endpoints in phase 2b study

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Roche	**Ocrelizumab:** Seven phase 3 trials, one phase 2 trial, one phase 1 trial – all for MS **MoA:** CD20 inhibitor **Importance:** FDA approved for treatment of adult patients with relapsing or primary progressive forms of MS, FDA grants Priority Review for Ocrevus (ocrelizumab) BLA, first product approved for primary progressive MS; substance ocrelizumab targets and binds to is called the CD20 protein, which is found on B cells **Fenebrutinib:** Three phase 3 trials for MS **MoA:** Agammaglobulinemia tyrosine kinase inhibitor **Importance:** Fenebrutinib is a dual inhibitor of both B-cell and myeloid lineage-cell activation, which may offer a novel approach to suppress disease activity and slow disease progression by targeting both acute and chronic inflammatory aspects of MS **RO7049665:** One phase 1 trial for UC and one phase 2 trial for autoimmune hepatitis **MoA:** Immunomodulator **Importance**: RG-7835 (RO7049665) is a conjugate of the IL-2 mutein N88D, which has reduced binding to IL-2Rβγ, fused with human IgG1, IgG–IL2 preferentially stimulates and expands T regulatory cells but not T effector cells **Obinutuzumab:** Three phase 3 trials (one for lupus nephritis and two for SLE), additional trials in chronic lymphocytic leukemia, small lymphocytic lymphoma, primary focal segmental glomerulosclerosis; the drug's potential to treat glomerulonephritis is also being investigated **MoA:** Antibody-dependent cell cytotoxicity **Designation:** FDA has granted breakthrough therapy designation for Roche's Gazyva (obinutuzumab) in lupus nephritis **Importance:** Obinutuzumab is a novel, first-in-class, type II, immunoglobulin-G1 monoclonal antibody with a higher efficacy than rituximab and has an established safely profile in patients with comorbidities and poor renal function. FDA has approved obinutuzumab for previously untreated follicular lymphoma **Crovalimab:** Three phase 3 trials for PNH, atypical hemolytic uremic syndrome, sickle cell disease **MoA:** Complement activation inhibitors **Importance:** Drug is investigated for PNH, MAb that targets C5, is safe and effective in treating PNH. Drug uses pH-dependent binding to target C5; complement C5 inhibition is the standard of care for patients with PNH **Etrolizumab:** Three phase 3 trials – two in Crohn's disease, one in UC **MoA:** Alpha4beta7 integrin antagonists **Importance:** First investigational dual anti-integrin studied in inflammatory bowel diseases. It is designed to target these on two fronts by selectively inhibiting α4β7 and αEβ7 to control both trafficking of immune cells into the gut and their inflammatory effects on the gut lining; etrolizumab does not bind to α4β1 integrin, underlying its favorable safety with regard to progressive multifocal leukoencephalopathy

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	Sanofi	**SAR441344:** Two phase 2 trials – in Sjögren's syndrome and MS, systemic lupus erythematosus **MoA:** CD40 ligand inhibitor **Importance:** This drug is being tried for Sjögren's syndrome and MS **Tolebrutinib (SAR442168):** Four phase 3 trials in MS, two phase 2 trials in MS and one in myasthenia gravis* **MoA:** Agammaglobulinemia tyrosine kinase inhibitor **Importance:** It will potentially be the first disease-modifying therapy to address sources of MS damage in the brain. Can cross blood-brain barrier **Sutimlimab (BIVV009):** One phase 3 in cold agglutinin disease **MoA:** Complement C1s inhibitor **Designation:** Sutimlimab has been granted breakthrough therapy, orphan drug designation and priority review for cold agglutinin disease **Importance:** It is designed to selectively target and inhibit C1s in the classical complement pathway, which is part of the innate immune system. By blocking C1s, it is thought that sutimlimab halts C1-activated hemolysis
Top 10	Takeda Pharma-ceutical	**TAK-755:** Two phase 3 trials for thrombotic thrombocytopenic purpura, sickle cell disease **MoA:** ADAM protein replacements **Designation:** Orphan drug designation for thrombotic thrombocytopenic purpura **Importance:** TAK-755 is the first and only ADAMTS13 replacement therapy currently in development for both types of TTP. It is first-in-class and a best-in-class therapy for the treatment of immune-mediated TTP **Darvadstrocel:** Three phase 3 trials in Crohn's disease **MoA:** Cell replacements **Designation:** Orphan drug designation for rectal fistula from Japan's Ministry of Health. Darvadstrocel was granted orphan drug designation by the European Commission and FDA, and is approved in the EU, Israel, Switzerland and the UK for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease **Importance:** Darvadstrocel is the first allogeneic stem cell therapy to be approved for the treatment of complex perianal fistulas in adult patients with Crohn's disease **Sibofimloc (EB-8018 or TAK 018):** One phase 2 trial for Crohn's disease **MoA:** *E coli* fimH protein inhibitor or microbiome modulator **Importance:** Sibofimloc (EB8018/TAK-018) is a first-in-class, orally administered, gut-restricted small molecule designed to reduce inflammation in Crohn's disease **Mezagitamab (TAK 079):** Two phase 2 trials (one each in myasthenia gravis and primary immune thrombocytopenia); one phase 2 trial in relapsed and/or refractory multiple myeloma (RRMM) **MoA:** T lymphocyte stimulant **Importance:** It is in phase 2 for idiopathic thrombocytopenic purpura and myasthenia gravis; however, this drug was discontinued for RA

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5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
Top 10	UCB Biopharma	**Bimekizumab:** Seven phase 3 trials (three for hidradenitis suppurativa, two for psoriatic arthritis, two for axial spondyloarthritis, one for plaque psoriasis) **MoA:** IL17A and F protein inhibitor **Importance:** First-in-class monoclonal antibody. The EMA's Committee for Medicinal Products for Human Use has recommended approval for Bimzelx as a treatment for moderate-to-severe plaque psoriasis; the FDA and EMA have accepted the BLA and marketing authorization application respectively for bimekizumab for the treatment of plaque psoriasis. Phase 2b trial found that Bimekizumab can improve outcomes of ankylosing spondylitis patients **Rozanolixizumab:** One phase 3 trial for myasthenia gravis, three phase 3 trials for primary immune thrombocytopenia, two phase 2 trials for autoimmune encephalitis and polyradiculoneuropathy; myelin oligodendrocyte glycoprotein antibody-associated disease (MOG-AD) **MoA:** Neonatal Fc receptor antagonists **Designation**: FDA and EMA have granted orphan drug designation for idiopathic thrombocytopenic purpura **Importance:** First-in-class subcutaneously infused MAb. Blocks the interaction of FcRn and IgG, inhibiting IgG recycling and inducing the removal of pathogenic IgG autoantibodies **Certolizumab:** Two phase 3 trials for juvenile idiopathic arthritis and psoriasis, two phase 1 trials for rheumatoid arthritis. Psoriatic arthritis, Crohn's disease, lupus anticoagulant disorder **MoA:** TNF alpha inhibitor **Importance:** It is a fragment of a monoclonal antibody specific to TNF alpha. Only PEGylated anti-TNFα biologic approved for the treatment of RA and Crohn's disease **Zilucoplan:** Two phase 3 trials for myasthenia gravis, amyotrophic lateral sclerosis **MoA:** Complement C5 inhibitors **Designation:** Orphan drug by FDA for myasthenia gravis and by European Commission for PNH **Importance:** Zilucoplan is small synthetic molecule, macrocyclic peptide that inhibits cleavage of complement component C5
11–20	Amgen	**Rozibafusp Alfa (AMG 570):** One phase 2 trial for SLE **MoA:** Antibody-peptide conjugate, B cell activating factor inhibitor **Importance:** First-in-class biospecific antibody-peptide conjugate targeting T- and B-cell activity **AMG 714:** One phase 2 trial for vitiligo, celiac disease **MoA:** Interleukin 15 inhibitor **Importance:** AMG 714 induces apoptosis of IELs in active celiac and refractory CD II explants **Apremilast:** Three phase 3 trials (two for psoriasis and one for psoriatic arthritis), one phase 2 trial for lichen planus, Behçet disease, atopic dDermatitis, acne conglobata **MoA:** Type 4 cyclic nucleotide phosphodiesterase inhibitor **Importance:** First-in-class, approved and marketed drug; approved for active psoriatic arthritis for adult patients and moderate-to-severe plaque psoriasis candidates for phototherapy or systemic therapy
11–20	Bayer	**Bay1817080 (eliapixant):** One phase 2 trial for peripheral neuropathy was terminated as of July 2022* **MoA:** Purinergic P2X3 receptor antagonist **Importance:** P2X3 is an ATP-activated ion channel expressed mainly in the peripheral nervous system **Aflibercept:** One phase 3 trial for type 1 diabetes **MoA:** Placenta growth factor inhibitor **Importance:** FDA approved for the treatment of diabetic macular edema and diabetic retinopathy

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5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
11–20	Boehringer Ingelheim	**BI 655130 (spesolimab):** Six phase 2 trials (one in UC, two in Crohn's disease, two in psoriasis, one in hidradenitis suppurativa); palmoplantar pustulosis, atopic dermatitis **MoA:** Interleukin 36 receptor antagonists **Designation:** Spesolimab has obtained CDE breakthrough therapeutic drug designation for generalized pustular psoriasis **BI 655064:** One phase 2 trial in glomerulonephritis **MoA:** CD40 antigen inhibitors **Importance:** BI 655064 is a humanized, non-depleting, antagonistic therapeutic antibody that selectively binds human CD40 and blocks the CD40-CD40L interaction
11–20	Eli Lilly & Company	**Mirikizumab:** Six phase 3 trials (three for UC, two for Crohn's disease and one for psoriasis), one phase 2 trial for UC **MoA:** Interleukin-23 subunit p19 inhibitors **Importance:** Mirikizumab is a potential treatment for Crohn's disease and UC. It demonstrates efficacy for up to 52 weeks in Crohn's disease **Baricitinib:** Three phase 3 trials for SLE, two phase 3 trials for RA and one phase 3 trial for uveitis, two phase 2 trials for giant cell arteritis, one phase 2 for idiopathic inflammatory myopathies, additional trials in COVID-19, cutaneous lichen planus, phase 4 RA, pyoderma gangrenosum, chronic kidney diseases, juvenile idiopathic arthritis, atopic dermatitis, Nakajo-Nishimura syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, STING-associated vasculopathy with onset in infancy, Aicardi Goutieres syndrome, allergic contact dermatitis, graft-versus-host-disease, vitiligo, alopecia areata, dermatomyositis, polymyalgia rheumatica, type 1 diabetes, amyotrophic lateral sclerosis, Alzheimer's disease; mild cognitive impairment, Sjögren's syndrome, Aicardi Goutieres syndrome **MoA:** JAK1 inhibitor **Designation:** FDA breakthrough therapy designation for baricitinib for the treatment of alopecia areata FDA decision delayed for baricitinib for atopic dermatitis **Importance:** FDA-approved for the treatment of moderately to severely active RA **LY3471851:** One phase 1 trial for psoriasis, one phase 2 trial for SLE and two phase 2 trials for UC Atopic dermatitis **MoA:** IL-2 conjugate **Importance:** Potential first-in-class resolution therapeutic that may address immune system imbalance in people with many autoimmune and inflammatory conditions **Ixekizumab:** Four phase 3 trials (two for PsA, one for plaque psoriasis, one for spondyloarthritis), one phase 2 trial for type 1 diabetes psoriatic arthritis, COVID-19, major depressive disorder, lichen planopilaris **MoA:** IL17A protein inhibitors **Importance:** Improves r-axSpA symptoms affecting quality of life. Approved for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation, active PsA, or active ankylosing spondylitis

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
11–20	Gilead Sciences	**Filgotinib:** Two phase 3 trials for Crohn's disease with Galapagos NV Rheumatoid arthritis, noninfectious uveitis, UC, inflammatory bowel disease **MoA:** JAK1 inhibitor **Importance:** The oral therapy filgotinib could be a more effective treatment for patients with active ankylosing spondylitis who fail treatment with NSAIDs. Filgotinib significantly reduced the ankylosing spondylitis disease activity score. Selective inhibition of JAK1 by filgotinib is effective in treating active ankylosing spondylitis Filgotinib is approved and marketed as Jyseleca in the EU, the UK and Japan for adults with moderately to severely active RA **GS-4875:** One phase 2 trial for UC **MoA:** MAP3K8 protein inhibitor **Importance:** It is a first-in-class TPL2 inhibitor that suppresses MEK-ERK inflammatory signaling and proinflammatory cytokine production in primary human monocytes
11–20	GSK	**Belimumab:** Five phase 2 trials (MS, scleroderma, SLE, and vasculitis); additional trials in nephrotic syndrome, idiopathic CD4 lymphopenia, chronic lymphoid leukemia, systemic sclerosis, chronic obstructive pulmonary disease, emphysema, IgG4-related disease, graft vs host disease, NMO spectrum disorder, antiphospholipid syndrome **MoA:** B cell activating factor inhibitor **Importance:** Approved for treatment of children with SLE and adults with active lupus nephritis **GSK2982772:** One phase 1 trial for psoriasis **MoA:** Receptor-interacting protein serine/threonine kinase inhibitor **Importance:** A first-in-class, RIPK1 small molecule inhibitor in patients with active plaque-type psoriasis **GSK3196165 (otilimab):** Four phase 3 trials in RA severe acute respiratory syndrome **MoA:** Granulocyte macrophage colony stimulating factor antagonists **Importance:** Has a novel mechanism of action which has shown compelling data across traditional endpoints for RA, supporting further and accelerated clinical development
11–20	Novo Nordisk	**NNC0361-0041:** One phase 1 trial for type 1 diabetes **MoA:** Immunostimulant **Importance:** NNC0361-0041 is an antihyperglycemics; the drug is in trial for type 1 diabetes

5.3 Index of large pharmaceutical companies (data extracted and analyzed as of March 2022)

Ranking tier	Company	Pipeline review
11-20	Regeneron Pharmaceuticals	**REGN3918 (pozelimab):** Five phase 3 trials for PNH, additional trials in type I diabetes, myasthenia gravis CHAPLE disease* **MoA:** Complement C5 inhibitors **Importance:** Pozelimab is used to treat PNH; phase 2 study showed promising results. Pozelimab is a fully human MAb, which is designed to block C5 and prevent hemolysis **Dupilumab:** In partnership with Sanofi, four phase 3 trials (two trials for urticaria and one each for bullous pemphigoid and eosinophilic esophagitis), one phase 2 trial for eosinophilic esophagitis, additional trials in severe eosinophilic chronic sinusitis, nummular eczema, atopic dermatitis (AD) Eosinophilic gastritis, chronic hand eczema, chronic rhinosinusitis, localized scleroderma, chronic sinusitis, Netherton syndrome, asthma, Aspirin-exacerbated respiratory disease (AERD), keloid, pruritus, allergic contact dermatitis, allergic fungal rhinosinusitis, allergic bronchopulmonary aspergillosis **MoA:** Interleukin 13 inhibitor **Designation:** FDA granted breakthrough therapy designation to dupilumab for the treatment of eosinophilic esophagitis in patients aged 12 years and older. Dupixent also was granted orphan drug designation for the potential treatment of eosinophilic esophagitis **Importance:** Dupilumab is used to treat for eosinophilic esophagitis disease. Dupixent is the first and only biologic to show positive and clinically meaningful results in a phase 3 trial. Dupilumab is a first-in-class biological treatment for atopic dermatitis (eczema) and is FDA approved for atopic dermatitis **Aflibercept:** One phase 3 trial for type 1 diabetes, additional trials in macular telangiectasia, neovascular age-related macular degeneration, retinal angiomatous proliferation, macular degeneration, diabetic macular edema, metastatic colorectal cancer **Importance:** FDA approved for the treatment of diabetic macular edema and diabetic retinopathy **Sarilumab:** Three phase 3 trials for RA; two phase 2 trials for juvenile idiopathic arthritis. COVID-19, indolent systemic mastocytosis, sarcoidosis **MoA:** Interleukin (IL)-6 receptor antagonist **Importance:** FDA approval for moderately to severely active RA
11-20	Sun Pharmaceuticals	**Tildrakizumab:** Three phase 3 trials (two for PsA and one For plaque psoriasis), one phase 2/3 trial in plaque psoriasis **MoA:** Interleukin-23 subunit p19 inhibitor **Designation:** FDA and EMA approved for moderate-to-severe plaque psoriasis **Importance:** Tildrakizumab, a novel anti-IL-23 monoclonal antibody, is unaffected by ethnic variability in Caucasian, Chinese and Japanese subjects **SCD-044:** Two phase 2 trials (one each in psoriasis and atopic dermatitis) **MoA:** Sphingosine 1 phosphate receptor agonist **Importance:** Orally bioavailable

*** Data reassessed and updated as of 22 July 2022**

Outlook

The Autoimmune Index presents an innovative way to estimate the growth potential of biopharma companies in autoimmune diseases that are of high investment and innovation interest, with significant unmet needs. Based on the drugs in the current pipeline and a training data set of 80,000 annotated clinical trial readouts, as well as companies' commercial competence, the index provides a comprehensive and systematic approach to evaluate new innovations in the continuously changing landscape of autoimmune diseases, and ready-to-use growth estimates for various stakeholders.

- For small to medium-sized originator biotech companies featured in the index, the inclusion in the top pharma lists of this report acknowledges their pipelines' innovation proposition, which positions them as (rising) stars. This helps further attract investment, funding or collaborations with large pharma, to accelerate their development and identify new partners to launch joint clinical trials in geographies of interest.
- For strategy, M&A and in-licensing teams in large pharma, the index can be used as a tool to refresh pipeline strategy and scout smaller companies for accelerated inorganic growth.
- For pharma venture capital firms, investors and industry experts, the index is a go-to list for identifying suitable opportunities to advise or invest in clinical-stage therapies for future commercialization.

The AI-based, data-driven approach offers a unique opportunity to keep refreshing the results at periodic intervals, to factor in the most recent clinical developments and commercial updates, making the index a living go-to tool across multiple use cases.

The methodology used for this index is applicable to other therapeutic areas and medical technologies. In future collaborations, EY and Innoplexus plan to expand the scope of this index to other important diseases and technologies.

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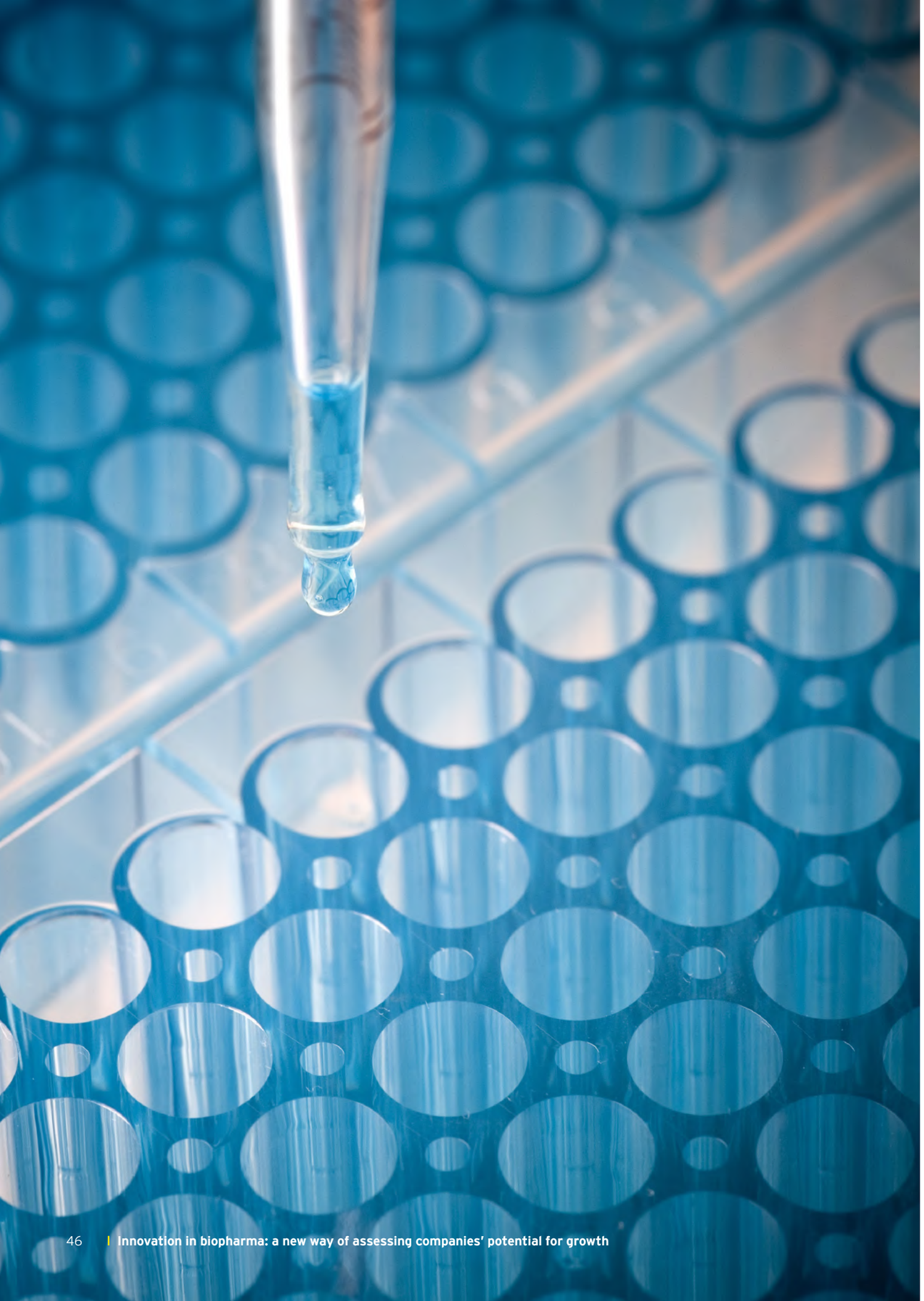

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