Healthcare outlook for 2024 | January 2024

LIFE SCIENCES — WHERE HAS THE CONVICTION GONE?

EDISON THEMES

As one of the largest issuer-sponsored research firms, we are known for our bottom-up work on individual stocks. However, our thinking does not stop at the company level. Through our regular dialogue with management teams and investors, we consider the broad themes related to the companies we follow. Edison themes aims to identify the big issues likely to shape company strategy and portfolios in the years ahead.

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Outlook for 2024

Life sciences – where has the conviction gone?

Edison themes

3 January 2024

2023 was another particularly tumultuous year for life sciences and, although the lingering effects of the last year are unlikely to change dramatically, the stabilisation of interest rates (off 16-year highs) and emerging direction of travel (market data points) tilt our bias to positive for the new year. We continue to view robust innovation for disease-modifying therapies as the focal point, but also value tangible solutions that may be more appealing to the broader investor base.

Advancements in drug development continue to rely heavily on highly focused and specialised technology developed by smaller and nimbler biopharma companies. Mechanisms will continue to evolve and fuel advancements in personalised and targeted treatments and combination therapies with more broad-based offerings in large pharma portfolios.

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Companies mentioned in this report

See Appendix for full list of companies mentioned in this report.

Out with the old…

As the smallest life science companies often champion innovation, they have the heaviest burden of proving safety and efficacy before commercialisation, which is either carried out by, or in some cases in collaboration with, big pharma on the back end. The required lengthy development horizon is particularly challenging in times of elevated interest rates as clinical activities are capital intensive. Although this was not a concern before 2021, elevated interest rates have adversely tainted investor sentiment, especially in 2023, reflected in the c 80% decline of microcap stocks included in the SPDR S&P Biotech ETF, XBI (since the peak on 8 February 2021 versus the c 25% overall ETF performance decline and a slight increase for large caps within the ETF), which has resulted in most of the smaller companies trading below cash.

…positive bias towards the new

We continue to believe robust science will prevail (as in previous cycles).

- An improving macro environment is expected to rally investor sentiment. With the stabilisation in rates, we have seen more market activity, including the announcement of large acquisitions to enter or expand into specialised areas, including AbbVie's foray into CNS (Cerevel for $8.7bn) and entry into immunotherapy (ImmunoGen for $10.1bn); Eli Lilly and Novo Nordisk's entry into cardiology (GLP-1s); and Bristol Myers Squibb (BMS) doubling down on CNS (Karuna Therapeutics for $14bn). Prior to these, we had observed tepid risk tolerance despite the approaching patent expirations for big pharma.
  - Big pharma companies cannot rely on their current portfolios (ie there is a need to refuel pipelines), resonating with Pfizer's announced plans to eliminate $3.5bn in overhead with the displacement of COVID revenues.
  - Increased activity from alternative investors (with longer investment horizons) as they take advantage of the unique arbitrage opportunity (higher biotech cash levels versus market caps).
  - Overall increased funding and IPO activity.
- Innovative therapies and devices are expected to stem from smaller, more agile/entrepreneurial biotechs as development requires specialised resources.
  - Pared-down preclinical/clinical activity has resulted in robust surviving studies in more viable areas (eg quality, commercial potential).
  - Although disease-altering or new mechanisms of action remain the holy grail, generalist and more conservative investors have buoyed solutions with niche expertise and/or shorter development horizons.

Macro environment burden

The last couple of years have been challenging for biotechs in particular. The elevated interest rate environment was unrelenting for capital-intensive, development-stage biotechs and was likely the linchpin that hampered overall funding, especially for small and emerging life sciences companies. Peeling back the layers of the life sciences index performance, we see that the smallest companies were the most affected (as would be expected) and have rationalised ongoing trial activity, which has led to pressured development timelines for the surviving entities. Microcap life sciences companies included in the SPDR S&P Biotech ETF, XBI (which for this analysis we assume have a market cap of less than $500m) have declined by c 80% since the peak (8 February 2021), in stark contrast to the c 3% increase in the share performance of large-cap, commercial-stage life sciences companies and a c 25% decline for the overall ETF. This poor market performance has put extreme pressure on funding ongoing clinical activity, negotiation for acquisitions/partnerships with large pharma and has hindered the initiation of new (traditional) public offerings despite the positive clinical/regulatory newsflow observed throughout the corresponding period.

Exhibit 1: S&P SPDR Biotech ETF proxy* (as of 12 December 2023)

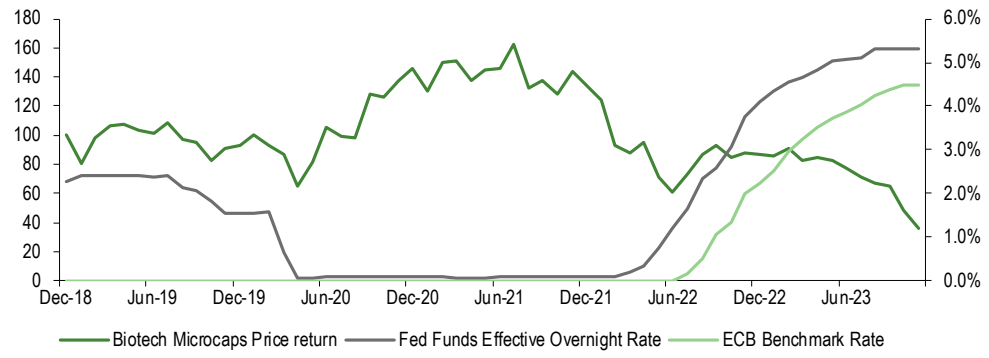
		Micro cap	Small cap	Large cap
Equal-weighted	% Price change - 1yr	-52.5%	4.1%	43.5%
	% Price change - 2yr	-67.0%	-13.0%	36.1%
	% Price change - 3yr	-75.2%	-15.3%	11.7%
	% Price change - Since 8 Feb 2021	-80.5%	-34.6%	2.6%

Source: Capital IQ, barchart.com, Edison Investment Research. Note: *We have constructed an equal-weighted index using the constituents of the S&P Biotech SPDR ETF as of 12 December 2023. There are 130 companies in the S&P Biotech SPDR ETF, of which 17 companies are micro-caps (less than $500m), 61 are small-caps ($500m to $2bn) and 52 are large-caps (more than $2bn).

High interest rates are the enemy of biotechs

As biotechs are focused on innovation that evolves over long periods (with an average development duration of 10 years), interest rate spikes further discount the distant (anticipated) cash flows. The group thrived during low Interest rate environments, where biotechs were able to raise funds easily to support preclinical and clinical activities. However, the elevated interest rates observed in the last couple of years (the Fed funds rate and ECB benchmark rate were at their highest in the last 16 years) have challenged overall investor activity. The inverse correlation between interest rates and biotech index stock performance can be seen in Exhibit 2, below. Based on Refinitiv consensus forecasts, it appears we may have hit an inflection point, with the Fed funds rate and the ECB benchmark rate expected to decline by c 175bp and c 125bp, respectively, until Q2 CY25. In fact, the Fed has indicated that it expects 75bp in rate reductions over 2024 (which likely translates into three cuts of 25bp each, albeit H224 weighted).

Exhibit 2: US biotech (microcaps) versus interest rate (last five years)

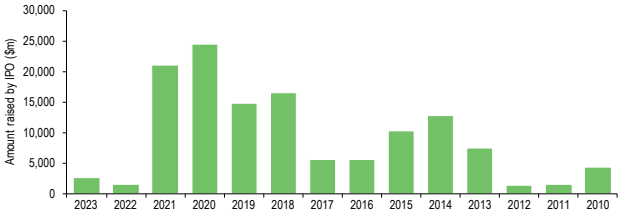


Source: Refinitiv, Edison Investment Research

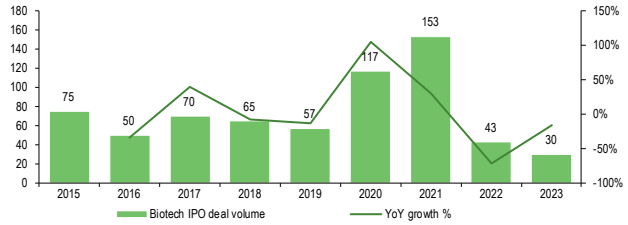
Increased fund-raising activity

After a relatively quiet start to 2023, we saw an increased incidence of fund-raises (announced and closed) down the stretch. There was a concentration of raises in the last two months of the year. In December, bluebird Bio announced a $150m follow-on public offering. Although the public offering was performed out of necessity, there were no material offerings in the sector earlier in the year. There were a couple of others to close the year, including 89bio's $150m follow-on (upsized on 7 December) and Wave Life Sciences' $100m follow-on (upsized on 7 December).

Exhibit 3: Healthcare IPO value and volume



Source: EvaluatePharma



Source: CapIQ

Albeit lower than typical historical levels, the amount raised in the second half of 2023 was higher than the amount raised in the whole of the prior year. Transactions were back-end loaded, with more than 20 of the 30 new IPOs taking place after June 2023.

Innovative biotechs feeds the big pharma funnel

On the acquisition front, the year started very quietly, accelerating in the second half and new year with more interesting acquisitions, which suggests there was pent-up demand. In the fourth quarter, there was a flurry of life sciences acquisitions of significant size. In December and November (respectively), AbbVie announced the acquisition of Cerevel ($8.7bn) and ImmunoGen ($10.1bn), marking material expansion on the company's core business, Humira. The announced acquisition of Cerevel marks AbbVie's meaningful entry into CNS, which further fuels interest in a segment primed for innovation. This follows AbbVie's announcement in November of its entry into immunotherapy (ImmunoGen). Down to the wire, BMS announced its expansion into CNS (Karuna Therapeutics for $14bn), specifically schizophrenia, an area in which we have seen increased activity.

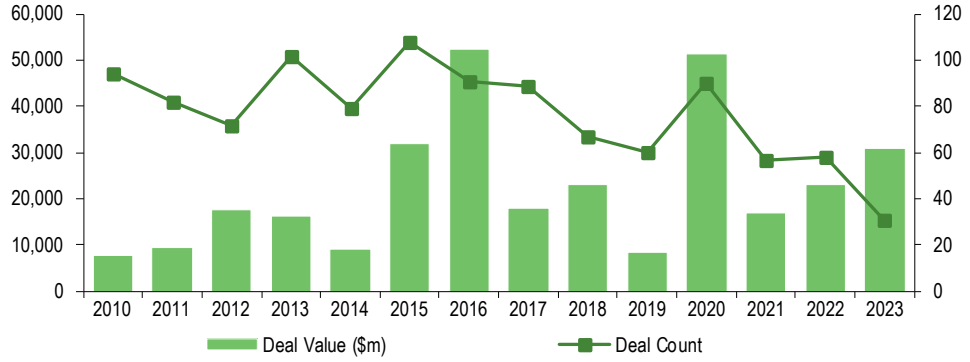
Also in December and in the new year, AstraZeneca announced a couple of transactions with two separate China-based biotechs, including plans to acquire Gracell Biotechnologies (China-US cell therapy) for $1.2bn ($1bn in upfront payments). Shortly after, the company also announced a collaboration with Allorion Therapeutics (Chinese autoimmune cell therapies) for more than $500m (a $40m upfront payment and more than $500m in milestones) to employ its existing asset as a potential treatment for EGFR-mutant non-small cell lung cancer.

Separately, Gilead announced plans to license Compugen's IL-18 protein antibody cancer programme ($60m, upfront). Overall transactions (by count) are down close to 10%, but are likely to pick up with an improving macro environment.

As we start the new year, several transactions have bubbled up. Bristol Myers Squibb announced that it will acquire RayzeBio (a radiopharmaceuticals biotech) for c $4.1bn, which is in a similar therapeutic area to Eli Lilly's recently completed (December) $1.4bn acquisition of Point Biopharma. Roche announced its antibody-drug conjugates (targeting c-Mesenchymal epithelial transition factor against solid tumours) collaboration with a Chinese biotech, MediLink Therapeutics, for a transaction potentially worth c $1bn (including $50m in upfront and near-term milestone payments and with additional development, regulatory and commercial milestone payments potentially reaching a total deal value nearing $1bn). Novartis bolstered its gene therapy collaboration with Voyager Therapeutics for a total consideration of c $1.2bn. The recent expansion is for candidates

in Huntington's disease and spinal muscular atrophy, with an upfront payment of c $100m, which includes a $20m equity purchase.

Exhibit 4: Biotechnology M&A activity, 2010–23



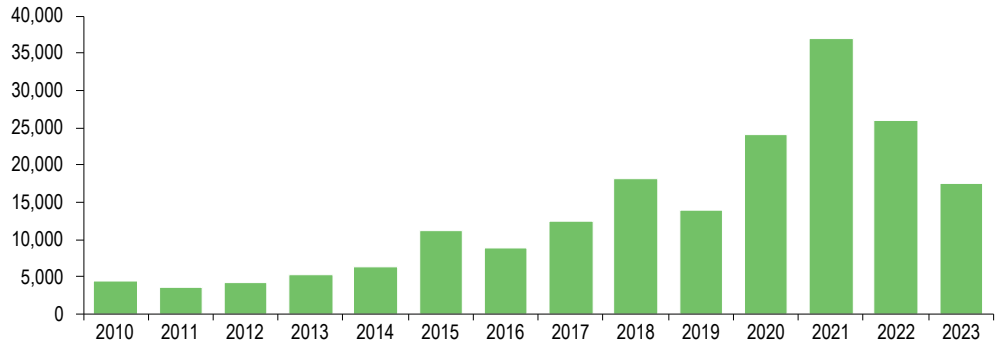
Source: EvaluatePharma

Alternative investors likely to lead the way, opportunistically

The market caps of early- to mid-stage life sciences companies have come under pressure as they continue to invest in clinical activities without the ability to add to the coffers. This upside scenario introduces arbitrage situations with an opportunity to invest in robust innovative therapies. Most early-stage funding has paused, likely exacerbated by the more than $200bn failure of Silicon Valley Bank early in the year.

Since late November, there has been increased funding of venture capital funds, including OrbiMed's more than $4.3bn raise (commitments for its latest private investment funds, including OrbiMed Private Investments IX, OrbiMed Asia Partners V and OrbiMed Royalty & Credit Opportunities IV). There were also a few other commitments, including $410m for Palo Alto-based Playground Global (third fund), $389m for Pivotal bioVenture Partners Fund II and $200m for Artis Ventures (TechBio II). Recent VC investments include Lassen Therapeutics ($85m, closed Series B, 19 December), Kimia Therapeutics ($55m, closed Series A, 19 December), Atavistik Bio ($40m raise or $100m to date, 19 December), Sudo Biosciences ($116m, Series B, 20 December) and Ratio Therapeutics ($50.7m, Series B, 21 December). Apollo Therapeutics also raised an additional $33.5m, bringing its Series C round to $260m.

Exhibit 5: Biotechnology VC investment (US$m), 2010–23



Source: EvaluatePharma

Development must go on; there is a human cost

Despite the macroeconomic challenges, activities towards robust scientific innovation in drug discovery and development have continued and we note that the environment has rationalised some of the less robust companies. As most innovative discoveries are fostered over decades, niche expertise is a core resource. Navigating new, unfamiliar and highly specialised areas in an effort to land the next big clinical breakthrough requires methodical diligence, patience and an entrepreneurial spirit. These are attributes possessed by many small biotechs, reflected in the inferred risk (90% fail rate for clinical drug development, which translates to an average cost of more than $1–2bn for each new drug across an average of 10–15 years). Due to the specialised nature and long duration of product development, we expect large pharma will need to heavily rely on the nimbleness of smaller biotechs to develop innovative mechanisms to fuel advancements.

The recent macro environment has amplified the importance of large pharma for overall drug discovery and development and, conversely, we expect the pending patent cliffs to drive big pharma to be more open towards acquiring small biotechs which are further along on their clinical studies. We view such acquisitions as a potential win-win for all parties and look to see a pick-up in activity as the macro environment improves.

Oncology: Combinations are better together

Despite the challenging market, oncology remains one of the largest and fastest growing segments in pharma. As cancer is the second most common cause of death (after heart disease), it is unsurprising that the field continues to grow. Immune checkpoint inhibitors (ICIs) have had the largest effect in the space over the past decade, having demonstrated durable benefits in a growing number of cancer patient populations. Although ICIs are used in a range of cancer types, there are likely more applications across more indications, so we believe that they have not been utilised to their full potential. Combination therapies are quickly becoming widely accepted as an important strategy to provide more desirable patient outcomes compared to monotherapies and, when effective, will likely be key for developing new ICI treatment protocols to disrupt existing standards of care.

Ultimovacs: UV1 cancer vaccine with universal potential

Ultimovacs, a Norway-based pharmaceutical company focused on the development of novel immunotherapies, has made notable headway in combination therapies with its lead asset, UV1, a peptide-based, off-the-shelf cancer vaccine with universal application. It is designed to activate the immune system to recognise the human telomerase reverse transcriptase, which has been consistently associated with cancer growth. It is estimated that this protein is expressed in up to 90% of human cancers but not in healthy tissues, making it an attractive immunotherapy target. The company expects a treatment synergy with ICIs, and hence its current strategic priorities involve five Phase II clinical trials assessing UV1 in combination with various ICIs for the treatment of a variety of cancers. We note that this range of clinical trials involves the use of five of the top currently approved ICIs, offering significant market opportunity.

The most significant upcoming inflection point for Ultimovacs will be top-line results from INITIUM in metastatic malignant melanoma. Guided timelines for these readouts have been pushed back multiple times (now to H124) due to patients taking longer than expected to experience disease progression which, in our view, could represent an encouraging sign for patients and the outcome of the trial (however, this is not assured as it is possible that the control arm may experience slower

than expected disease progression). The company has confirmed that the amended study protocols should ensure that the readouts are not delayed further. Top-line results for INITIUM are expected in March or April 2024. In October 2021, Ultimovacs received Fast Track designation for UV1 as an add-on therapy to ipilimumab or pembrolizumab for the treatment of advanced malignant melanoma. Further, in December 2021, the FDA granted Orphan Drug designation to UV1 for the treatment of stage IIB–IV melanoma.

OSE Immunotherapeutics: Tedopi, OSE-279 and BiCKI platform

OSE Immunotherapeutics is a French biotechnology company focused on developing and partnering therapies to harness the natural capabilities of the immune system. Its lead asset, Tedopi, is also a peptide-based cancer vaccine. Tedopi has thus far been investigated as a monotherapy in the Phase III ATALANTE-1 trial, demonstrating a statistically significant survival benefit. The results showed median overall survival (OS) of 11.1 months with Tedopi versus 7.5 months with chemotherapy (docetaxel or pemetrexed) in patients with HLA-A2-positive NSCLC who have developed secondary resistance to ICIs. In addition, OSE is engaged in three Phase II trials, led and funded by external clinical oncology groups, which aim to expand the clinical utility of Tedopi through various combination approaches: with nivolumab (for NSCLC), with pembrolizumab (for ovarian cancer) and with chemotherapy (for pancreatic cancer).

Another of OSE's proprietary assets is OSE-279, a high-affinity anti-PD1 monoclonal antibody ICI. OSE-279 is currently in a Phase I/II dose-escalation trial for the treatment of solid tumours or lymphomas. While OSE-279 is currently being investigated as a monotherapy, we understand that OSE may look to differentiate itself in the competitive ICI space by evaluating OSE-279 in combination with other proprietary assets such as Tedopi, or with external partnerships in the search for novel and effective cancer treatments. Management anticipates that such combinations could overcome the challenges associated with cancer resistance mechanisms. In October 2023, OSE presented initial positive data supporting the efficacy of OSE-279. This asset forms the backbone of the company's bifunctional checkpoint inhibitor platform, BiCKI, which is a bispecific ICI fusion protein platform designed to address primary (lack of response to treatment) and secondary resistance (resistance after an initial response) mechanisms.

Chosa: iCIP as a companion for the clinical trials of tomorrow

Chosa Oncology is a Danish precision oncology company focused on the development of iCIP, a cisplatin-based technology. iCIP consists of two core components: an artificial intelligence-powered drug response predictor intended to identify patients with a greater probability of responding to cisplatin treatment, and LiPlaCis, a liposomal cisplatin formulation designed to offer more desirable safety and efficacy profiles over conventional cisplatin. While cisplatin is one of the most widely prescribed drugs in oncology (c 10–20% of newly diagnosed cancer patients receive cisplatin), the drug's limitations include its toxicity, off-target side effect profile and resistance in certain patient populations. There is a growing body of clinical evidence to suggest that cisplatin may work synergistically with ICIs to provide clinically meaningful benefits to cancer patients. This has been exemplified by the approval of pembrolizumab in combination with platinum chemotherapy (including cisplatin) as first-line treatments for conditions such as NSCLC, head and neck squamous cell carcinoma, esophageal cancer and, more recently in November 2023, pembrolizumab plus gemcitabine and cisplatin for the treatment of biliary tract cancer. At present, Chosa is looking to identify and secure strategic partnerships or buyers to advance iCIP into follow-on clinical studies, and we believe that such advancements could potentially support the next generation of combination treatments in oncology.

Potential combinations beyond checkpoints

Mendus: Cancer vaccine plus chemotherapy in the pipeline

Mendus, a Sweden-based company focused predominantly on the development of its lead cancer vaccine, vididencel, a cell-based, off-the-shelf vaccine designed as maintenance therapy to prevent relapse in patients with acute myeloid leukaemia (AML). AML is a relatively rare cancer, for which first-line treatment relies on chemotherapy, which usually involves a 3+7 regimen (three days of an anthracycline antibiotic and seven days of cytarabine chemotherapy), while chemo-unfit patients are typically treated with venetoclax and oral azacitidine (Onureg). The competitive landscape for AML treatments is an active space and, in particular, an emerging paradigm in AML treatment is maintenance therapy, which involves the complete eradication of residual cancerous cells from the body following a patient's complete response to induction therapy, to prolong remission duration, prevent relapse and improve overall survival.

The Phase II trial, ADVANCE II, is investigating vididencel in AML patients who have previously responded to therapy and achieved complete remission, but still have measurable residual disease. The ADVANCE II trial (n=20) is in the long-term follow-up stage, and as of 24 November 2023, median follow-up was 31.6 months. Median relapse-free survival (RFS) was reported as 30.4 months and median OS had not yet been reached, with 14/20 patients still alive and 11/14 still in complete remission. While we advise against a direct read across between clinical trials, we note that Onureg demonstrated a median RFS of 7.1 months and a median OS of 14.6 months in its registrational trial.

With the encouraging data to date, management is now focused on investigating vididencel in combination with Onureg to assess whether the two treatments may act synergistically. In our opinion, this represents a sensible strategic decision and one that could maximise the potential of the company's lead cancer vaccine. Details on the design of this clinical trial were reported in December 2023 and, according to management, it is on track to commence in H124.

CAR-T: A higher calling

While cell and gene therapies represent distinct therapeutic approaches in healthcare, both have topped the list of clinical buzzwords over the last few decades. However, CAR-T cell therapies is a hybrid of the two as a gene-modified cell therapy. This involves the removal of immune T-cells from a patient, genetic modification of these cells and re-administration of the cells to the patient, allowing the targeting and destruction of disease-causing cells. There are currently six approved CAR-T cell therapies which, to date, have found application in the treatment of hematological malignancies. The two most recently approved CAR-Ts include BMS's Abecma (March 2021) and Johnson & Johnson's Carvykti (February 2022), both for the treatment of multiple myeloma (MM). In November 2023, the FDA announced an investigation into the risk of T-cell malignancies in patients that have received CAR-T therapies. However, while the risk was identified in all currently approved CAR-T therapies, the FDA emphasised that the overall benefits outweigh the potential risks. Furthermore, clinicians do not seem to be put off by the announcement, with many remaining confident that CAR-T therapies represent an effective treatment option for challenging diseases. Additionally, the FDA investigation does not appear to have hampered interest from big pharma, as in December 2023, AstraZeneca announced the acquisition of Gracell, a clinical-stage biotechnology company focused on the development of novel CAR-T therapies.

Risk versus benefit is naturally a theme in all healthcare research, but is of particular focus for emerging CAR-T therapies. Current CAR-T therapies are often associated with neurotoxicity and high-grade cytokine release syndrome. A direct consequence of this is that patients receiving these

therapies must endure long hospital stays (c 14 days on average) to monitor potential toxicity, and accessibility is limited (with only c 5% of US hospitals able to administer this type of treatment).

Immix Biopharma

Immix Biopharma believes it can address this ongoing medical need with NXC-201, which is currently in a Phase Ib/IIa clinical trial for the treatment of patients with MM and amyloid light chain amyloidosis (ALA). The trial has shown encouraging readouts to date, including overall response rates of 90% in 50 MM patients and 100% in 10 ALA patients. Immix (through its majority owned subsidiary, Nexcella) is developing NXC-201 with long-term hopes that it will become the first outpatient CAR-T therapy with a differentiated safety profile, showing notably low neurotoxicity (4% for MM; none for ALA) in clinical results to date, and only low-grade Cytokine Release Syndrome events that have been associated with short onsets. The data to date are encouraging and we look forward to more rolling data readouts as the trial progresses. Immix intends to submit a Biologics License Application to the FDA for MM once 100 patients have been treated, and for ALA once 40 patients have been treated.

CNS: Neuroscience comeback

Following on from our last CNS thematic, Neuroscience comeback (published in November 2022), CNS has been a tougher nut to crack, likely hindered by the lack of objective measures and relatively longer time horizon. However, the recent uptick in transactions and increased concentration of CNS in pipelines suggest that we could be at a tipping point.

While we appreciate the level of jargon associated with this area of research (whether referred to as neuroscience, neurology or brain disorders), CNS as a therapeutic area can be broadly divided into two main categories:

- Neurological conditions: characterised by cognitive and motor dysfunction, thought to be caused by damaged neurons or nerves. Examples that we have chosen to focus on include:
  - Alzheimer's disease (AD), due to the breadth of current ongoing research expanding our understanding of the condition, and
  - Parkinson's disease (PD), as it has a growing unmet medical need and is representative of the complex nature of CNS as a therapeutic area.
- Neuropsychiatric conditions: characterised by aberrant behaviour and emotions. Examples that we have chosen to focus on include:
  - schizophrenia, as we believe it is at the precipice of a new era of treatments, offering improvements on therapies that have not advanced since the 1950s, and
  - anxiety, which is considered the most prevalent mental health condition, but there has been a lack of effective treatment options in patients resistant to first-line therapies.

There are a number of ongoing studies assessing novel therapies for schizophrenia, and we believe they highlight progress in a field that has been otherwise relatively stagnant since the 1950s. We believe that emerging medications with unique mechanisms of action and therapeutic targets are primed to potentially drive a new era of schizophrenia treatments.

Key transactions from the final quarter of 2023 include the announcement that AbbVie will be acquiring Cerevel in a deal worth $8.7bn. Most notably, this gives AbbVie access to Cerevel's promising Phase II asset, emraclidine, which is being developed for the treatment of schizophrenia. Another key transaction, which also came in December 2023, was BMS's acquisition of Karuna Therapeutics for $330/share in cash (total equity value of $14bn or $12.7bn net of estimated cash acquired). At the centre of this deal is Karuna's KarXT, which is the same class of therapeutic as for the treatment of schizophrenia, albeit at a later stage; the FDA has set a Prescription Drug User

Fee Act (PDUFA) decision date of 26 September 2024. We highlight that both emraclidine and KarXT are also being investigated in AD.

Parkinson's disease primed to pick up pace

PD is a complex and progressive neurodegenerative disease, characterised by a triad of cardinal motor symptoms (rigidity, bradykinesia and tremor), although non-motor symptoms (psychosis, dementia and cognitive impairment, or CI) are as debilitating and remain undertreated. It is estimated that PD afflicts c one million people in the US alone, and more than 10 million people worldwide; this figure is expected to double by 2040 due to an ageing population.

Levodopa firmly remains the current standard of care as a first-line treatment for PD. The cause of PD is thought to be the degeneration of nerve cells in the substantia nigra (a part of the brain that controls movement) and when these nerve cells are impaired, they lose the ability to produce dopamine. Levodopa was developed in the 1960s to directly address this as a dopamine replacement agent, and was approved by the FDA in 1970. However, the drug is associated with a myriad of side effects and long-term use can lead to dyskinesia. Furthermore, while several targets are being explored as potentially disease-modifying approaches for PD, symptomatic treatment remains the mainstay. In our opinion, there is widespread opportunity for innovative novel treatment options to provide a better outcome for PD patients.

IRLAB: A biotech with a comprehensive PD pipeline

IRLAB Therapeutics is a biotech seeking to differentiate itself from other companies via its comprehensive approach to CNS therapeutics, with a particular focus on PD. Central to its strategy for drug development is its proprietary Integrative Screening Process (ISP) research platform. The ISP marries systems biology, chemistry and AI-based machine learning methods, designed to expedite the discovery of novel drugs for CNS indications. The platform contains a database of c 1,400 CNS drug-like compounds, with each compound profiled in various assays and animal models to capture dose-dependent data on a range of biological responses. This has generated a wealth of information, including pharmacokinetics, receptor binding, chemical properties and safety. Comparisons drawn across these data sets, alongside the machine learning capabilities, have generated a comprehensive map of the CNS drug property space, designed to enable a focus on higher-quality drug candidates.

We believe that this multifactorial approach is well matched for the complexity of CNS-related diseases. The company's comprehensive approach to CNS and PD has been demonstrated by the progress of lead assets, pirepemat and mesdopetam. Pirepemat is currently in a Phase IIb trial for impaired balance and falls in PD. It passed a safety review in July 2023 and top-line results are on track for H124. Mesdopetam did not reach statistical significance on the primary endpoint (good ON-time) in a Phase IIb trial for levodopa-induced dyskinesias, but the results showed significant ON-phase anti-dyskinetic efficacy, measured by UDysRS. IRLAB is preparing to present detailed data to the FDA supporting further development of mesdopetam and believes it is Phase III ready. In January 2024, IRLAB Therapeutics scheduled an end-of-Phase II meeting (on 20 February) with the US FDA for the mesdopetam programme, which marks an important milestone for the biotech, as it will evaluate the clinical data generated to date and aim to reach a conclusion for the design of the planned Phase III programme.

Beyond these clinical-stage assets, IRLAB has a preclinical portfolio which includes symptomatic treatments for PD: IRL757 for the treatment of apathy and IRL942 to improve cognitive function, as well as a novel treatment for PD: IRL117 as a once-daily oral drug, either as a monotherapy aiming to replace levodopa or as an add-on therapy.

Not all about primary endpoints in CNS

While we advise against a read across between clinical outcomes of drug candidates and across indications, we refer to Leqembi, regarded as one of the most significant clinical breakthroughs in AD. We highlight that the antibody drug had previously missed its primary efficacy endpoint measurement of 12-month clinical change on the Alzheimer's disease composite score (ADCOMS) as part of a Phase IIb trial. However, the trial did meet a key secondary endpoint as measured by the Clinical Dementia Rating Sum of Boxes (CDR-SB) showing cognitive and functional performance. The secondary CDR-SB measure was subsequently used as the primary endpoint in the pivotal Clarity AD study, which formed the basis of the FDA's approval for the drug.

Based on the results of IRLAB's Phase IIb mesdopetam study, we believe that the drug is in a strong position to progress into pivotal Phase III trials, having hit its key, clinically recognised secondary endpoint. Supporting this, mesdopetam has also demonstrated safety and tolerability throughout its trials, and it met an additional secondary endpoint with an unchanged measurement in the MDS-UPDRS Part II scale.

MindMed

Interest in the field of psychedelic therapies has largely been driven by the gap in available treatment options and, with a growing body of clinical evidence, the use of this family of drugs to treat mental illnesses is gaining momentum in psychiatry. Notably, in June 2023 the FDA provided its first formal guidance on the use of psychedelic drugs in clinical trials. Also, in December 2023, MAPS PBC made headlines following the announcement that it had filed the first New Drug Application (NDA) for MDMA to the FDA for the treatment of post-traumatic stress disorder. We believe these milestones are important as they mark a key step on the path to broader acceptance for the use of psychedelic therapies.

MindMed is a clinical-stage US biopharmaceutical company aiming to leverage psychedelic medicines to target life-debilitating mental health conditions. The company's lead target indication is generalised anxiety disorder (GAD). Global spending on medicines for anxiety-related disorders is expected to reach c $5bn by 2026 (according to IQVIA). Furthermore, it is estimated that c 20.2 million adults suffer from GAD in the US (c 10% of the adult population), representing a potentially sizeable addressable market. With side effects and unsatisfactory efficacy in a considerable proportion of patients associated with currently available treatment options, we believe there is a significant opportunity for MindMed to address this medical need. The company's lead asset is MM-120, a pharmaceutically optimised form of LSD, and top-line readouts from the Phase IIb trial in GAD were reported in December 2023. The results showed that the primary endpoint was met, with MM-120 exhibiting a statistically significant and dose-dependent improvement in Hamilton Anxiety Rating Scale (HAM-A) scores across the duration of the trial. MindMed intends to request an end-of-Phase II meeting with the FDA in H124 and, provided the outcome is successful, launch a Phase III programme in H224.

Newron Pharmaceuticals

Newron Pharmaceuticals is a biopharmaceutical company focused on developing innovative treatments for CNS diseases. Royalties from the company's marketed drug Xadago, an adjunctive therapy for PD, continue to drive top-line revenues for Newron. Beyond PD, the company's focus is firmly on the clinical development of evenamide, a drug designed for glutamate modulation and voltage-gated sodium channel blockade with the aim of providing an effective add-on therapy for schizophrenia patients. Newron is looking to treat both poorly managed and treatment-resistant schizophrenia (TRS) with its range of clinical programmes. We note that current approved treatments do not address each of these subtypes separately. This is perhaps reflective of the challenge in developing effective therapies for schizophrenia, highlighting the potential opportunity for Newron, for which we anticipate multiple potential upcoming catalysts in the near term from its

active clinical pipeline. These include full one-year data from study 014/015 in Q124 (Phase II in TRS), the launch of study 003 in H124 (Phase III in TRS), full results from study 008A in H124 (Phase III in schizophrenia patients already receiving antipsychotics but not classed as having TRS).

Oryzon Genomics

Oryzon Genomics is a leading biotech focused on epigenetics, with two lead assets that collectively cover CNS (with vafidemstat) and oncology (with iadademstat) indications. Both these drugs are inhibitors of a novel target, lysine-specific demethylase 1 (LSD1), which is suggested to regulate the expression of genes involved in the onset and progression of both CNS disorders and certain cancers. In CNS, Oryzon is focused on several programmes:

- Within its CNS portfolio, Oryzon's most advanced project is the Phase IIb PORTICO trial, which is investigating vafidemstat for the treatment of borderline personality disorder (BPD). This trial is ongoing, and an interim analysis from an independent data monitoring committee, based on the first 90 patients who completed the treatment, recommended that the trial continue without any modifications. An interim safety review, based on the first 167 patients treated in the trial, confirmed that there had been no reported cases of treatment-related serious adverse events. Top-line data are expected in early 2024, at which point Oryzon will assess all endpoints and decide the next steps for vafidemstat in CNS; this may involve a follow-on Phase III trial in BPD.
- The company's Phase IIb EVOLUTION trial is assessing vafidemstat for the treatment of negative symptoms and CI associated with schizophrenia. The study is ongoing and actively recruiting patients; an update is expected in 2024.
- Additionally, management is finalising plans for the Phase I/II HOPE trial, which will evaluate vafidemstat for the treatment of Kabuki syndrome, a rare congenital disorder. We believe this is particularly noteworthy, as it combines numerous unique features that characterise interesting CNS programmes, including targeting a monogenic CNS orphan indication with no clinical competitors (to our knowledge), applying a precision medicine approach in CNS with an understanding of the disease pathology and addressing a novel drug target in CNS.

Alzheimer's: Not for the lack of effort

We would be remiss to exclude AD within CNS. Despite the decades of effort, we had not seen much movement in the subsegment. However, certain recent advances in AD have garnered decent mindshare. Around the halfway mark (6 July 2023), the FDA granted full approval of Biogen/Eisai's anti-amyloid antibody, lecanemab (or Leqembi), which is expected to broaden patient access significantly, as it crosses the line for coverage by the Centers for Medicare & Medicaid Services, meaning that its portal-based registry for the drug will be available for same-day utilisation. This regulatory designation should improve sales of the drug, which comes with a $26.5k annual price tag, estimated to reach $4.8bn in worldwide sales in 2028 (according to EvaluatePharma). Eli Lilly is also developing an anti-amyloid antibody, donanemab and, while it is still awaiting a regulatory decision, it is projected to generate $2.2bn in sales in 2028 (according to EvaluatePharma). The FDA is expected to confirm the decision in early 2024.

Actinogen Medical

Actinogen Medical has taken a different approach from classic anti-amyloid therapies. It is advancing Xanamem for cognitive disorders, including CI associated with AD. Xanamem is an inhibitor of enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) and is designed to penetrate the brain. Scientific literature suggests that excessive cortisol is associated with CI, including age-related CI and AD. The naturally present enzyme 11β-HSD1 normally converts cortisone to cortisol inside cells and Xanamem is designed to reduce excessive cortisol production in the brain. Actinogen's lead programme for Xanamem is the treatment of CI associated with AD,

and it expects to start the upcoming Phase IIb portion of the XanaMIA trial in AD patients in the next few weeks. The XanaMIA Phase IIb trial aims to assess Xanamem versus placebo in AD patients with an elevated level of phosphorylated Tau-181 protein in their blood, over a 36-week treatment duration. Actinogen is also assessing Xanamem for CI associated with major depressive disorder (MDD). MDD has c 5% prevalence globally. CI is a feature in most MDD patients and often persists even when depressive symptoms subside. Actinogen began the XanaCIDD study in Q422 in patients with CI associated with MDD. The study aims to enroll about 160 patients across Australia and the UK who have persistent depressive symptoms and CI despite standard-of-care anti-depression therapy, with 50% of targeted recruitment reached in November. Actinogen expects to report study results in Q2 CY24.

Niche areas with expertise in high demand

Basilea Pharmaceutica

Antimicrobial resistance represents a growing issue, which has often been referred to as a silent pandemic, with forgotten superbugs including bacterial and fungal pathogens. The World Bank estimates that antimicrobial resistance could cause $1tn in additional healthcare costs by 2050, and $1–3.4tn in GDP losses per year by 2030.

Despite the lack of historical investment in this area, there is a need for therapeutic agents that are efficacious against drug-resistant strains of bacteria and fungi. Basilea Pharmaceutica is a Switzerland-based biotechnology company specializing in this niche where it has been able to follow through and commercialise via partnerships with large pharma. Its lead asset, Cresemba (or isavuconazole), is an antifungal therapy, approved in 76 countries and marketed in 71 countries, and has Orphan Drug designation in the US, Europe and Australia. It is an azole-based therapy for the treatment of aspergillosis and mucormycosis, available as both IV and oral formulations, and has driven recent top-line revenues for the company. It also boasts the largest antifungal market share in the US, at c 36%, compared to competitor best-in-class antifungal therapies. Basilea's second asset is Zevtera (or ceftobiprole), an antibiotic therapy, which is marketed in selected countries in Europe, Latin America, the Middle East, North Africa and Canada. In October 2023, Basilea announced that the FDA had accepted its NDA, and has set a Prescription Drug User Fee Act date of 3 April 2024. This regulatory decision could represent the next most significant catalyst for the company.

In November and December 2023, Basilea expanded its preclinical pipeline, most notably to include fosmanogepix, a potential first-in-class, broad-spectrum antifungal therapy. We believe that fosmanogepix could offer a solution to the issue of antifungal resistance with its novel mechanism of action and look forward to following the progress of this asset in Phase III studies, which are expected to launch from mid-2024.

SIGA Technologies

The COVID-19 pandemic and its aftermath has raised awareness of infectious diseases, the potential threat of biological weapons and overall global unpreparedness to tackle such exigencies. Government agencies have become more aware of the need for pre-emptive measures, which highlights the importance of health security-focused companies. SIGA Technologies is the only global company to have an approved antiviral treatment, TPOXX, for smallpox which, although eradicated, continues to carry the threat of being unleashed as a bioweapon. Developed with backing from the US Biomedical Advanced Research and Development Authority, TPOXX was approved by the US FDA in 2018 for the treatment of smallpox and in the EU and UK under the broad label including all orthopox pathogens in 2022. With recent orders (to the tune of $18m) from the European Health Emergency Preparedness and Response Authority, we believe that SIGA's

international evolution is taking wing, with value to be unlocked. Profit making to boot, with a strong balance sheet and a history of rewarding investors (through dividends and buybacks), SIGA presents a relatively more resilient business case in what has been an otherwise challenging period for biotechs.

AFT Pharmaceuticals

Not your traditional biotech, AFT Pharmaceuticals' appeal comes from its more 'consumer' focused positioning, a broad product portfolio and wide presence flanking the over-the-counter, prescription and hospitals space. A profitable business and a well-known name in its domestic ANZ market (with more than 150 proprietary, branded and generic products), its medium-term growth strategy is built on expanding its international presence through distribution and out-licensing partnerships. Central to this is the company's Maxigesic range of products (a proprietary combination of paracetamol and ibuprofen), which have been gaining significant traction in international markets. With the recent approvals of Maxigesic IV and Rapid providing a foothold for the company in the lucrative US market, we foresee a faster sales ramp-up in the near to medium term, helping the company achieve its rolling target of NZ$200m in revenues. A strengthening balance sheet allowed AFT to pay its maiden dividend in FY23 and we anticipate this trend to continue with improving profitability.

Shield Therapeutics

Armed with its US commercialisation partnership deal (55:45) with Nasdaq-listed Viatris (Upjohn+Mylan merger), Shield Therapeutics aims to tackle the unmet need in the iron deficiency space (with or without anaemia), which remains a key disease burden globally, affecting c 40% of the global population including c 10 million people in the US alone. The World Health Organization has recognised iron deficiency anaemia as the most common nutritional deficiency in the world, effecting 30% of the population. Despite these jarring figures, treatment options remain restricted to previous-generation, salt-based supplements which are associated with low absorbability and severe gastrointestinal side effects, resulting in as many as 40% of patients discontinuing treatment. Shield offers a novel alternative in its lead drug Accrufer/Feraccru, which carries greater absorbability and a superior side effect profile to conventional treatments (resulting in c 10x lower discontinuation rates), with the potential to reshape the treatment paradigm in this space. A growing prescription volume, supported by a commercial deal with Viatris in December 2022 and c $50m in fund-raising in 2023, de-risks near-term operational viability and creates a strong foundation for the business to break even in 2025. This presents a compelling bet for investors with a longer-term horizon.

Creo Medical

Healthcare cost containment has increased the importance of more convenient surgical solutions offering shorter patient recovery time. With its innovative suite of six electrosurgical devices, Creo Medical offers one such solution. Backed by its Kamaptive Technology and Croma platform (which uses a combination of bipolar radiofrequency and microwave energy), the company's novel electrosurgical devices allow for the dissection, resection, ablation and haemostasis of diseased tissue using only a single instrument. Led by its Speedboat range (including the most recently launched UltraSlim version) and supported by its clinician training programmes, Creo has been steadily gaining traction in its target gastrointestinal space, with the goal of expanding into the lung and pancreas. The proprietary Kamaptive Technology has also invited considerable interest and its potential utility in the growing robotics space (and recent deals with Intuitive and CMR Surgical) is very interesting. Intuitive is, by far, the largest player in the robotics-assisted surgical systems market with an estimated global market share of 57%. The company has more than 7,500 of its da Vinci systems installed across hospitals globally and more than 12 million procedures were performed in 2022 using these robots. With Creo's top line gathering momentum, we see the company breaking even in the next two to three years while remaining comfortably funded.

VolitionRx

VolitionRx is an innovative US-based clinical diagnostics company developing easy-to-use and cost-effective blood tests for early diagnosis and monitoring of a range of diseases in humans and animals, including cancer and sepsis. The company's diagnostic Nu.Q tests are backed by its patented Nucleosomics technology, which identifies and measures nucleosomes in the bloodstream and other bodily fluids as biomarkers for disease. The most advanced programme is the Nu.Q Vet Cancer Test, an early cancer screening test for animals, currently available for canines through reference labs from IDEXX, Heska (acquired by Mars Petcare in June 2023) and the GI Lab at Texas A&M University. A point-of-care test being developed in collaboration with Heska is expected to launch soon. Another key area of focus for Volition is its Nu.Q NETs test, a CE-marked diagnostic test which detects NETosis as a biomarker of inflammatory diseases, with the initial focus on sepsis (global mortality rate estimated at c 25%). The total addressable market for Nu.Q Vet and Nu.Q NETs is estimated to be $11bn in 2023 and $22bn in 2024/25. Volition's technology and portfolio is backed by strong IP, with 95 granted and 126 pending patents across 46 patent families globally. In October 2023, Volition announced its potentially disruptive, first-of-its-kind, early-stage cancer detection method CTCF-ChIP/qPCR for early-stage cancer screening, which claims to be able to isolate and extract circulating tumour DNA from blood samples without the need for lengthy DNA sequencing (the mainstay of current liquid biopsy tests).

Recce Pharmaceuticals

Recce Pharmaceuticals is an ASX-listed Australian biotech developing a novel class of broad-spectrum, synthetic, anti-infective drugs to which, so far, all tested bacteria have been unable to develop resistance. This could be a very desirable trait given widespread concerns about antimicrobial resistance, identified as a major public health threat by the World Health Organization and the US Centers for Disease Control and Prevention. The lead indication for Recce's synthetic polymer antibiotic, Recce 327 (R327), is sepsis, a substantial area of unmet need with significant mortality and high costs of care. Sepsis affects 1.7 million people in the US each year and has been reported as the country's most expensive condition (in aggregate) to treat in hospital. We view significant opportunities for treatments that may reduce morbidity or hospital utilisation. The company's priority is to advance the IV formulation of R327, particularly for sepsis (and/or urosepsis) and complicated urinary tract infections (UTIs). The company is conducting a Phase I/II study assessing R327 IV at faster infusion rates (than its earlier R327-001 trial). The Phase I/II clinical trial is expected to inform optimal dosing levels and infusion rates for a subsequent Phase II study, to be conducted in patients with uncomplicated or recurrent UTIs. We expect this Phase II trial to commence shortly, with likely readouts (including ex-vivo analysis) in Q2 CY24. In addition to advancing the IV R327 formulation, Recce is developing topical (and spray-on) formulations of R327. A topical R327 formulation is being assessed in a Phase I/II study for diabetic foot infections. Topical R327 formulations are also being assessed in a Phase I/II investigator-sponsored trial for burn wound infections, with the second stage of this study expected to assess the R327G gel formulation head-to-head against a standard of care. Recce recently reported that the Australian government has committed to providing up to A$55m in future cash rebates to reimburse upcoming R&D expenditure directed towards its proprietary synthetic ant-infective programmes to June 2025.

Sareum Holdings

Made famous by the best-selling drug of all time, Humira, the autoimmune space is vast, with more than 80 identified inflammatory diseases, of which the most common are rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease and lupus. The landscape is extremely competitive but, given the market expanse, even a small piece of the pie could be sufficient to whet commercial appetites. In a space dominated by biologics, Sareum Holdings offers a more convenient oral alternative in its small molecule JAK kinase inhibitor SDC-1801 (the initial focus will

be on psoriasis). A new-generation, selective inhibitor of JAK1 and TYK2, SDC-1801 promises to overcome the toxicity and off-target effects of the previous generation of JAK inhibitors, while maintaining efficacy. Currently undergoing Phase Ia safety studies in Australia (which commenced in May 2023), top-line results are expected in H1 CY24 which, if positive, will lead to Sareum undertaking a Phase Ib clinical trial in psoriasis patients (expected to complete by end-2024). The global psoriasis treatment market was valued at $27.1bn in 2022 and is estimated to reach $57.7bn by 2032 (CAGR of 7.9%), indicating the sizeable commercial opportunity. Potential market prospects can be gauged from the $3bn+ peak sales potential assigned to BMS's TYK2 inhibitor Sotyktu and the $4bn in upfront payment made by Takeda to acquire Nimbus Therapeutics' Phase III-ready TYK2 programme. Further traction could also come from a second clinical candidate (Phase II), SRA737, a highly selective checkpoint kinase 1 inhibitor targeting the DNA damage response network for the treatment of solid tumours. Development and commercial rights to the asset were recently out-licensed to an unnamed private US-based pharma company for up to c $290m in milestone payments in addition to tiered high single-digit royalties. Sareum holds a 27.5% economic interest in SRA737 and is entitled to receive $137.5k in an upfront payment and a proportionate share of other milestone payments and royalties.

Sequana Medical

Based in Belgium, Sequana Medical develops products to treat diuretic-resistant fluid overload, a frequent complication of liver disease and heart failure (HF). Its proprietary alfapump and Direct Sodium Removal (DSR) approaches aim to provide significant clinical and quality-of-life benefits. Given positive efficacy, safety and quality-of-life data from its POSEIDON North American registration study for the alfapump in recurrent and refractory ascites, Sequana submitted a US Premarket Approval application in December 2023, with US approval anticipated in H224. Management expects the addressable market to be worth more than $2.5bn by 2035 and will initially target a market subset worth c $500m. Supported by encouraging data from its Phase IIa SAHARA DSR study in HF patients with persistent congestion, in July 2023 Sequana started the MOJAVE US Phase I/IIa study, assessing its second-generation product (DSR 2.0) in a similar patient population. Positive results from the non-randomized cohort of the first three MOJAVE patients was reported in November, including the safe and effective treatment of congestion with maintenance of euvolemia without the need of loop diuretics, as well as material benefits in cardiorenal status and in diuretic response. Data from first randomized cohort are expected in H224. Management plans to seek development and commercial partners for DSR 2.0 following top-line data readouts from the MOJAVE study anticipated in H225.

Respiri

Respiri is an Australia-based medical technology company offering remote respiratory patient monitoring (RPM) services (following the acquisition of Access Telehealth in August 2023) across a Software as a Service platform. The company has aspirations of expanding wheezo into the monitoring and health management of chronic conditions such as cardiovascular, diabetes and obesity, in addition to respiratory diseases. Management is currently focused on the US market, where RPM services qualify for Current Procedural Terminology code reimbursement. Following the acquisition of Access, Respiri expects to net a monthly RPM fee of $85/patient (vs $10–20 previously), allowing it to break even once 9,000 patients are onboarded for wheezo, which it expects will happen as early as H2 CY24. With the recent A$6.5m private placement, we believe Respiri is sufficiently funded to reach break-even, which we estimate in H125/H2 CY24.

Biodexa Pharmaceuticals

Biodexa Pharmaceuticals is a Nasdaq-listed, clinical-stage biopharmaceutical company which has had a strategic pivot. In December 2023, it expanded its clinical pipeline with the acquisition of

Adhera Therapeutics' Phase II-ready asset, tolimidone, a novel lyn kinase activator, with the intention of developing it for type I diabetes (T1D), a market with no currently available curative therapies and estimated to be worth $13.6bn by 2030. Biodexa plans to conduct a Phase Ib dose-finding study to establish the minimum effective dose in patients with T1D, to be followed by a Phase II double blinded study in patients with T1D. This supplements its legacy focus on primary and metastatic cancers of the brain, including recurrent glioblastoma (rGBM) and diffuse midline glioma (DMG). It also has three proprietary drug delivery technologies focused on improving the bio-delivery and bio-distribution of medicines. Of these, MidaSolve (which solubilises otherwise insoluble drugs) forms the foundation of the company's lead asset, MTX110, a soluble formulation of the multiple myeloma drug, panobinostat, currently in Phase I trials for rGBM and DMG, both aggressive cancers with very few, if any, therapeutic options available.

Pain avoidance is the name of the game

Pain management and treatment represents a significant market targeted by both big pharma and biotech. The market is estimated to be worth c $81bn in 2021 and projected to surpass a valuation of c $191bn in 2030. This corresponds to a sizeable CAGR of 8.8%. While the field can be broken down into drugs, devices and different types of pain, two companies in particular are focused on pain implicated in specific indications: Oxford Cannabinoid Technologies (LSE: OCTP) in neuropathic pain associated with chemotherapy-induced peripheral neuropathy (CIPN) and visceral pain in irritable bowel syndrome (IBS) and Paradigm Biopharma (ASX: PAR) in knee pain associated with osteoarthritis (kOA).

Oxford Cannabinoid Technologies

Oxford Cannabinoid Technologies (OCT) is a UK-based company focused on developing cannabinoid derivatives, phytocannabinoids (synthetic plant-derived cannabinoids) and new chemical entities (NCEs) for the treatment of pain (and other indications). With the stigma that has come to be associated with opioids, we believe that alternative therapies for pain management remain an ongoing medical need. The company's leading pipeline asset is OCT461201, a cannabinoid receptor type 2 (CB2) selective NCE agonist being investigated as a potential treatment for neuropathic pain associated with CIPN and visceral pain in IBS. We note that OCT461201 is a synthetic endocannabinoid system-targeting NCE. The advantages of using synthetic active pharmaceutical ingredients, as opposed to natural isolates, are clear and recognised by regulators worldwide. Quality control, especially in relation to purity and concentration, is easier and more reliable with synthetic compounds. Further, while CB1 is primarily involved in mediating the psychoactive effects of cannabinoids, we highlight that CB2 is responsible for regulating anti-inflammatory and immunosuppressive responses. It is the CB2 receptor that OCT is aiming to selectively target with OCT461201, which has been designed to trigger the desired therapeutic effect and circumvent the unwanted psychotropic side effects associated with CB1 agonists. In October 2023, OCT reported that its Phase I trial for OCT461201 in healthy volunteers had been completed, demonstrating desirable safety and tolerability. Management plans to progress this asset to Phase II studies once sufficient funding is sourced.

Paradigm Biopharma

Paradigm Biopharma is an Australia-based company, focused on the clinical development of injectable pentosan polysulfate sodium (iPPS) for the treatment of kOA pain, as well as potentially a disease-modifying osteoarthritis (OA) drug. The Phase II PARA_OA_008 programme recently shared positive readouts, including durable responses based on measures of pain and function, while confirming that the company will be pursuing an iPPS (2mg/kg) twice-weekly regimen for six weeks. Paradigm's most advanced programme is PARA_OA_002, which is in Phase III.

Management is in the process of requesting a protocol review from regulators to include the determined optimal dosing regimen in this programme, and hopes to continue with clinical studies in H124. With more than 450 patients treated as part of its lead programme and with support from NFL Alumni Health to highlight strong interest, we believe that the clinical development of iPPS for this indication serves as a good example of teaching an old drug new tricks. We look forward to monitoring the progress of all of Paradigm's clinical programmes in OA.

Delivery platforms

Biotechs focused on drug delivery platforms represent one of the most unsung heroes of healthcare. Innovative emerging therapies, such as cell and gene therapies, RNA approaches and even clustered regularly interspaced short palindromic repeats therapeutics, are demanding more sophisticated approaches for delivery to targeted areas in the body. We believe the importance of delivery should not be forgotten, as efficacy is heavily dependent on timing and presence of the therapeutic modality at the right place. For a more detailed discussion on the role that drug delivery plays in drug discovery, we direct readers to our prior thematic note on this topic.

ReNeuron Group

ReNeuron Group is a UK-based biotechnology company focused on the objective of drug delivery and committed to advancing its proprietary CustomEX^{TM} stem cell-derived exosome platform. It operates as a research and development organisation with early-stage revenue from exosome research services, but management's longer-term ambition is to establish partner programmes with licensing agreements, consisting of development milestones and sales-based royalties. CustomEX^{TM} is a stem cell-derived exosome platform with a unique delivery mechanism for a variety of therapeutic payloads, including small molecules, nucleic acids, proteins and gene-editing technologies. ReNeuron's exosome populations are derived from a catalogue of seven proprietary stem cell lines: four neural stem cell lines and three stem cell lines from areas outside of the brain. While the most advanced competitor programmes use exosomes derived from HEK293 cells (immortalised human embryonic kidney cells), we believe that CustomEX^{TM} could differentiate via its diversification in stem cell lines. The most recent operational highlight for ReNeuron was the announcement of in vivo data, demonstrating the cellular and tissue-targeting capabilities of proprietary exosomes, including an example with delivery of a therapeutic payload. Importantly, the data confirmed that exosome targeting was dependent on the cell source, which may offer broader capabilities compared to the HEK293 approach used by competitors (for further details, see our update note). Although in the early stages of development, we believe ReNeuron's approach could potentially also differentiate on the safety front, including in comparison to alternative delivery vehicles such as liquid nanoparticles. Management now aims to broaden its capabilities with a focus on the functional delivery of specific payloads and hopes that such advancements could facilitate discussions with potential partners.

AI in healthcare: Show me the money

Artificial intelligence (AI) and machine learning (ML) are phrases that grabbed headlines throughout 2023 but there has not been much movement, likely due to the complexity of healthcare. There has been notable interest from big pharma companies in employing AI/ML to expedite drug discovery and several deals around healthcare and AI/ML stand out from what is considered a challenging macroeconomic environment.

Most notably, we see Exscientia (Nasdaq: EXAI, c $815m market cap) as a leader in the space with its proprietary computational drug discovery platform focused on using ML to design and optimise

drug molecules. The company also has a strong track record of collaborations, including with BMS, Sanofi and the Bill & Melinda Gates Foundation. In our view, BenevolentAI (AS: BAI), with a current market cap of c €70m, is also noteworthy. BenevolentAI boasts an end-to-end drug discovery platform powered by AI, and has ongoing partnerships with AstraZeneca focused on target identification and with Merck for the design of compounds focused on targets in oncology, neurology and immunology.

While there has been much hype suggesting that innovations in the technology sector could lead to faster drug development, we will soon see whether this claim holds up. We believe that as we track through 2024, the gap will widen to separate the hype from science and those using AI/ML most effectively will stand out more with candidates progressing through the clinic. Having said that, we appreciate that a true apples-to-apples comparison of AI versus non-AI drug discovery will likely never exist, and rather, if AI/ML can perhaps be used as a tool to accelerate or de-risk any of the many components that comprise the drug discovery process, it should be considered a win. We look forward to tracking the array of progressions expected in this field throughout 2024.

e-therapeutics

e-therapeutics is a UK-based biotechnology company focused on utilising its computational biology and RNA interference platforms to identify novel targets and advance its pipeline of short interfering RNA therapies (siRNAs). A key strategic priority for the company in 2023 was its commitment to the use of AI/ML to create a purely computational approach to siRNA drug discovery. HepNet is e-therapeutics' proprietary computational biology platform, designed to accelerate and de-risk efforts in identifying high-quality hepatocyte-expressed therapeutic targets. The platform leverages large and complex datasets, computational capabilities and a hepatocyte-centric knowledge base to create and analyse biological network models, providing a novel and mechanistic approach to target identification. For novel targets associated via HepNet, e-therapeutics uses its proprietary GalOmic platform to expedite the development of siRNA therapies, and recently introduced two leading preclinical assets:

- ETX-291 is being developed for the treatment of cardiometabolic diseases. This is a group of related disorders considered to be a leading cause of death globally. According to the World Health Organization, cardiometabolic diseases take approximately 17.9 million lives worldwide each year. Management has communicated that ETX-291 has the potential to provide a disease-modifying benefit and, in a representative disease model, the therapy was found to have a pleiotropic benefit across multiple cardiometabolic disease drivers.
- ETX-148 is being developed for the treatment of haemophilia, a group of rare genetic disorders in which blood clotting is impaired. ETX-148 data from a preclinical joint bleed model suggest it may provide protection against bleed-induced joint damage, a key unmet need in the area. Management claims that the therapy provides this protection without increasing the risk of thrombosis. Management plans to present further details on these preclinical data packages in the near future.

Further details on the company, including HepNet and GalOmic, can be found in our initiation note and prior update note.

Insilico Medicine

Insilico Medicine is a private biotechnology company based in Hong Kong and it is considered one of the earlier players in the AI/ML game. It launched what is considered the first clinical study of an AI/ML-designed candidate (ISM001_055) for an AI/ML-designed therapeutic target in February 2022. Notably, the company advanced the candidate from the discovery stage, through preclinical studies, to a Phase I trial in idiopathic pulmonary fibrosis in just 30 months, marking a significantly reduced duration in contrast to traditional drug discovery programmes. We also highlight that Insilico was able to complete its preclinical studies in less than 18 months with a budget of just

$2.6m, a fraction of the cost of a typical preclinical programme. This attracted attention from big pharma, with Sanofi entering into a strategic research collaboration in November 2022. Powered by its generative AI-driven Pharma.AI platform, Insilico now has a total of 31 active programmes for 29 novel targets, with indications in fibrosis, oncology and immunology. In recent news, in December 2023, the company announced the successful design of multiple small molecule hits showing activity and selectivity against a CNS target, marking a key milestone as part of its multi-year and multi-target agreement with Janssen Pharmaceutica, part of Johnson & Johnson. We look forward to monitoring the progression of Insilico Medicine's ongoing programmes and partnerships, as it is perhaps one of the more experienced biotechs with a focus on AI/ML and, in our view, has a strong and evidenced track record of reducing the time and costs associated with drug development.

Appendix: Companies mentioned in this report

Company	Stock exchange/ticker
89bio	NASDAQ: ETNB
AbbVie	NYSE: ABBV
Actinogen Medical*	ASX: ACW
AFT Pharmaceuticals*	ASX: AFT
AstraZeneca	NASDAQ: AZN
Atavistik Bio	Private
Basilea Pharmaceutica*	SIX: BSLN
Biodexa Pharmaceuticals*	NASDAQ: BDRX
Biogen	NASDAQ: BIIB
bluebird bio	NASDAQ: BLUE
Bristol Myers Squibb	NYSE: BMY
Cerevel Therapeutics Holdings	NASDAQ: CERE
Chosa*	XSAT: CHOSA
Compugen	NASDAQ: CGEN
Creo Medical*	AIM: CREO
CRISPR Therapeutics	NASDAQ: CRSP
Eisai	OTC: ESALY
Eli Lilly	NYSE: LLY
e-therapeutics*	LSE: ETX
Exscientia	NASDAQ: EXAI
Gilead Sciences	NASDAQ: GILD
IDEXX Laboratories	NASDAQ: IDXX
Immix Biopharma*	NASDAQ: IMMX
ImmunoGen	NASDAQ: IMGN
Insilico Medicine	Private
Intuit	NASDAQ: INTU
IRLAB Therapeutics*	Nasdaq Stockholm: IRLABA
Johnson & Johnson	NYSE: JNJ
Karuna Therapeutics	NASDAQ: KRTX
Kimia Therapeutics	Private
Lassen Therapeutics	Private
Mars/Heska	Incorporated/private
Mendus*	STO: IMMU
Merck & Co	NYSE: MRK
MindMed*	NASDAQ: MNMD
Newron Pharmaceuticals*	SIX: NWRN
Novartis	NYSE: NVS
Oryzon Genomics*	BME: ORY
OSE Immunotherapeutics*	PAR: OSE
Oxford Cannabinoid Technologies*	LSE: OCTP
Paradigm Biopharma*	ASX: PAR
Pfizer	NYSE: PFE
Ratio Therapeutics	Private
Recce Pharmaceuticals*	ASX: RCE
ReNeuron Group*	AIM: RENE
Respiri*	ASX: RSH
Roche Holding	SIX: RO
Sareum Holdings*	AIM: SAR
Sequana Medical*	BRU: SEQUA
Shield Therapeutics*	AIM: STX
SIGA Technologies*	NASDAQ: SIGA
Sudo Biosciences	Private
Ultimovacs*	NO: ULTI
Viatris	NASDAQ: VTRS
VolitionRx*	NYSE: VNRX
Voyager Therapeutics	NASDAQ: VYGR
Wave Life Sciences	NASDAQ: WVE
*Edison client	

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