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Managing European Medical Innovation

Auditory Science Review

Treating hearing loss as people age

By Jean-Claude Muller

Page 7

Research Strategy

How a lung delivery issue unlocked RNA

By Carsten Rudolph

Page 19

Commentary

New opportunities awaited travellers to San Francisco

By Sean Morgan-Jones

Page 5

Licensing and Collaboration Briefs

Page 4

Plus

Editorial

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Market Research: Janet Barrie
Production Editor and Art Director: Melissa Sterry
Website Designer: Keith Jay

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MedNous Editorial Board

Editorial

Search as a prime indicator

There are lots of ways professional forecasters can try to predict the future. If the subject is the economy, forecasters can analyse data for gross domestic product, employment and inflation. If the subject is an election, they can conduct surveys of public opinion. When it comes to biotech however, predicting the future is less formulaic. In recent months, some commentators have predicted a slow recovery of the market for initial public offerings (IPOs). Others have not. Some expect the pace of new company launches to accelerate. Some do not. Going into the JP Morgan Healthcare Conference in January however sentiment appeared to be shifting to a more positive outlook. The indicator was recruitment activity.

In a commentary on page 5, Sean Morgan-Jones, an executive search professional in the UK, reports more activity for his business. Looking to the future, he uses a simple metric. This is the number of professionals who are looking for new jobs in the industry versus the number of jobs that are, or will be, available. With typical lead times of three to four months, organisations giving mandates to search firms were looking to land hires in the second quarter or early in the third quarter of this year. This level of engagement at JP Morgan suggests the outlook for the second half of this year is more positive than it was only 12 months earlier, he writes.

In fact, IPO activity did pick up at the turn of the year and continued into the weeks after the conference ended. CG Oncology Inc was the first to go to market in order to raise money for a bladder-sparing therapy for patients with bladder cancer. They were followed by ArriVent Biopharma Inc, a developer of antibody-drug conjugates, and by Alto Neuroscience Inc with treatments for neurological diseases. Next came Metagenomi Inc, which has a gene editing platform, and finally Kyverna Therapeutics Inc with a programme for using CAR T cell therapies for autoimmune diseases.

Another indicator of industry health is spending on research and development. In a survey which appears on pages 20 to 21 we report on the R&D activity of a cohort of European companies representing a cross-section of therapeutic interests. This shows a significant amount of activity in Denmark, starting with the diabetes and obesity work at Novo Nordisk A/S to industrial biotechnology projects at Novozymes A/S, which recently merged with Chr. Hansen Holding A/S to create the new entity Novonesis. The ratio of R&D to sales at Novo Nordisk was 14% in 2023, and was 11.3% at Novozymes.

Genmab A/S, which produces antibody therapeutics in collaboration with other companies, had an R&D ratio of 46%. The ratio has been over 30% for the past three years. Switzerland-based Basilea Pharmaceutica Ltd, which is developing treatments for bacterial and fungal infections, had an R&D ratio of 49.4% in 2023.

– Victoria English, 21 February 2024

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Contents

European Licensing and Collaboration Briefs

	Licensor/Vendor		Licensee/Acquirer	Product/Company	Comment	Date
US	CymaBay Therapeutics Inc	US	Gilead Sciences Inc	Acquisition of company with asset for biliary cholangitis	Deal value is $4.3b	Feb-24
UK	Autolus Therapeutics Plc	DE	BioNTech SE	Collaborate on autologous CAR T cell programmes	$200m share purchase	Feb-24
DE	Evotec SE	US	Advanced BioScience Laboratories Inc	Manufacture broadly neutralising antibodies against HIV	Expands existing agreement	Feb-24
NO	CEPI	US	Pan American Health Organization	Support regional vaccine development	Financial terms not disclosed	Feb-24
US	C2i Genomics Inc	US	Veracyte Inc	Acquisition of company with whole genome residual disease capabilities	F=$70m + M=up to $25m	Feb-24
FI	DelSiTech Ltd	IE	Tolmar International Ltd	Rights to delivery platform for drug development	Undisclosed F + M + R	Feb-24
US	GE HealthCare Technologies Inc	AT	European Congress of Radiology	Advance precision medicine using radiotherapies	Early breast cancer detection is priority	Feb-24
BE	Institute of Tropical Medicine	BE	European Commission consortium	Develop treatment for sarbecoviruses	Grant funding of €7.7m for project	Feb-24
KR	Handok Inc	SE	Swedish Orphan Biovitrum AB	Joint venture for rare disease business in South Korea	Financial terms not disclosed	Feb-24
US	Aptar Digital Health	US	Biogen Inc	Digital technologies for neurological and rare diseases	Financial terms not disclosed	Feb-24
US	Saama Technologies Inc	US	Pfizer Inc	AI-based technologies to expedite clinical research	Expands existing agreement	Feb-24
US	Multiply Labs Inc	US	Thermo Fisher Scientific Inc	Automate cell expansion and separation in cell therapy manufacture	Expands existing agreement	Feb-24
US	DNAnexus Inc	DE	Lorenz Life Sciences Group	Enable collaborative validation of regulatory submissions	Real-time links between sponsors and regulators	Feb-24
SE	Orexo AB	SE	Swedish Orphan Biovitrum AB	New formulation for one of Sobi's biomolecules	Goal is to add new properties	Feb-24
US	Inhibrx Inc	FR	Sanofi SA	Acquisition of treatment for alpha-1 antitrypsin deficiency	Deal value is up to $2.2b	Jan-24
DE	ITM Isotope Technologies Munich SE	CA	Alpha-9 Oncology Inc	Support development of radiopharmaceutical for cancer	Supply radioisotope Lutetium-177	Jan-24
IE	ERS Genomics Ltd	FI	StemSight Oy	Rights to CRISPR/Cas9 technology for cell therapy	Therapies for corneal blindness	Jan-24
DE	CENTOGENE NV	FR	Institut Imagine	Rare disease research collaboration	Validate novel genetic targets	Jan-24
UK	Science Card Ltd	UK	University College London	Support research into neurodegenerative diseases	UCL's Department of Mechanical Engineering	Jan-24
US	Vivtex Corp	JP	Astellas Pharma Inc	Expedite development of orally available biologic drugs	Foundational technology from MIT	Jan-24
UK	CN Bio Innovations Ltd	US	Altis Biosystems Inc	Develop human gut-liver *in vitro* model for ADME studies	Use organ-on-a-chip technology	Jan-24
IN	Serum Institute of India Pvt	NO	CEPI	Expand manufacturing network for future vaccines	Investment of $30m	Jan-24
US	Houston Methodist Research Institute	NO	CEPI	Develop new circular RNA vaccines	Funding of $3.8m	Jan-24
US	Microsoft Corp	KR	Seegene Inc	Apply digital technologies to molecular diagnostics	Financial terms not disclosed	Jan-24

(F) front-end fee (M) milestone payments (A) research funding (L) licensing fees (R) royalties on net sales (E) equity investment, CEPI=Coalition for Epidemic Preparedness Innovations

A personal perspective: Sean Morgan-Jones

New opportunities awaited travellers to San Francisco

The well-known Scottish poet and novelist Robert Louis Stevenson is often cited for the expression: 'to travel hopefully is a better thing than to arrive.' This has been widely interpreted to mean that life is a journey that should be continuously enjoyed. All well and good. But in the world of business there are always intervals when the travel stops and deals have to be done. This is how I would describe the dynamic of the annual JP Morgan Healthcare Conference in San Francisco, California. It is sometimes more rewarding to travel. This year, it was just as good to arrive.

In saying this, I am taking a three-year perspective. Going back to 2022, the US Nasdaq market was still covered in permafrost at JP Morgan and showing no signs of a thaw. Pfizer was allegedly poised for great things on the back of a sizeable war chest built up during the pandemic. But very little was disclosed in the way of M&A at that time. In 2023, the *Inflation Reduction Act* loomed large with concerns over how the legislation would affect spending on research and development. The uncertainty surrounding the use of artificial intelligence in drug development was a constant theme.

By early 2024, the zeitgeist had started to change. Nasdaq was still frozen but corporate shake-ups were underway leading to changes in the strategies of many companies. Albert Bourla, Pfizer's chief executive, announced a cost-cutting exercise of up to $4 billion following the drop-off in Covid-related product sales. He talked about a challenging year ahead. Yet just weeks before the meeting, Pfizer completed the takeover of Seagen Inc, a global leader in the development of antibody-drug conjugates (ADC) for cancer. The deal value was valued at $43 billion.

Merger and acquisition deals weren't as large as in previous years, but they were still being executed this year. Bristol Myers Squibb Co took over the neuroscience company Karuna Therapeutics and Novartis acquired Calypso Biotech BV, a spin out of Merck KGaA which is developing antibody therapeutics for a range of chronic autoimmune diseases. Merck & Co Inc bought Harpoon Therapeutics to develop T cell engager compounds for cancer, and GSK Plc bought Aiolos Bio to get a respiratory product in-licensed from China. Not to be overtaken by Pfizer, Johnson & Johnson Inc announced an agreement to acquire Ambrx Biopharma Inc, a developer of ADCs.

What are the omens for 2024? Executive search, which is my profession, is a useful lagging indicator of sentiment because of the lead time involved in identifying candidates for jobs and securing senior executive positions. With typical lead times of three to four months, organisations giving mandates to search firms were looking to land hires in the second quarter or early in the third quarter of this year. This level of engagement suggests that the outlook for the second half of the year is more positive than 12 months earlier.

Furthermore, the underlying macroeconomic outlook is improving with inflation easing on both sides of the Atlantic and growth accelerating in the US. Figures released by the US Department of Commerce in late January showed that real gross domestic product increased by 2.5% in 2023. This exceeded predictions by Wall Street of a 2% increase. In 2022 GDP growth was 1.9%. It is still uncertain how this economic data will feed into interest rates. But assuming a gradual rate decline, this would reduce the cost of capital. Right now, wary investors are sitting on mountains of their clients' cash. This needs to be deployed. And with patents expiring on many top selling medicines, the 12 largest companies are waiting to spend an estimated $180 billion to buy new products and/or take over the companies that are developing them.

At Biotech Showcase, a parallel event to the main JP Morgan event, I moderated sessions at which many entrepreneurial chief executives displayed their wares. It was enlightening to see the quality of the science emerging from the new technologies and from different geographies. The UK had a particularly strong cohort of young companies this year.

IPO activity picks up

Now, four weeks after the end of the conference, market activity has picked up. As I write this commentary, there have been five IPOs since the start of the year. All but one raised, or was hoping to raise, over $100 million. The first was CG Oncology Inc, a late clinical stage biopharma company, which is developing a bladder-sparing therapy for patients with bladder cancer. Proceeds from the offering were $437 million.

The second IPO came from ArriVent BioPharma Inc, a developer of oncology drugs with a special focus on ADCs. Proceeds from the offering were expected to be $175 million. The third offering, from Alto Neuroscience Inc, was expected to raise $128.6 million for diagnostics and treatments for neurological diseases. The target diseases include depression, post-traumatic stress disorder and schizophrenia.

The genetic medicines company Metagenomi Inc was expected to raise $86.9 million from an IPO to support its gene editing platform. Still in the advanced therapy arena, Kyverna Therapeutics Inc announced proceeds of $366.9 million from an IPO for an autologous chimeric antigen receptor (CAR) T cell therapy for B cell driven autoimmune diseases. If successful, Kyverna would be one of the first companies to advance a CAR T therapy into an indication other than cancer.

Looking ahead, all the available evidence points to more merger and acquisition activity and potentially more IPOs. It was indeed as good to arrive in San Francisco this year as it was to take the actual trip.

This article was written by Sean Morgan-Jones, chief commercial officer at Morgan Prestwich, life sciences executive search.

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Research Strategy: Jean-Claude Muller

The challenge of treating hearing loss as people age

Hearing loss, a health issue affecting around one billion people, has been ranked as the third highest cause of disability worldwide and the main modifiable risk factor for cognitive decline and dementia. Its prevalence is greater than that for cancer or diabetes. According to the World Health Organization (WHO) publication *World Report on Hearing*, issued in 2022, the incidence of hearing loss is surging and by 2050 nearly 2.5 billion individuals will experience varying degrees of deficiency during their lives, of whom 700 million will require care.

The primary drivers of this health crisis are an ageing population, noise-induced damage to the ears, the intake of ototoxic medications, and an increase of chronic diseases. To those affected, deafness can lead to social isolation, a deterioration in the quality of life, reduced work productivity, and higher rates of depression. Then there is the ongoing problem of being able to communicate in private and professional settings.

Hearing loss is not just a decrease in the perception of sound. It is also a loss of the ability to distinguish different types of speech. This involves a complex mix of health problems, including almost unbearable fatigue. The WHO estimates that the economic and social burden of hearing loss for entire communities represents a global cost of more than $980 billion annually.

Scientists have identified multiple hearing impairments that may require treatment. Some of these deficiencies are described below:

Otology, the branch of medicine which studies the anatomy and physiology of the ear, covers four types of impairments. Auditory processing disorders occur when the brain does not properly process information contained in a sound. Conductive hearing loss affects the ear's ability to conduct sound through the outer ear to the cochlea. Sensorineural hearing loss occurs when the cochlea or the auditory nerves are damaged. Mixed hearing loss describes the appearance of several of these disorders. Hearing loss can be bilateral or single-sided.

Otitis media is a suppurative or nonsuppurative ear condition characterised by inflammation of the inner ear. It results in a disruption of sound vibrations through the middle ear. Chronic suppurative otitis media commonly follows acute otitis media and may be associated with life-threatening complications. It is a major cause of conductive hearing loss, with soft sound being impaired and loud sound muffled.

Tinnitus, a condition which affects about 15 to 20% of the population, is the perception of ringing in one or both ears when no external sound is present. Although the pathophysiology of tinnitus is not clearly understood, both cochlear and central ear causes are described.

Hyperacusis is a hearing disorder that makes it hard to deal with everyday sounds. This hypersensitivity to sound is caused by changes in the way the brain processes sound and is usually centered on certain frequencies.

Vertigo is a condition with several causes. The most frequent is benign paroxysmal positional vertigo (BPPV) which occurs within the vestibule of the ear and causes tiny auditory crystals to move out of place and send false signals to the brain.

Ménière's disease, which mostly affects one ear and usually starts between youth and middle-age, appears to be linked to an abnormal amount of fluid in the inner ear.

Inner ear infections can also lead to moderate to severe vertigo and hearing loss side effects due to delayed treatment.

Cisplatin-induced hearing loss (CIHL) has a high prevalence, ranging from 20% to 80% of children treated with chemotherapy. The degree of cisplatin ototoxicity and hair cell loss is linked to high doses and multiple treatments of the chemotherapy. This can lead to the accumulation of platinum in the cochlea which was described in a study by Andrew Breglio and colleagues, published in *Nature Communications* in 2017. More than 200 marketed drugs are understood to elicit ototoxic side effects.

Cochlear synaptopathy, first described in 2009 by Kujawa and Liberman[1], is a clinical condition where patients have difficulty understanding speech in a noisy environment. This is despite the fact that they have normal hearing thresholds. The underlying cause is a deafferentation of auditory fibres to inner hair cells, altering the transmission of signals to the brain. Cochlear synaptopathy is involved in several pathologies of hearing impairment and is now considered to be an early sign of age-related diseases. The prevalence is even higher in patients with chronic diseases. As with other neurological disorders, cochlear synaptopathy is the result of a combination of neurocognitive and inflammatory disorders.

Tumours. Finally, in some rare cases, benign or malignant tumours can also induce significant hearing loss.

The most prevalent causes of hearing loss are excessive noise and ageing. Nevertheless, according to the WHO, 11 hearing loss syndromes have been identified with a monogenetic cause. These include Usher syndrome, Alport syndrome and Pendred syndrome. Currently more than 250 genes have been associated with syndromic and non-syndromic types of hearing loss. Analogic or digital hearing aids provide real benefit when the task is to amplify and deliver sound. But they are ineffective for many of the other hearing impairments. Similarly, cochlear implantation can address profound hearing loss, but it requires highly invasive surgery.

Recent progress in hearing biology

There is now a host of literature linking age-related hearing loss, also called presbycusis, to cognitive decline in the elderly. Until recently, hearing loss was not a priority of the biopharmaceutical industry, leaving companies that

Table 1

Name of Company	Country	Approach	Route of Administration
Acousia Therapeutics GmbH	Germany	Small molecules	TT
Akouos/Eli Lilly and Co	USA	Gene therapy	IC
Aposense Ltd	Israel	si-RNA	IC
Audiocure Pharma GmbH	Germany	Small molecules	TT
Audion Inc	USA	Small molecules	TT
Autigen Inc	USA	si-RNA	IC
Cilcare SAS	France	Small molecules	TT
Decibel Therapeutics/Regeneron Inc	USA	Gene therapy	IC
Dendrogenix SA	Belgium	Small molecules	NS
Heyu Pharma Ltd	USA and China	NS	NS
iN Therapeutics	Korea	Small molecules	TT
Oricula Therapeutics LLC	USA	Small molecules	Oral
Rinri Therapeutics Ltd	UK	Cell therapy	Graft
Sensorion SAS	France	Small molecules	Oral
Sensorion SAS	France	Gene therapy	IC
Spiral Therapeutics Inc	USA	Small molecules	TT
Sound Pharmaceuticals Inc	USA	Small molecules	Oral
Ting Therapeutics LLC	USA	Small molecules	NS

TT = Transtympanic, IC = Intracochlear, NS = not specified

provide prosthetic hearing aids to dominate the field. To date, the only novel drug to treat hearing loss is Pedmark (sodium thiosulfate), a prescription medicine from Fennec Pharmaceuticals Inc which was approved by the US Food and Drug Administration in 2022 to decrease the risk of hearing loss in children from one month and over who are receiving cisplatin to treat cancer.

However recent progress in understanding the root causes of the disorder and the discovery that a biological intervention might be effective in treating impairments linked to neurodegenerative conditions of the inner ear, have dramatically changed the landscape. This is illustrated by recent merger and acquisition activity in the industry. This activity includes Eli Lilly and Co's acquisition of Akouos Inc in 2022 for an upfront payment of $487 million. Akouos is developing gene therapies for inner ear conditions, including sensorineural hearing loss. This was followed by Regeneron Pharmaceuticals Inc's takeover of Decibel Therapeutics for an upfront payment of $109 million in August 2023. Decibel is also developing a gene therapy – in this case for a rare form of congenital hearing loss caused by mutations in the OTOF gene.

In late 2023, Jazz Pharmaceuticals Plc entered into a licensing agreement with Autifony Therapeutics Ltd to discover and develop drug candidates aimed at two different ion channel targets associated with neurological disorders. Autifony has a pre-clinical programme in schizophrenia and hearing loss. The value of the deal, including upfront and milestone payments, is $770.5 million. Besides Lilly, Regeneron and Jazz Pharmaceuticals, Astellas Pharma Inc and Boehringer Ingelheim GmbH have also become players in the hearing sector.

A recent report in the journal *Biomedicines*[2] listed as many as 40 ongoing gene therapy clinical trials in hearing loss. Besides Akouos and Decibel, these companies include Myrtelle Inc and Rescue Hearing Inc, which are developing gene therapies for hearing loss and Sensorion SA which is developing both small molecules and gene therapies. Among the exceptional clinical events was the disclosure by Lilly and Akouos in January of positive results from a Phase 1/2 trial of a gene therapy in an 11-year old patient who had been suffering from a profound hearing loss since birth. The therapy restored hearing in the patient within 30 days of administration. The treatment enabled the transfer of a functional copy of the OTOF gene and the expression of otoferlin protein to the inner hair cells of the cochlea. In addition to gene transfer therapies, gene editing programmes are also underway, but at an earlier stage.

In addition to Sensorion, there are at least 40 companies or academic institutions developing small molecule drugs for hearing loss, however these drugs are more difficult to deliver. Systemically administered drugs are often poorly taken up by the cochlea, which lies behind the blood-labyrinth barrier which protects the inner ear from toxic substances. Innovative delivery technologies are in development. Companies with clinical-stage products in this field are listed in Table 1.

Hearing loss and chronic diseases

Recent research suggests that peripheral and central auditory system dysfunction occur in the prodromal stage of Alzheimer's disease and may be an early valuable and underestimated indicator of the disease[3]. Hearing loss is also an important complication of diabetes. Patients with prediabetes have a 30% higher rate of hearing loss than normal subjects.

Although the causal relationship between diabetes and hearing loss is not fully understood, there seems to be increasing evidence that hearing loss is a comorbidity factor of diabetes mellitus, especially type 2 diabetes with insulin resistance. Recent studies are pinpointing systemic inflammation, cochlear microangiopathy and peripheral neuropathy as triggers of damage to the inner ear. They represent known biological targets. Cilcare SAS, a clinical-stage biotechnology company based in Montpellier, France, and Boston, US, has put forward the hypothesis that progressive hearing loss in type 2 diabetes may start with auditory peripheral neuropathy affecting 'speech-in-noise' intelligibility. The company notes that inadequate glycaemic control is likely to trigger early presbycusis.

Digital auditory signatures

In November 2023, the journal *Scientific Reports-Nature* published an article by Stéphane Maison et al[4] citing evidence that cochlear neural degeneration (CND) is linked to the appearance of tinnitus in human subjects. In their conclusion, the authors say that "developing diagnostic assays in CND is therefore key to identifying candidates for future therapeutics."

An increasing number of digital markers have become available in several diseases, and are already useful tools for early adopters in clinical settings. However, these new tools are not yet recognised by many health and regulatory authorities as markers for the identification of surrogate clinical endpoints.

Collaborations between academic and private institutions will be needed to further confirm the value of digital auditory markers. Non-invasive auditory signatures are expected to play a pivotal role in otology clinical settings and serve as functional biomarkers, just as the electrocardiogram (ECG) does for cardiovascular investigations.

People with cochlear synaptopathy do not have their hearing thresholds (41 to 68 dB) affected. Their symptoms, due to a neural-evoked output of the auditory nerve, cannot be evidenced by standard audiometry across the 0.125 to 8Hz frequency range and therefore remain a 'hidden' hearing deficit. Auditory profiling will become a necessary tool for detecting and assessing the intensity of cochlear synaptopathy in a given subject.

Damages to synapses between hair cells and auditory nerve fibres are a possible cause of poor auditory responses. Digital auditory profiling will progressively include measures like optoacoustic emissions (OAEs), a sound that is generated within the inner ear, auditory brainstem responses (ABRs), an electrophysiologic response to rapid auditory stimuli, and speech evoked responses. This is in addition to the standard 0.25-8Hz audiogram that could be extended in the high frequency range.

Hearing and vision loss

Traditionally, both sight and hearing disabilities have been treated with external physical devices. In the case of sight, these devices are optical rectifying glasses; in the case of hearing, they are amplifier hearing aids. In recent years however biological interventions have successfully tackled and treated ophthalmologic diseases. Beta blockers and prostaglandins have been used to treat glaucoma, and anti-angiogenic agents to treat both age-related macular degeneration and diabetic retinopathy. Based on the results in ophthalmology, biological interventions might be applied for the targeted treatment of hearing loss from neurological origins. In both cases local administration of the treatment would be feasible, allowing for a high concentration of the drug at the point of injection.

As with other neurodegenerative induced diseases, combining auditory profiling with imaging techniques like functional magnetic resonance imaging (MRI) or positron emission tomography (PET) will substantially increase knowledge of the dysfunction of the auditory system. Artificial intelligence algorithms are already being conceived to recognise subtle patterns associated with cochlear synaptopathy and will contribute to the emergency of novel, non-invasive useful auditory signatures for the diagnosis and prognosis of hearing loss.

Celia Belline, chief executive of Cilcare, told the recent JP Morgan healthcare conference in San Francisco, US, that "we are identifying highly specific auditory signatures (DAS) of auditory-related diseases selecting new targeted therapies to pave the way for new clinical developments. Combining DAS and innovative approaches in rehabilitation of functional circuits will restore high quality hearing comprehension in patients who long waited for a therapeutic solution."

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3. Swords, Gabriel M., et al, Auditory System Dysfunction in Alzheimer Disease and Its Prodromal States: A Review. *Ageing Research Reviews*, vol. 44, 2018, pp. 49–59.

4. Vasilkov, V. et al. Evidence of cochlear neural degeneration in normal-hearing subjects with tinnitus. *Sci Rep*. 2023 Nov 30;13(1):19870.

This article was prepared by Jean-Claude Muller, special advisor to several international institutions and previously senior vice president of research and development at Sanofi SA. He is a member of the *MedNous* Editorial Board.

US & European Regulatory Actions

Drug or Device	Comment	Sponsor	Action	Agency	Date
Xolair (omalizumab)	Immunoglobulin E-mediated food allergy	Roche	AP	FDA	Feb-24
Tagrisso (osimertinib)	In combination for EGFR-mutated advanced lung cancer	AstraZeneca Plc	NI	FDA	Feb-24
Amtagvi (lifileucel)	Unresectable or metastatic melanoma	Iovance Biotherapeutics Inc	AP	FDA	Feb-24
Aurlumyn (iloprost)	Injection to treat severe frostbite	Actelion Pharmaceuticals Ltd	AP	FDA	Feb-24
Edwards Evoque Tricuspid Valve Replacement System	Replace tricuspid valve of heart without open-heart surgery	Edwards Lifesciences LLC	AP	FDA	Feb-24
Onivyde regimen	First line treatment for metastatic pancreatic adenocarcinoma	Ipsen SA	NI	FDA	Feb-24
Eohilia (budesonide oral suspension)	Treatment of eosinophilic esophagitis	Takeda Pharmaceutical Co Ltd	AP	FDA	Feb-24
Genius Digital Diagnostics	Digital cytology system for detecting cervical cancer	Hologic Inc	AP	FDA	Feb-24
Vyvgart (efgartigimod alfa)	Generalised myasthenia gravis	argenx SE	AP	MHRA	Feb-24
Exblifep (cefepime/enmetazobactam)	Complicated urinary tract infections, hospital-acquired pneumonia	Advanz Pharma Ltd	PO	EMA	Jan-24
Ryzneuta (efbemalenograstim alfa)	Reduction in duration of neutropenia and incidence of febrile neutropenia	Evive Biotechnology Ireland Ltd	PO	EMA	Jan-24
Niapelf (paliperidone)	Generic treatment for schizophrenia	Neuraxpharm Pharmaceuticals SL	PO	EMA	Jan-24
Nezglyal (leriglitazone)	Refusal for treatment for cerebral adrenoleukodystrophy	Minoryx Therapeutics SL	NO	EMA	Jan-24
Syfovre (pegcetacoplan)	Refusal for geographic atrophy secondary to age-related macular degeneration	Apellis Pharmaceuticals Inc	NO	EMA	Jan-24
Abecma (idecabtagene vicleucel)	Multiple myeloma after two prior therapies	Bristol Myers Squibb Co	NI	EMA	Jan-24
Prevenar 20 (conjugate vaccine)	Prevent invasive disease from Streptococcus pneumoniae in children	Pfizer Inc	NI	EMA	Jan-24
Aspaveli (pegcetacoplan)	Monotherapy for paroxysmal nocturnal haemoglobinuria	Swedish Orphan Biovitrum AB	NI	EMA	Jan-24
Retsevmo (selpercatinib)	RET fusion-positive thyroid cancer	Eli Lilly and Co	NI	EMA	Jan-24
Translarna (ataluren)	Non-renewal for Duchenne muscular dystrophy	PTC Therapeutics Inc	NO	EMA	Jan-24
Pseudoephedrine (sympathomimetic drug)	Not to be used in patients with severe high blood pressure	Multiple companies	SU	EMA	Jan-24
Eylea (aflibercept)	Wet age-related macular degeneraton and diabetic macular oedema	Bayer AG	AP	MHRA	Jan-24
Balversa (erdafitinib)	Urothelial carcinoma with FGFR3 mutations	Johnson & Johnson Inc	NI	FDA	Jan-24
Dupixent (dupilumab)	Children with eosinophilic oesophagitis	Sanofi SA	NI	FDA	Jan-24
Yescarta (axicabtagene)	Manufacturing change for CAR T cell therapy	Kite (Gilead Sciences Inc)	NI	FDA	Jan-24

AP=approval (FDA), APL=appeal, CRL=complete response letter, LU=label update, NI=new indication, NO=negative opinion (EMA), PO=positive opinion (EMA), RE=recall, R=restriction, S=suspension, SL=suspension lifted, SR=safety review, SU=safety update, W*=warning, WD=withdrawal, MHRA=UK Medicines & Healthcare Products Regulatory Agency

African Medicines Agency

More financial support was announced in late January for the African Medicines Agency (AMA), a regulatory project that will see the 55 countries in the African Union have a dedicated healthcare institution to meet the needs of their combined populations of 1.3 billion people. A treaty formally establishing the agency has been ratified by 27 countries to date. All governments will need to get parliamentary approval of the treaty for the agency to take effect in their countries.

On 26 January, the European Medicines Agency announced receipt of a €10 million grant from the European Commission to support the development of the agency and its national counterparts. The agency is headquartered in Rwanda.

The EU's support is part of a broader partnership that includes the governments of Belgium, France and Germany and the Bill & Melinda Gates Foundation. Altogether the partnership is expected to mobilise more than €100 million over five years for the project.

With the Covid pandemic a recent experience, the project will put a priority on establishing manufacturing capacity on the continent for new medicines and vaccines. This was emphasised in a statement by Ibrahim Assane Mayaki, the head of the African Union Development Agency, who noted that "a health-secure continent can only be achieved if we can produce 60% of the total vaccine demand in Africa by 2040."

A key function of the new agency will be to harmonise regulatory procedures across the African Union so that medicine reviews, the monitoring of safety, and manufacturing practices reach uniformly high standards.

"It will be exciting to see AMA build its own regulatory model and practices to increase availability of safe and affordable medicines in Africa. EMA will support this journey by sharing our learnings and experiences gained working together as a network of thousands of experts from across Europe," said Emer Cooke, the EMA's executive director, in a prepared statement.

Priority review for RSV vaccine Arexvy

The US Food and Drug Administration is to give a priority review to Arexvy, a vaccine for the prevention of respiratory syncytial virus (RSV) disease, in the new indication for adults from the ages of 50 to 59 years. Developed by GSK Plc, the vaccine is currently approved for adults 60 years and above. If authorised, Arexvy would be the first vaccine to help protect the new age group against lower respiratory tract disease caused by RSV. Announcing the review on 6 February, GSK said its application is supported by positive results from a Phase 3 trial which evaluated the immune response and safety of the vaccine in the 50 to 59 year age group, including those with underlying medical conditions. A decision on the application is expected on 7 June.

GSK's competitors in the RSV field include Pfizer Inc, and Sanofi SA and AstraZeneca Plc.

New drug for EoE

The US Food and Drug Administration has approved a new drug for the treatment of eosinophilic oesophagitis (EoE), a chronic, immune-mediated inflammatory disease that can cause difficulty swallowing and affect individuals of any age. The drug, Eohilia, is an oral suspension of budesonide which was developed by Takeda Pharmaceutical Co Ltd and shown to be effective in two trials of adult and paediatric patients. The drug was compared with a placebo and administered for a period of 12 weeks. The first study enrolled patients 11 to 56 years of age and the second, 11 to 42 years of age. In both trials, the patients were able to reduce esophageal inflammation and improve their ability to swallow.

Eohilia is the first and only authorised oral treatment for EoE. Until now the disease has been treated off-label with budesonide, or with proton pump inhibitors. Patients have also been advised to eliminate certain foods from their diet such as dairy, wheat and soy in order to help reduce swelling of the oesophagus.

Eohilia is a mucoadherent, topically active, oral viscous formulation of budesonide that works to treat the localised oesophageal inflammation caused by EoE. It is also based on a well known chemical entity. According to Drugsite Ltd, budesonide was first approved in 1997 by the FDA with the commercial name Pulmicort as an oral inhalation formulation for the treatment of asthma. It has also been authorised in delayed or extended-release oral formulations as Entocort ER for the treatment of Crohn's disease; Uceris for the treatment of ulcerative colitis; and Tarpeyo, to reduce the loss of kidney function in immunoglobulin A nephropathy.

Breakthrough designation for radiotherapy

An early clinical-stage radionuclide therapy for neuroendocrine tumours received a 'breakthrough therapy designation' from the US Food and Drug Administration on 12 February – the first targeted alpha therapy to do so. The therapy, AlphaMedix, is being developed by RadioMedix Inc of the US and Orano Med of France to treat patients with somatostatin receptor expressing gastroenteropancreatic neuroendocrine tumours. Neuroendocrine tumours mostly occur in the gastrointestinal tract and pancreas, but also can be found in other tissues such as the thymus. Radionuclide therapies are being developed by multiple pharmaceutical companies owing to their ability to emit ionising radiation within close proximity to their targets. Most neuroendocrine tumours strongly express somatostatin receptors.

The FDA designation is based on the results of a Phase 1 and ongoing Phase 2 trial of AlphaMedix which showed that the treatment was well tolerated with a response rate of 62.5% for the neuroendocrine patients who had never received a peptide receptor radionuclide therapy. The breakthrough designation is a scheme for drugs that are intended to treat a serious condition and may show benefits compared with those of a marketed therapy. Companies with products that receive this designation are eligible for extra regulatory guidance from the FDA.

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EMA reflects on 2023

The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended 77 products for approval during 2023, slightly fewer than in previous years. However, 39 of these products contained a new active ingredient, a number described by Steffen Thirstrup, the EMA's chief medical officer, as more in line with prior years. Dr Thirstrup was speaking at a press briefing held in January 2024 to launch the EMA's annual review, *Human medicines highlights 2023*.

The therapeutic category with the highest number of recommendations in 2023 was oncology, with 25 (32% of the total). New anticancer products representing significant therapeutic progress are shown in the table below.

Other therapeutic areas with significant numbers of products recommended for approval in 2023 were neurology, with 11, cardiovascular (six), and endocrinology, dermatology and haematology (five each). Among these therapeutic areas, stand-out products included: Reata Ireland Ltd's Skyclarys (omaveloxolone), indicated for the treatment of Friedreich's ataxia; and Bristol Myers Squibb Pharma EEIG's Camzyos (mavacamten), for the treatment of symptomatic obstructive hypertrophic cardiomyopathy.

In the haematology area, Dr Thirstrup also highlighted Vertex Pharmaceuticals (Ireland) Ltd's Casgevy (exagamglogene autotemcel), the first gene-editing product based on CRISPR-Cas9 technology to be approved for human use. Casgevy is a one-off treatment that was developed to treat two rare blood disorders: severe sickle cell disease and transfusion-dependent β-thalassaemia. Dr Thirstrup said it is a one-off treatment that significantly reduces the incidence of severe painful episodes in sickle cell disease and eliminates dependence on blood transfusions in β–thalassaemia.

In the area of respiratory disease, Dr Thirstrup referred to growing concern about infections caused by respiratory syncytial virus (RSV), which mainly affects neonates and the elderly: an estimated 250,000 elderly patients are hospitalised every year with RSV infection, of whom around 17,000 die, he said. In 2023 the CHMP recommended approval for two RSV vaccines: GlaxoSmithKline Biologicals SA's Arexvy and Pfizer Europe MA EEIG's Abrysvo. Both vaccines are indicated for the protection of older patients (over 60 years) against RSV infection; in addition, Abrysvo is indicated for the protection of newborn children via vaccination of the mother during pregnancy.

Also in the area of child health, two paediatric-use marketing authorisations (PUMAs) were endorsed during 2023. PUMAs were introduced by the Paediatric Regulation for medicines that are already authorised, no longer covered by a supplementary protection certificate or equivalent, and which are exclusively developed for use in children. The two products given the go-ahead in 2023 were Proveca Pharma Ltd's Aqumeldi (enalapril), for use in children and adolescents to treat heart failure, and Fennec Pharmaceuticals (EU) Ltd's Pedmarqsi (sodium thiosulfate), for the prevention of ototoxicity in patients aged under 18 years who are undergoing cisplatin treatment.

In collaboration with the World Health Organization, the EMA may approve products for use in low- to middle-income countries outside the EU under the Medicines for All procedure. In 2023, the CHMP recommended two products for neglected tropical diseases. The first of these was Merck Europe BV's Arpraziquantel, which is intended for the treatment of schistosomiasis in young children; worldwide, schistosomiasis is estimated to affect approximately 50 million children. The second product was Sanofi Winthrop Industrie's Fexinidazole Winthrop, which is used to treat human African trypanosomiasis (sleeping sickness). The product originally received a positive opinion for sleeping sickness caused by *Trypanosoma brucei gambiense* in 2018, and the CHMP's opinion extends the use to now include treatment of the more acute and lethal form of the disease caused by *Trypanosoma rhodesiense*.

Among the other highlights of 2023 referred to by Dr Thirstrup were the approval of eight biosimilars, bringing the total number of biosimilars currently approved to 97, and the approval of Hipra Human Health SL's Bimervax for the prevention of Covid-19 and as a booster in people who have previously received an mRNA Covid-19 vaccine. The existing approvals of three Covid-19 vaccines (BioNTech Manufacturing GmbH's Comirnaty, Moderna Biotech Spain SL's Spikevax and Novavax CZ as's Nuvaxovid) were updated to reflect inclusion of the Omicron XBB.1.5 variant.

During 2023 the CHMP adopted a negative opinion for three medicines: Amylyx Pharmaceuticals EMEA BV's Albrioza (sodium phenylbutyrate/ursodoxicoltaurine), for the treatment of amyotrophic lateral sclerosis; Merck Sharp & Dohme BV's Lagevrio (molnupiravir), for the treatment of Covid-19 in adults; and Ipsen Pharma's Sohonos (palovarotene) to treat fibrodysplasia ossificans progressiva, a rare genetic disease that affects the musculoskeletal system. In addition, important new safety advice was issued for a total of eight products. These included fluoroquinolone antibacterials, which continue to be misused. – *By Peter Charlish*

Product	MA holder	Indication
Columvi (glofitamab)	Roche Registration GmbH	Diffuse large B-cell lymphoma
Tepkinly (epcoritamab)	AbbVie Deutschland GmbH & Co KG	Diffuse large B-cell lymphoma
Elrexfio (elranatamab)	Pfizer Europe MA EEIG	Adults with relapsed or refractory multiple myeloma
Jaypirca (pirtobrutinib)	Eli Lilly Nederland BV	Relapsed or refractory mantle cell lymphoma
Krazati (adagrasib)	Mirati Therapeutics BV	Adults with advanced non-small cell lung cancer with a G12C mutation in the KRAS gene
Lytgobi (futibatinib)	Taiho Pharma Netherlands BV	Cholangiocarcinoma
Omjjara (momelotinib)	GlaxoSmithKline Trading Services Limited	Myelofibrosis
Talvey (talquetamab)	Janssen-Cilag International NV	Adults with relapsed or refractory multiple myeloma

Initiation of US & European Clinical Trials					
Name of drug or device	**Sponsor**	**Treatment**	**Phase**	**Comment**	**Date**
ELC-301 (cell therapy)	Elicera Therapeutics AB	CD20-positive B cell lymphoma	1/2	Patients who no longer respond to standard treatment	Feb-24
ACOU085 (small molecule)	Acousia Therapeutics GmbH	Reduce cisplatin-induced hearing loss	2a	Patients have been given chemotherapy for testicular cancer	Feb-24
RVU120 (kinase inhibitor)	Ryvu Therapeutics	Acute myeloid leukaemia and myelodysplastic syndromes	2	Being investigated as a monotherapy	Feb-24
OLX75016 (RNAi therapy)	Olix Pharmaceuticals Inc	Metabolic dysfunction linked to obesity	1	Reduces liver fat content and inflammation	Feb-24
EXS74539 (small molecule)	Exscientia Plc	Acute myeloid leukaemia	N/A	Observational study of LSD1 inhibitor	Feb-24
SonoCloud-9 (device)	Carthera SAS	Recurrent glioblastoma	Pivotal	Device temporarily opens blood brain barrier	Feb-24
Pelareorep and atezolizumab	Oncolytics Biotech Inc	Squamous cell carcinoma of anal canal	1/2	Early data showed 37.5% objective response rate	Feb-24
AX-158 (small molecule)	Artax Biopharma Inc	Treatment of psoriasis	2a	Targets Nck function to affect T cell receptor response	Feb-24
ONP-002 (small molecule)	Oragenics Inc	Mild traumatic brain injury	2	Powdered delivery into nasal cavity	Feb-24
VVD-130850 (small molecule)	Vividion Therapeutics Inc	Advanced solid and haematologic tumours	1	STAT3 inhibitor binding to an allosteric pocket	Feb-24
ZH9 (bacterial immunotherapy)	Prokarium Ltd	Non-muscle invasive bladder cancer	1/1b	Immunotherapy built with synthetic biology	Feb-24
AMX0035 (two small molecules)	Amylyx Pharmaceuticals Inc	Treatment of Wolfram syndrome	2	Genetic disease leading to neurodegeneration	Feb-24
TAK-861 (small molecule)	Takeda Pharmaceutical Co	Treatment for narcolepsy type 1	3	Oral orexin receptor 2 agonist	Feb-24
NVG-2089 (biologic)	Nuvig Therapeutics Inc	Inflammatory myopathies and dermatologic autoimmune disease	1	Targets type II Fc receptors	Feb-24
SION-109 (small molecule)	Sionna Therapeutics Inc	Treatment for cystic fibrosis	1	Normalise function of the CFTR protein	Jan-24
OBT076 (antibody-drug conjugate)	Oxford BioTherapeutics Plc	Adenoid cystic carcinoma of head and neck	1b	Targets CD205 receptor on tumour cells	Jan-24
EVO756 (small molecule)	Evommune Inc	Chronic spontaneous urticaria	1	Antagonist of G-protein coupled receptor X2	Jan-24
BNT323/DB-1303 (antibody-drug conjugate)	BioNTech and Duality Bio	HR+ and HER2-low metastatic breast cancer	3	ADC to be compared with single-agent chemotherapy	Jan-24
EC5026 (small molecule)	EicOsis Human Health Inc	Treat pain and inflammation	1b	Non-opioid approach for treating severe pain	Jan-24
R-2487 (synthetic biology-based therapy)	Rise Therapeutics LLC	Rheumatoid arthritis	1	Resets regulatory T cell deficiencies to reduce cytokines	Jan-24
JAG201 (gene therapy)	Jaguar Gene Therapy LLC	Autism spectrum disorder and Phelan-McDermid syndrome	1	Deliver functional SHANK3 gene into the CNS	Jan-24
UVAX-1107 and UVAX-1197 (vaccines)	Uvax Bio LLC	Candidate vaccines for HIV-1	1	Developer is spin-off from Scripps Research Institute	Jan-24

Clinical Trials: a round-up of recent advances and setbacks

US-based **Gilead Sciences Inc** is to discontinue studies of magrolimab, a monoclonal antibody targeting CD47 on cancer cells, following evidence that the risks associated with the drug outweigh the benefits. On 7 February the company said it was stopping a clinical programme in haematologic cancers. On 15 February it announced a partial clinical hold on four Phase 2 studies in solid tumours at the request of the US Food and Drug Administration. Magrolimab is an investigational antibody that was being tested in patients with myelodysplastic syndromes and acute myeloid leukaemia (AML) as well as several solid tumours. Top-line data from the Phase 3 ENHANCE-3 trial in AML showed that magrolimab versus placebo in combination with the chemotherapy azacitidine plus the small molecule venetoclax, showed futility and an increased risk of death, primarily driven by infections and respiratory failure. The patients who were administered magrolimab for AML had not received any other treatments for their cancer and were ineligible for intensive chemotherapy. "The complexity of treating blood cancer is highlighted in these results," said Merdad Parsey, Gilead's chief medical officer, in a prepared statement.

A combination of Opdivo (nivolumab) and Yervoy (ipilimumab) has been effective in reducing the risk of disease progression in patients with metastatic colorectal cancer – the first dual immunotherapy regime to show significant benefits as a first-line treatment, according to **US**-based **Bristol Myers Squibb Co**. BMS, which developed both drugs, announced the results of the Phase 3 CheckMate-8HW trial on 20 January. In the trial, 830 patients with microsatellite instability-high (MSI-H) or mismatch repair deficit (dMMR) colorectal cancer were randomised to receive Opdivo plus Yervoy compared with Opdivo alone or the trial investigator's choice of chemotherapy with or without the marketed cancer drugs Avastin or Erbitux. The trial showed that the Opdivo/Yervoy combination reduced the risk of disease progression or death by 79% compared with chemotherapy. The improvements in progression free survival, the primary endpoint, started at approximately three months and continued until the trial read-out. Opdivo and Yervoy are both checkpoint inhibitors which block specific protein interactions enabling T cells to be freed to kill cancer cells. Both drugs were first approved to treat melanoma, respectively in 2014 and 2011. Their investigation in colorectal cancer is being guided by DNA mismatch repair protein deficiencies, a biomarker of the disease. "These results demonstrate the meaningful efficacy of this combination with practice-changing potential for this patient population," said Thierry Andre of Sorbonne University and Hospital Saint-Antoine, France, in a prepared statement.

A small molecule drug developed by **US**-based **Vertex Pharmaceuticals Inc** has shown statistically significant results in a Phase 3 programme in patients with moderate-to-severe acute pain. The drug, VX-548, is an inhibitor of the NaV1.8 voltage-gated sodium channel. Voltage-gated sodium channels are the basic ion channels for neuronal excitability. The Phase 3 programme consisted of two randomised controlled trials where patients received VX-548 after abdominoplasty surgery and bunionectomy surgery as well as a single-arm study of patients with a broad range of surgical and non-surgical pain conditions. Treatment with VX-548 following the two surgical procedures resulted in an improvement in a pain intensity measure compared with a placebo as well as a reduction in pain on a pain rating scale. On a secondary endpoint, VX-548 had a more rapid onset to meaningful pain relief than the placebo in the two randomised trials. Vertex's chief executive, Reshma Kewalramani, said the drug's benefit-risk profile positions it to "potentially fill the gap between medicines with good tolerability but limited efficacy and opioid medicines with therapeutic efficacy but known risks, including addictive potential."

Novartis reported positive results on 19 January from a Phase 3 trial of its radioligand therapy Lutathera in patients with advanced gastroenteropancreatic neuroendocrine tumours (GEP-NETs), the first trial to demonstrate Lutathera's potential as a first-line treatment for the disease. GEP-NETs are tumours occurring along the gastrointestinal tract. The trial showed that Lutathera, plus long-acting release octreotide, extended median progression free survival to 22.8 months compared with 8.5 months for octreotide. Octreotide is an octapeptide that mimics natural somatostatin. "These positive results for Lutathera are practice-changing and offer new first-line treatment data for patients who have a significant unmet need," said Simron Singh, associate professor of medicine at the University of Toronto, Canada.

MetrioPharm AG, a **Swiss** biotech company, has reported positive results from a trial of its small molecule immune modulator in patients hospitalised with Covid-19. The Phase 2a study showed that the drug, MP1032, was effective when administered with a standard of care and delivered lower mortality compared with patients receiving a placebo and standard of care. According to the company, the results showed that MP1032 is comparable to remdesivir (Veklury), an approved antiviral, with additional safety benefits. The trial results were announced on 31 January and published in *The Lancet Regional Health – Europe*. "Most importantly, while most antiviral drugs target specific viruses, MP1032 acts as a host-directed therapy," said Wolfgang Brysch, the companies co-founder and chief scientific officer, in a prepared statement. This means it can potentially treat emerging and even completely novel viruses, without prior application, which is essential for pandemic preparedness, he added. In addition to being tested in Covid-19, MP1032 is being studied in four inflammatory diseases and in the rare diseases Duchenne muscular dystrophy (DMD) and juvenile idiopathic arthritis.

European Biotech Financings

	Recipient	Type of Finance	Use of Proceeds	Comment	Date
US	Vektor Medical Inc	$16 mln Series A financing	Non-invasive analysis of arrhythmias	Co-led by TVM Capital Life Science	Feb-24
DE	Earlybird Health	€173 mln for new investment fund	European companies across pharma and devices	British Patient Capital is investor	Feb-24
CH	Vandria SA	€3.8 mln in grant funding	Mitophagy inducers for age-related diseases	Innosuisse and Eurostars	Feb-24
UK	Silence Therapeutics Plc	$120 mln from private share placement	Support siRNA therapy for polycythemia vera	Investors include 5AM Ventures	Feb-24
US	Lineage Cell Therapeutics Inc	$14 mln from registered direct offering	Support development of cell therapies	Broadwood Partners LP is investor	Feb-24
US	Alto Neuroscience Inc	$128.6 mln expected from Nasdaq IPO	Treatments for neurological disorders	Jefferies is book-runner	Feb-24
US	Metagenomi Inc	$93.7 mln expected from Nasdaq IPO	Advance gene editing platform	JP Morgan is book-runner	Feb-24
US	Kyverna Therapeutics Inc	$366.9 mln from Nasdaq IPO	Cell therapies for autoimmune diseases	JP Morgan is book-runner	Feb-24
FR	Vivet Therapeutics SAS	€4.9 mln from the French government	Gene therapy for cerebrotendinous xanthomatosis	France Health Innovation Plan	Feb-24
UK	NeoPhore Ltd	£9.6 mln Series B extension bringing total to £31.1 mln	Cancer drugs targeting DNA mismatch repair pathway	Syndicate includes Claris Ventures	Feb-24
US	Scion Life Sciences	$310 mln in start-up capital for new venture fund	Finance creation of new biotech companies	Investors are Samuel Hall, Aaron Kantoff	Feb-24
CH	Stalicia SA	$17.4 mln in Series B financing	Portfolio of medicines for neurological disorders	Led by SPRIM Global Investments Pte	Jan-24
NL	Intravacc BV	$633,000 in grant funding	Vaccine against *Neisseria gonorrhoeae*	Award from CARB-X	Jan-24
BE	PDC*line Pharma SA	€8.1 mln in grant funding	Therapeutic vaccine for colorectal cancer	Walloon region of Belgium	Jan-24
UK	Sky Engine AI	$7 mln to develop synthetic data cloud platform	Applications in robotics, medical diagnostics	Led by Cogito Capital Partners	Jan-24
UK	ProteinLogic Ltd	$1.3 mln in grant funding	Blood test to monitor response to TB antimicrobial chemotherapy	Bill & Melinda Gates Foundation	Jan-24
SE	Medivir AB	SEK 20 mln ($1.91 mln) from directed share issue	Support development of prodrug for liver cancer	Hallberg Management AB is investor	Jan-24
NO	Calluna Pharma AS	€75 mln in Series A financing	Antibody therapies for inflammatory, fibrotic diseases	Led by Forbion, with Norwegian funds	Jan-24
UK	IMU Biosciences Ltd	£11.5 mln in Series A funding	Build an immune atlas spanning human health and disease	Led by Molten Ventures	Jan-24
US	CG Oncology Inc	$437 mln from IPO on Nasdaq	Bladder-sparing therapy for patients with bladder cancer	Morgan Stanley is book-runner	Jan-24
US	ArriVent BioPharma Inc	$175 mln expected from IPO on Nasdaq	Develop antibody-drug conjugates	Goldman Sachs is book-runner	Jan-24
IL	RedHill Biopharma Inc	$8 mln from registered direct offering	Products for gastrointestinal and infectious diseases	HC Wainwright & Co is placement agent	Jan-24
JP	Renalys Pharma Inc	New company launch with venture finance	Medicines for treating renal disease in Japan	Catalys Pacific, SR One are investors	Jan-24
BE	Protealis NV	€22 mln Series B financing round	Use AI, genetic fingerprinting in plant production	V-Bio Ventures, VIB are investors	Jan-24
UK	Enterprise Therapeutics Ltd	£26 mln Series B follow-on financing	Support Phase 2a study in cystic fibrosis	Led by new investor Panakes	Jan-24
DK	Vesper Bio ApS	$873,000 in grant funding	Assess sortilin inhibition in Parkinson's disease	Michael J Fox Foundation	Jan-24
US	Accent Therapeutics Inc	$75 mln in Series C financing	Support DHX9 inhibitor for cancer	Mirae Asset Capital Life Science	Jan-24
FR	Fabentech SA	€7.7 mln in grant funding	Consortium to develop therapy against new viruses	European Commission is funder	Jan-24

Source: Company announcements

IMU secures Series A funding

IMU Biosciences Ltd, a two-year old UK company, has raised £11.5 million from private investors to create a map of the human immune system using artificial intelligence. The goal is to be able to monitor the presence of immune disorders early and guide the development of targeted drugs, also known as precision medicines. The Series A financing was announced on 24 January and led by Moulton Ventures Plc. It also included LifeX Ventures and several individuals.

The IMU platform is based on a database of immune cell samples from healthy donors, biobanks and research projects. This can be used for immunophenotyping for cancer, enabling patients to be matched with a therapy most likely to be effective. Or it can be used in the manufacture of cell therapies to identify the immune signatures in cell donors, according to the company.

IMU Biosciences was founded in 2021 by Adam Laing, Tom Hayday and Mario Cantero on the back of research conducted by Adrian Hayday at King's College London, UK. Dr Laing is the company's chief executive, Dr Hayday, the chief scientific offer, and Mr Cantero, the chief operating officer. Professor Hayday is known for his contribution to the identification of gamma delta T cells and their application to immunotherapy. "With our technology, we're building the world's largest immune data assets across health and disease which allows us to perform analyses with a level of depth and granularity that was previously unthinkable," Dr Laing said.

Series A for Calluna Pharma

A group of European venture funds led by Forbion of the Netherlands has raised €75 million in Series A financing to support the launch of a new biotech company based in Oslo, Norway. Calluna Pharma AS will develop antibody therapeutics for the treatment of inflammatory and fibrotic diseases. It has been created from a merger of Oxitope Pharma BV of the Netherlands and Arxx Therapeutics AS of Norway. Besides Forbion, the financing syndicate includes the Norwegian funds Sarsia Management, p53 Invest AS and Investinor AS. The venture finance was announced on 23 January.

The company has a pipeline of four potential products, of which one is in clinical development for a series of fibrotic and inflammatory diseases. The approach is to engage the innate immune system, the body's first line of defence against infection, enabling the disruption of downstream signalling pathways. The lead programme CAL101 is an antibody that neutralises the activity of a damage associated molecular pattern (DAMP) protein that has been implicated in several diseases including idiopathic pulmonary fibrosis, and chronic kidney disease, systemic sclerosis, rheumatoid arthritis and asthma. CAL101 is currently in Phase 1. Next in the queue is CAL102, a preclinical programme that is being developed to treat myocardial infarction induced by reperfusion injury. This antibody is designed to neutralise oxidised phospholipids in the myocardium.

New research on long Covid

Changes in our blood proteins caused by our body's own immune defences are the likely cause of long Covid, according to new research.

Long Covid is a life-changing condition that around one in 20 people with Covid-19 go on to develop. Symptoms include chronic fatigue, breathlessness, 'brain fog', anxiety and stress, leading to significant impact on daily life. 41% of long Covid patients report serious health issues lasting at least two years. Currently there are no diagnostic tests and few therapeutic solutions for long Covid.

Scientists from the UK, Switzerland, the US, and Sweden followed 113 Covid-19 patients and 39 healthy controls for up to one year after initial confirmation of acute SARS-CoV-2 infection to identify biomarkers associated with long Covid.

After six months, 40 patients had long Covid symptoms. Repeated clinical assessments were paired with blood draws, resulting in a total of 268 longitudinal blood samples. The team measured more than 6,500 proteins in serum by proteomics. Top candidate biomarkers were identified using computational tools and further evaluated experimentally.

The team found that those with long Covid exhibited changes to their blood serum proteins, which abnormally activated their 'complement system'. This is a major part of the body's immune defences that normally helps to clear infections and clean up damaged cells.

Long Covid patients showed imbalanced terminal complement complex (TCC) formation, marked by increased soluble C5bC6 complexes and decreased levels of C7-containing TCC formations that can incorporate into cell membranes. This suggested increased membrane insertion of TCCs in long Covid patients, contributing to tissue damage. Accordingly, long Covid patients showed elevated tissue injury markers in blood and a thromboinflammatory signature, characterised by markers of endothelial activation, such as von Willebrand factor (vWF), and red blood cell lysis.

Long Covid patients also had elevated platelet activation markers and monocyte–platelet aggregates at six-month follow-up, particularly in cases where long Covid persisted for 12 months or more.

The team added that their findings suggest that complement activation may be driven by antigen–antibody complexes, involving autoantibodies and antibodies against herpesviruses, as well as cross-talk with a dysregulated coagulation system.

It is hoped that a simple blood test could now be developed to identify people with long Covid, and the findings will also provide support for clinical research on complement modulators for patients suffering from long Covid. The research was published in *Science* on 19 January 2024.
– *Rosie Bannister*

Blood test for Alzheimer's

Detecting Alzheimer's disease using a blood test could be as accurate as a lumbar puncture, a new study has found.

The blood test detects p-tau217, a form of the protein tau. This is a hallmark protein of Alzheimer's disease, which causes a build-up of proteins in people's brains. Alzheimer's is generally diagnosed based on people's symptoms, such as thinking or memory problems. However, only 2% of people with a dementia diagnosis receive one through 'gold standard' methods, such as PET scans or lumbar punctures.

In this study, scientists found that levels of p-tau217 in the blood reflected the levels of amyloid and tau proteins seen in brain scans and lumbar punctures. They looked at 786 participants with an average age of 66.3 years, across three observational cohorts: the Translational Biomarkers in Aging and Dementia (TRIAD), Wisconsin Registry for Alzheimer's Prevention (WRAP), and Sant Pau Initiative on Neurodegeneration (SPIN).

Dr Sheona Scales, director of research at Alzheimer's Research UK, said: "...as we see more and more different types of tests becoming available, studies like this are key to understanding which are most accurate". The researchers say that the wider availability of high-performing assays may expedite the use of blood bio-markers in clinical settings, though blood tests would need to go through regulatory approvals before they can be used. The findings were published in *JAMA Neurology* on 22 January 2024.

Amyotrophic lateral sclerosis study

A new possible treatment for amyotrophic lateral sclerosis (ALS) stops the loss of motor neurons and mitigates disease progression in a mouse model.

Researchers from Heidelberg University showed that treatment with FundaMental Pharma GmbH's TwinF interface inhibitor, FP802, resulted in reduced neurological scores and mortality in a gold standard mouse model of ALS. The ALS clinical biomarker neurofilament light chain (Nf-L) was reduced in line with the positive treatment effects.

The team went further to demonstrate that FP802 also protected human ALS patient-derived brain organoids from glutamate neurotoxicity, a key driver of ALS pathogenesis, highlighting the likely translatability of the preclinical findings to patients.

ALS is the most common adult-onset human motor neuron disease, affecting both upper motor neurons in the cerebral cortex and lower motor neurons in the brain stem and spinal cord. It is untreatable, progressing rapidly and ultimately causes death by respiratory failure.

TwinF interface inhibitors constitute an entirely new class of drugs that safely ameliorate glutamate neurotoxicity, a common cause of neurodegeneration. Professor Hilmar Bading, co-founder of FundaMental Pharma, said: "The success of FP802 in protecting brain organoids derived from human ALS patients underscores the translatability of our preclinical findings, offering a glimpse into the potential impact of TwinF interface inhibitors on patients." The study was published in *Cell Reports Medicine* on 6 February 2024.

Commentary: How a lung delivery issue unlocked RNA

Since the discovery of messenger RNA (mRNA) in the early 1960s, researchers have consistently explored its potential, paving the way for future breakthroughs. In the 1970s, investigations about delivering mRNA into cells began, with the first successful use of *in vitro* transcribed mRNA in animals reported two decades later. Despite the progress made since those early days to overcome obstacles and refine techniques, challenges still demand our attention for further breakthroughs in mRNA delivery. Overcoming these challenges will be pivotal in unlocking the full potential of mRNA-based therapies.

Reflecting on my early days in RNA medicine, I am struck by the unexpected and far-reaching implications of my quest to conquer a singular challenge: delivering RNA to the lungs. What began as a focused endeavour to develop a therapeutic for cystic fibrosis would eventually lead me to abandon my aspirations to become a professor and instead become a biotech founder. My decision became apparent when I realised that success would require inventing several technologies. As it turned out, these advances would have far-reaching applications beyond the initial goal. Our journey at Ethris underscores a fundamental truth about scientific inquiry: the pursuit of answers to specific questions often leads us to discoveries that have broad applications.

While leading a working group at the Dr von Hauner Children's Hospital in the early 2000s, I focused on delivering plasmid DNA to the lungs to advance DNA-based therapies for cystic fibrosis. A big problem in using plasmid DNA is the difficulty of delivering it into the nucleus, particularly when targeting cells in the post-mitotic lung tissue where the nuclear membrane breakdown poses a limitation. I then had the idea to try mRNA. In those days, we already understood that our delivery systems and nanoparticles effectively transported mRNA into the cytoplasm and could be directly translated at the ribosome to produce the missing protein. mRNA was a promising alternative to the challenges of DNA, but there was not much research on using mRNA as a therapeutic. Thus began my lab's efforts to discover new technology for mRNA delivery to the lungs.

Delivering RNA to the lungs is a task fraught with obstacles, from overcoming the body's natural defence mechanisms to the fragile nature of RNA molecules. The initial challenge was reducing the immunogenicity of mRNA. Standard mRNA was found to be immunogenic due to the detection system within the immune system – sensors designed to identify foreign RNA molecules and signal viral infection. This could cause some treatments to trigger excessive immune responses, potentially leading to unwanted inflammatory or immune reactions against the therapy. Effectively mitigating immunogenicity is crucial for ensuring the safety and effectiveness of inhaled mRNA medicines. We introduced modified nucleotides to resolve this, reducing the immune response towards the RNA molecule. Altering the pattern of the RNA molecule made it unrecognisable by the immune system, providing a way to exploit its therapeutic potential while mitigating immune responses.

Findings from our research and my ongoing collaboration with Professor Christian Plank, PhD - a specialist in carrier systems for nucleic acids who led a research group at the Technical University of Munich - revealed the significant therapeutic potential of mRNA. Recognising this promise, I embraced the opportunity to combine our research efforts, and Ethris was founded.

In the initial stages of research at Ethris, it became apparent that beyond immunogenicity, unlocking the full potential of mRNA would require addressing challenges, including storage as well as biodistribution and nebulisation.

The success of mRNA is incredibly dependent on stable supply chains and manufacturing capabilities. However, mRNA is highly sensitive to elevated temperatures, posing challenges during manufacturing, storage, and transportation. Additionally, nebulising lipid nanoparticles (LNPs) has been historically challenging because they tend to aggregate easily. Nebulising these formulations with a vibrating mesh nebuliser introduces stress, causing aggregation and prolonged inhalation times due to device clogging. In the protein field, aggregates are known to increase immunogenicity.

We are developing alternative storage and distribution methods that don't rely on deep freezing. We are investigating the potential of room-temperature storage to allow easier handling throughout the entire supply chain from wholesalers all the way to patients. We're now seeing positive results from a freeze-dried formulation with 15 months of stability at room temperature.

To resolve the nebulisation challenges of LNPs, we developed a stabilising excipient technology, an additive included in the LNP formulation to enhance stability, in combination with an optimised nebulisation technology to prevent aggregation during nebulisation. This ensures the maintenance of particle properties throughout the nebulisation process, addressing the issues associated with stress-induced aggregation. Now, aggregation is not a concern, even after vigorous shaking.

Our platform technologies not only enable the delivery of mRNA to the lungs but also have far-reaching applications to all RNA-based modalities, including vaccines. Today, by overcoming challenges in storage, biodistribution, nebulisation, and immunogenicity, Ethris is using this technology to deliver potent mRNA-based drug products, offering promising solutions for respiratory diseases and beyond. We recently entered the clinic with a therapy for prevention of severe disease following respiratory viral infections in patients at risk such as in asthma and have programmes in rare pulmonary diseases approaching the clinic, including a potential first-in-class treatment for primary ciliary dyskinesia (PCD), a debilitating autoimmune lung disease with high unmet needs, expected to enter the clinic this year.

This article was written by Carsten Rudolph, PhD, co-founder and CEO of Ethris GmbH in Munich, Germany.

European biopharma R&D in 2023

The amount of money a biotech company spends on research and development, relative to sales, every year is an important indicator of how it is positioning itself in the evolving world of science and the marketplace. This ratio can fluctuate depending on how many clinical trials a company undertook during the year, or how many new assets it added to its portfolio. The following article is a review of the R&D to sales ratio for 12 European companies based on information from their 2023 annual reports. The cohort is made up of publicly listed companies with significant projects underway. It includes three multinationals and nine medium-sized enterprises. Geographically, the majority of companies are located in the Nordic region.

The three multinational groups are Novartis of Switzerland and GSK Plc and AstraZeneca Plc of the UK. A big theme for the largest companies in 2023 was making the transition from portfolios that deliver a broad selection of healthcare products, to those that focus on proprietary medicines. In 2023, **Switzerland**-based **Novartis** spun out its Sandoz generics and biosimilars business in order to become a 'pure play' innovative medicines company. Novartis' R&D spend last year was $11.4 billion, or 25% of group sales of $45.4 billion. Vas Narasimhan, the Chief Executive, singled out four areas for product development and four product modalities. One of the therapy areas is neuroscience and one of the modalities is RNA-based therapeutics. This was illustrated by the company's 2023 acquisition of DTx Pharma Inc, a preclinical stage company focusing on siRNA therapies for neuroscience indications. The company's lead product targets the root cause of Charcot-Marie-Tooth Type 1A disease. Separately in February, Novartis announced plans to buy MorphoSys with whom it has had a long relationship in antibody therapy development.

In the **UK, GSK Plc** spent £6.223 billion on R&D which was 20.5% of sales. Group sales were £30.328 billion. GSK spun out its consumer division in July 2022 and since then, has been building its vaccine and respiratory portfolio. Oncology is also a therapeutic focus. Emma Walmsley, the chief executive, signalled during her press conference in late January that she wants to maintain the momentum generated by the company's vaccines against shingles and respiratory syncytial virus. The late-stage pipeline includes a vaccine for meningitis, a product for severe asthma, and a new antibiotic for patients with uncomplicated urinary tract infections.

UK-based **AstraZeneca Plc** spent $10.9 billion on R&D in 2023 or 23.9% of revenue, which was $45.8 billion. Some $7.76 billion of the revenue figure came from products for rare diseases, the result of AstraZeneca's acquisition of Alexion Pharmaceuticals Inc in 2021. By disease area, oncology is the main R&D focus with new modalities being continually tested. These include cell therapies, T cell engagers, and antibody-drug conjugates. Pascal Soriot, the chief executive, told journalists on 8 February that the company is developing its own ADC pipeline with six candidate ADCs already in the clinic.

Denmark-based **Novo Nordisk A/S** spent DKK 32.4 billion ($4.69 billion) on R&D in 2023, or 14% of sales of DKK 232.3 billion. R&D spending was higher than that of the previous four years reflecting late-stage clinical trial activity for obesity and diabetes drugs as well as research activities generated by the acquisition of Forma Therapeutics in 2022. Novo acquired a small molecule product for sickle cell disease with the takeover. Novo also took over Inversago Pharma in 2023 which has a pipeline of products to treat serious metabolic diseases with potential application for obesity.

Denmark-based **H. Lundbeck A/S** spent DKK 3.5 billion ($499.7 million) on R&D in 2023 which represented 17.4% of sales of DKK 19.9 billion. This was less than the ratio of 20.6% in 2022 when the company conducted late-stage trials for two drugs for major depressive disorder. The clinical focus in 2023 was on a drug for post-traumatic stress disorder. Lundbeck has identified four biological clusters that underpin its R&D strategy: targeting pathways of pain signalling and stress; targeting synaptic dysfunction; targeting neuronal loss due to an overactive immune system and targeting neurodegenerative proteinopathies such as Alzheimer's and Parkinson's diseases.

Denmark-based **Genmab A/S** spent DKK 7.6 billion ($1.1 billion) or 46% of revenue of DKK 16.47 billion on R&D in 2023. This ratio has been high for several years: in 2022 it was 38%; in 2021, 50%; and in 2020, 31%. Genmab has a portfolio of antibody-based therapeutics for cancer, two of which have been commercialised with partners. The partnership business model is continuing but with increasingly complex technologies. Under a partnership with BioNTech, Genmab is advancing a bispecific antibody targeting both the human programmed death-ligand 1 (PD-L1) and 4-1BB into late-stage development. The antibody is currently being studied in non-small cell lung cancer and advanced endometrial cancer. Genmab is also advancing an antibody-drug conjugate in the clinic for cervical cancer.

Finland-based **Orion Corp** spent €126.9 million ($137.02 million) on R&D in 2023 which was 10.7% of sales of €1.189 billion. Orion markets Nubeqa, a drug for prostate cancer which it co-developed with Bayer AG. Going forward the company has drugs for the treatment of insomnia and solid tumours in its pipeline.

Denmark-based **Novozymes A/S**, an industrial biotechnology company which operates across the agricultural, animal health and human health sectors, spent DKK 2.1 billion ($300 million) on R&D in 2023. This was 11.3% of revenue of DKK 17.9 billion. The company launched 18 new products across its large portfolio during the year, but the most significant event was its merger with Chr. Hansen Holding A/S. This is due to complete on 1 February. Chr Hansen is a producer of bacteria cultures, probiotics and enzymes. The combined company will trade under the name Novonesis. In 2023, Novozymes joined a project with the Novo Nordisk Foundation and the Bill & Melinda Gates Foundation to convert carbon dioxide into

protein for human consumption – an attempt to address the dual need amongst countries for food security and to prevent greenhouse gas emissions from agriculture.

Switzerland-based **Basilea Pharmaceutica Ltd**, which is developing treatments for bacterial and fungal infections, invested CHF 77.9 million ($88.39 million) in R&D in 2023. Group revenue for the year was CHF 157.6 million, giving an R&D ratio of 49.4%. Basilea invested heavily in new products including the recently acquired or in-licensed compounds fosmanogepix, BAL2062, and tonabacase. Fosmanogepix is a broad-spectrum antifungal with activity against *Candida auris* which is classified as a priority pathogen by the World Health Organization. BAL2062 is an antifungal derived from a natural product which has demonstrated activity against moulds such as *Aspergillus spp*, including azole-resistant strains. Tonabacase is an antibiotic which has been in-licensed for evaluation as a potential treatment for *Staphylococcus aureus*, including multi-drug resistant strains and those forming biofilms.

Ipsen SA, the **French** specialty pharma group, spent €619.3 million ($669.24 million) on R&D in 2023 which represented 19.8% of the group's sales of €3.13 billion. Ipsen's portfolio includes oncology and neuroscience products with a recent focus on rare diseases. In 2023 it acquired Albireo Pharma Inc, a developer of bile-acid modulators to treat paediatric and adult cholestatic liver diseases. The focus of the transaction was Bylvay, a bile acid transport inhibitor. In oncology, Ipsen received US Food and Drug Administration approval on 13 February for a new indication for Onivyde (irinotecan liposome injection) to treat metastatic pancreatic adenocarcinoma. It was approved as a first-line treatment for the disease.

Swedish Orphan Biovitrum AB (Sobi), the **Swedish** developer of medicines for rare diseases, spent SEK 2.8 billion ($270 million) on R&D in 2023. This represented 12.6% of group revenue of SEK 22.12 billion and covered investment in the company's haematology, immunology and specialty care portfolios. At the start of the year, Sobi received FDA approval for efanesoctocog alfa, a factor 8 therapy for haemophilia A. The treatment, known commercially as Altuviiio, provides patients with normal to near-normal factor 8 activity levels for a significant part of the week with once-weekly dosing. Sobi is now generating more clinical data on the treatment while awaiting a regulatory decision in the EU.

Bavarian Nordic A/S, the **Danish** vaccine developer, issued preliminary 2023 financial results on 21 February.

European Biotech Financings

	Company	R&D to Sales Ratio
CH	Novartis	25%
UK	GSK Plc	20.5%
UK	AstraZeneca Plc	23.9%
DK	Novo Nordisk A/S	14%
DK	H. Lundbeck A/S	17.4%
DK	Genmab A/S	46%
FI	Orion Corp	10.7%
DK	Novozymes A/S	11.3%
CH	Basilea Pharmaceutica Ltd	49.4%
FR	Ipsen SA	19.8%
SE	Swedish Orphan BioVitrum AB	12.6%
DK	Bavarian Nordic A/S	12%

Source: Company announcements

The full results will be published on 6 March. The unaudited data show a R&D spend of DKK 850 million ($123.13 million) for the year, representing 12% of group revenue. Revenue for 2023 was DKK 7.1 billion. Since 2020 the company has been transitioning towards being a 'pure play' vaccine company. This plan has now been put into effect with the discontinuation of its only active immune-oncology project. Going forward, Bavarian Nordic will focus on travel vaccines and vaccines for potential public health emergencies. The company has increased its manufacturing capacity in order to be able to respond to surges in vaccine demand. – *By Victoria English*

AstraZeneca grows platforms

AstraZeneca Plc delivered a third consecutive year of revenue growth in 2023 as medicines across three of its therapy areas delivered a double-digit increase and the company launched new products. Speaking to journalists on 8 February, Pascal Soriot, the chief executive, predicted more growth in 2014 and at least 15 new product launches by 2030. "We are seeing growth across all geographies," he said, adding that this is being driven by new technologies.

Revenue was $45.8 billion in 2023, consisting of product sales of $43.7 billion and alliance and collaboration revenue of $2 billion. The total revenue figure was up by 3% in actual exchange rates, and by 6% at constant rates. Operating profit for the year was $8.2 billion, giving an operating margin of 17.9%. Using a 'core' measure that excludes impairments and amortisations, the operating profit was $14.5 billion, giving a margin of 31.7%.

Mr Soriot said the goal is to raise the core operating margin to the mid-30%s in the medium term. This would be propelled by product launches across the company's main therapy areas.

Oncology is the biggest segment, generating sales of $17 billion in 2023, up by 17%. This was followed by medicines for cardiovascular, renal and metabolic diseases at $10.6 billion, up by 15%; medicines for respiratory and immunology at $6 billion, up by 6% and rare diseases at $7.8 billion, up by 10%. Following a drop in Covid-related sales, vaccines and immune therapy turnover dropped by 79% to $1 billion.

AstraZeneca won three regulatory approvals for new drugs during the year, two of which were authorised in the US and the third in Japan. A new small molecule cancer drug, Truqap (capivasertib), was approved by the US Food and Drug Administration to treat hormone receptor positive breast cancer targeting the protein kinase AKT. In a Phase 3 trial combining Truqap with an endocrine therapy, the combination reduced the risk of disease progression or death by 50%. The other two approved products are Wainua (eplontersen), a treatment for transthyretin amyloidosis, authorised in the US, and Voydeya (danicopan), for paroxysmal nocturnal haemoglobinuria, authorised in Japan.

Four technology platforms are driving research and development. These are antibody-drug conjugates (ADCs), cell therapies, T-cell engagers, and gene therapy. "ADCs will replace chemotherapy in the future," Mr Soriot predicted.

After co-developing the breast cancer drug Enhertu with Daiichi Sankyo Co Ltd, AstraZeneca is now working on its own in-house ADC pipeline. Six candidate ADCs are in the clinic and the goal is to investigate these with immunotherapies, including checkpoint inhibitors in cancer, he said. Following the acquisition of Gracell Biotechnologies Inc in December, AstraZeneca is investigating CAR T cell therapies for autoimmune diseases as well as cancer.

And obesity? In November, AstraZeneca in-licensed an early clinical-stage compound for the treatment of obesity, diabetes and cardiometabolic diseases from Eccogene Co Ltd in China. Mr Soriot said the important obesity issue going forward is attaining weight loss that is sustainable.

GSK builds its pipeline

GSK Plc ended 2023 with a pipeline of 71 vaccines and specialty medicines in clinical development and a forecast for sales of more than £38 billion by 2031 – an upgrade from earlier financial projections. Underlying the forecast are plans for the launch of at least 12 new products from 2025. These are vaccines and medicines in development for infectious diseases, HIV, respiratory diseases and oncology.

"We are really pleased with the progress this company is making, based on the strengths of the pipeline and portfolio and it is still not done," Emma Walmsley, the chief executive, told journalists on 31 January.

The forecast includes an upgrade of the company's compound annual growth rate (CAGR) for sales of more than 7% between 2021 and 2026 and a CAGR for adjusted operating profit of more than 11% over the same period. The operating profit forecast is a non-IFRS figure that excludes the amortisation and impairment of intangible assets.

Ms Walmsley said the company is declaring a dividend of 58 pence per share for 2023. This is expected to rise to 60 pence per share for 2024.

In the 2023 fourth quarter, group turnover was £8.1 billion, up by 9% in actual exchange rates and by 15% at constant rates. For the year, turnover reached £30.3 billion, up by 3% in actual rates and by 5% at constant exchange rates. Operating profit for the final quarter fell to £573 million, in part because of liabilities related to a Pfizer Inc put option on shares of ViiV Healthcare, the developer of HIV medicines which is majority owned by GSK. Operating profit for the full year was £6.7 billion, or 22% of sales.

The biggest contributor to group turnover in 2023 was the specialty medicines division which reported sales of £10.2 billion from drugs for HIV, respiratory and immunology diseases, and oncology. This was followed by £10.2 billion generated from sales of general medicines and £9.86 billion from vaccines. GSK's vaccine against shingles, which was approved in 2017, had sales of £3.4 billion, the largest single contributor to group sales.

Not far behind were sales of Arexvy, a vaccine for adults 60 years and older against respiratory syncytial virus that was approved in April 2023. In less than a year, the vaccine generated sales of £1.2 billion. GSK is seeking to expand the indication to adults from the ages of 50 to 59 years.

Besides Arexvy, GSK received regulatory approvals in 2023 for new medicines to prevent HIV and to treat myelofibrosis and endometrial cancer. It acquired Bellus Health Inc of Canada which has a Phase 3 product for refractory chronic cough. And in January of this year, it reached an agreement to acquire US-based Aiolos Bio Inc for up to $1.4 billion. Aiolos has a respiratory product in-licensed from China that targets a pathway which regulates the immune response to allergens and viruses.

Ms Walmsley initiated major changes to GSK's strategy in 2021, four years after becoming CEO.

Novartis to acquire MorphoSys

Novartis is to acquire MorphoSys AG for €2.7 billion in cash in order to gain access to pelabresib, a late-stage drug for the treatment of myelofibrosis, a blood cancer caused by genetic abnormalities in bone marrow stem cells. The deal, announced on 5 February, unites two companies with a long history of collaboration in the development of antibody therapeutics.

Pelabresib is a small molecule BET inhibitor which entered MorphoSys' portfolio in 2021 when the German company acquired Constellation Pharmaceuticals Inc of the US. The drug's efficacy was only recently confirmed – in a Phase 3 trial that reported positive results in late November 2023.

In the trial, pelabresib was combined with the JAK inhibitor ruxolitinib and showed a statistically significant improvement in patients' spleen volume. One of the hallmarks of myelofibrosis is an enlarged spleen and anaemia. Pelabresib is designed to promote anti-tumour activity by inhibiting the function of bromodomain and extra-terminal domain (BET) proteins to decrease the expression of abnormally expressed genes in cancer. The drug is also being studied in a Phase 2 trial in patients with essential thrombocythemia, a rare blood cancer that can cause problems with blood clotting.

The acquisition will also give Novartis ownership of the small molecule drug, tulmimetostat, which inhibits the proteins EZA2 and EZH1 and is being studied in patients with advanced solid tumours. The drug is said to work by reactivating silenced genes such as tumour suppressor genes.

MorphoSys was co-founded in 1992 by Simon Moroney who led the creation of a large library of human antibodies that were used to synthesise new medicines. Novartis was one of MorphoSys' earliest partners, signing a research collaboration with the German company in 2007. As of 5 February, MorphoSys was still partnered with Novartis on two antibody projects: NOV-8, a treatment for pulmonary sarcoidosis and severe atopic dermatitis, and ianalumab, a treatment for lupus nephritis and other autoimmune indications.

MorphoSys has one antibody therapeutic on the market which is Monjuvi (tafasitamab) for diffuse large B cell lymphoma and a second marketed product out-licensed to Janssen Biotech Inc.

Dr Moroney stepped down as chief executive officer in 2020 and was replaced by Jean-Paul Kress who expanded the late-stage portfolio to include small molecules. The takeover agreement with Novartis includes an agreement to sell rights to tafasitamab to Incyte Corp for $25 million. Incyte is co-developer of the drug. Tafasitamab is currently being investigated in several other indications including follicular or marginal zone lymphoma.

On 30 January, MorphoSys reported preliminary US net sales data for Monjuvi of $24 million for the 2023 fourth quarter and $92 million for the full year. This year it expects sales in the range of $80 to 95 million.

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Sanofi gets new asset

Sanofi SA is to acquire an experimental biologic for the treatment of alpha-1 antitrypsin deficiency (AATD), a rare disease of the lungs and liver, in a deal valued at up to $2.2 billion. The asset is currently being developed by Inhibrx Inc, a Nasdaq-listed company in the US, which has a pipeline of four main assets. Sanofi will acquire INBRX-101, a recombinant fusion protein which is in a registrational trial for patients with AATD. The deal was announced on 23 January.

The acquisition of INBRX-101 will follow the spin-out of Inhibrx's three other pipeline assets into a new company to be called Inhibrx Biosciences Inc. The new company will be publicly traded and led by the current Inhibrx chief executive Mark Lappe and other members of his management team. Sanofi will have an 8% equity stake in the new company and has agreed to capitalise it with $200 million in cash and retire its outstanding debt.

The bulk of the acquisition value relates to Sanofi's payments to shareholders of the currently listed Inhibrx Inc, as well as payments for contingent value rights to the same shareholders for the achievement of an undisclosed regulatory milestone. Sanofi will pay $30 per share in cash for the Inhibrx shares and $5 in cash for each contingent value right. The closing of the deal is subject to the completion of the Inhibrx Biosciences spin-out and regulatory approvals. This is expected to happen in the second quarter.

INBRX-101 will join Sanofi's portfolio of products for rare diseases which include treatments for lysosomal storage disorders, a group of rare genetic conditions caused by enzyme deficiencies. The new asset for AATD works by inhibiting neutrophil elastase, an enzyme responsible for lung tissue damage. According to the US National Institutes of Health, AATD can lead to chronic obstructive pulmonary disease or cause liver disease.

TVM Capital finances Vektor Medical

Germany-based TVM Capital Life Science has co-led a $16 million Series A financing for Vektor Medical Inc, a US medical technology company that has developed a device for the non-invasive analysis of arrhythmias, a condition characterised by irregular or abnormal heartbeats. The co-investor was Solas BioVentures of the US.

Proceeds from the funding will be used to commercialise the company's vMap tool which was approved by the US Food and Drug Administration in 2021 to help improve the outcomes of ablation procedures. The device uses data from electrocardiograms to detect arrhythmias anywhere in the heart. The technology is based on artificial intelligence. It has been approved to analyse several arrhythmias including atrial and ventricular arrhythmias, tachycardia, and fibrillation. Following the financing, Luc Marengère, managing partner at TVM, will join Vektor Medical's board of directors and Sascha Berger, general partner at TVM will serve as a board observer. Dr Marengère is responsible for TVM Partners' overall investment strategy.

Sanofi plans drug launches

Sanofi SA plans to generate more than €10 billion in sales from the launch of new pharmaceuticals by 2030 as part of a restructuring outlined by Paul Hudson, the chief executive, in 2023. Updating the plans on 1 February, Mr Hudson said that Sanofi is on track to complete development of 12 new medicines, of which two are indicated for multiple sclerosis and one for atopic dermatitis. At the same time, the company is moving ahead with plans to spin out its consumer healthcare business in order to focus exclusively on biopharmaceutical and vaccine development.

2023 was a transition year for the company, with sales and spending on research and development essentially unchanged. IFRS operating profit was lower at €7.9 billion compared with €10.6 billion in 2022 on higher operating and restructuring costs. Unchanged was the very significant contribution of Dupixent, developed with Regeneron Pharmaceuticals Inc, to group sales. Total sales at Sanofi were €43.1 billion in 2023, up by 0.2% in euros, and by 5.3% in constant exchange rates. Sales of Dupixent were €10.7 billion, or 25% of the total. The therapy has already been approved for 12 indications, starting with eczema, in the US. Recently, regulatory applications were submitted in the US, EU and China for a new indication in chronic obstructive pulmonary disease.

In 2023, Sanofi's specialty care division, which includes Dupixent and medicines for rare diseases, generated sales of €18 billion; general medicines produced €12.4 billion; vaccines produced €7.5 billion; and consumer healthcare generated €5.2 billion. The consumer business is expected to be spun out in the fourth quarter of 2024 at the earliest. Concurrently, Sanofi expects to expand its pipeline and portfolio. Among recently approved products is Tzield, a monoclonal antibody indicated to delay the onset of Stage 3 Type 1 diabetes. Tzield is also in Phase 3 for another diabetes indication.

In late January, Sanofi acquired a new rare disease asset – a treatment for alpha-1 antitrypsin deficiency, a disease of the lungs and liver. The deal was valued at up to $2.2 billion.

Sanofi appoints new CFO

Sanofi SA has appointed François-Xavier Roger as chief financial officer, effective 1 April, to succeed Jean-Baptiste Chasseloup de Chatillon who is leaving the company to lead a charitable foundation. Mr Roger will join from Nestlé SA, the Swiss multinational food and beverage company where he has been CFO since 2015. He will be a member of Sanofi's executive committee. Mr Roger has been CFO at Takeda Pharmaceutical Company Ltd in Japan and before that, CFO at Millicom International Cellular SA, a Nasdaq listed mobile phone operator. He was an executive at Sanofi-Aventis, a predecessor company to Sanofi, in the late 1990s.

Novartis enters new era

Novartis completed the spin-out of its Sandoz generics and biosimilars business in 2023, ending the year with sales of $45.4 billion from continuing operations which consist entirely of proprietary medicines. On 31 January, Vas Narasimhan, the chief executive, restated the company's goal of focusing on four therapeutic areas in the future. He also singled out four countries where the company will concentrate its marketing efforts. They are the US, China, Germany and Japan. Novartis has now completed its strategic transformation into a "pure-play innovative medicines company," Dr Narasimhan commented.

The four areas singled out for drug development are cardiovascular, kidney and metabolic conditions; immunology; neuroscience and oncology. Novartis will continue to develop small molecules and biologics. But it will also further expand into cell and gene therapies, radiopharmaceuticals and RNA-based therapies.

The 2023 sales figure of $45.4 billion represented an increase of 8% from a year earlier in US dollars. In constant currencies, the increase was 10%. IFRS operating income for the year was $9.8 billion, up by 23%, and represented 21.5% of sales. Twenty drugs generated sales of $34.9 billion in 2023, or 77% of group turnover. Of this group, 13 had sales of more than $1 billion. The two best-selling drugs were Entresto for heart failure, with sales of $6 billion and Cosentyx for psoriasis, with sales of $4.9 billion. One of the biggest year-on-year gains came from the breast cancer drug Kisqali where sales were $2.1 billion, up by 69% from the previous year. In December, Novartis announced data from a Phase 3 trial of Kisqali supporting a new indication in early breast cancer.

In the fourth quarter, the company won regulatory approval for a new indication for Cosentyx in hidradenitis suppurativa, a chronic skin condition. And it got approval for Fabhalta (iptacopan), a new drug for paroxysmal nocturnal haemoglobinuria, a rare blood disorder.

Novartis has proposed a dividend of CHF 3.30 ($3.86) per share for 2023, an increase of 3.1%.

Sandoz nominates board member

Sandoz Group AG, the Swiss generics and biosimilar medicines' company, has nominated Graeme Pitkethly to its board of directors to lead the company's audit, risk and compliance committee. The appointment is expected to take effect after Sandoz's annual general meeting on 30 April. Mr Pitkethly is an experienced executive having served as chief financial officer at Unilever Plc for 21 years until December 2023. Earlier in his career he held senior corporate finance roles in the telecommunications industry.

Sandoz, formerly a division of Novartis, became an independent company on 4 October 2023. It is listed on the SIX Swiss Exchange in Zurich. It has a portfolio of more than 1,500 products that address diseases from the common cold to cancer. Among its breakthroughs is the development of the first oral penicillin in 1951 and the first biosimilar medicine in 2006.

Roche moves on from Covid

The Roche Group reported sales of CHF 58.7 billion ($68.6 billion) in 2023, a decline of 7% from a year earlier in Swiss francs. At constant exchange rates, however, the results showed a small 1% rise. The decline reflected the absence of sales for Covid-19 products in the most recent period – a reflection of the global recovery from the pandemic. During 2023, Roche also faced biosimilar competition for three of its legacy products – the cancer medicines Herceptin, Avastin and Rituxan. Rituxan is also approved for autoimmune diseases. This competition was estimated to have cost Roche CHF 1.1 billion in lost revenue for the year. Altogether, the pharmaceutical division generated sales of CHF 44.6 billion, down by 2% from a year earlier, and the diagnostics division had sales of CHF 14.1 billion, down by 20%. IFRS operating profit for the year was CHF 15.4 billion compared with CHF 17.5 billion the previous year.

The Roche management team was nevertheless upbeat in a presentation to investors on 1 February. The company is forecasting an increase in sales by a mid-single-digit range this year and is expecting to increase its dividend. Ocrevus for multiple sclerosis was the best-selling product with revenue of CHF 6.4 billion, up by 13% for the year. The biggest year-to-year gains however were reported for Vabysmo, a bispecific antibody treatment for eye disease. In the US, the product has been approved for wet, age-related macular degeneration, diabetic macular oedema and retinal vein occlusion. More recently, data from two Phase 3 trials showed that the vision improvements achieved by the drug were maintained for more than a year.

Roche further grew its business in 2023 with the acquisition of a new point-of-care diagnostic platform from LumiraDx. Separately, it paid $7.1 billion upfront to buy Telavant Holdings which has a late-stage antibody therapeutic for inflammatory bowel disease. In December, Roche entered the weight loss space with the acquisition of Carmot Therapeutics for $2.7 billion upfront. Carmot has an early-stage obesity drug.

Enthera board member appointed CEO

Lisa M. Olson has been appointed chief executive officer of Italy-based Enthera Pharmaceuticals Srl where she was previously a member of the board and chair of the company's scientific advisory board. The appointment comes as Enthera starts enrolment in a trial of patients with moderately to severely active ulcerative colitis. The antibody therapeutic, Ent001, has passed its first safety test in a study in healthy volunteers.

The development of Ent001 and other assets will be led by Dr Olson, who has worked as a pharma executive for more than 20 years. Fifteen of these years were spent at AbbVie Inc and Abbott Laboratories. This culminated in her position as vice president of immunology discovery and site head of the AbbVie Bioresearch Center in the US. She has also been a research fellow in inflammation and immunology at Pfizer Inc.

Novo lifts diabetes share

Novo Nordisk A/S lifted its share of the global diabetes market to 33.8% in 2023 from 31.9% a year earlier, driven by demand for its glucagon-like-peptide-1 medicines for type 2 diabetes. These drugs, Ozempic, Victoza and Rybelsus, help manage blood sugar by triggering the pancreas to release more insulin. Novo generated revenue of DKK123 billion ($17.81 billion) from the three medicines in 2023, representing 53% of group sales.

Total sales for the year were DKK 232.3 billion. Revenue consisted of the GLP-1 medicines for diabetes, as well as insulins; two GLP-1 medicines for obesity; and drugs for rare diseases, including rare blood and endocrine disorders.

The diabetes and obesity medicines delivered DKK 215.1 billion in sales or 93% of the total, while the drugs for rare disease, contributed DKK 17.2 billion, or the remaining 7%. By far the biggest increase in sales was generated by Wegovy, one of the two obesity drugs, which had sales of DKK 31.3 billion, up by 407% from a year earlier. Clinical studies leading up to Wegovy's approval in both the US and the EU showed that a significant proportion of participants taking the drug were able to reduce their weight by at least 5% when using it as an adjunct to diet and exercise. Demand for the drug in 2023 was so strong that Novo had to reduce the supply of lower dose strengths in the US. From January 2024 this supply was being restored.

Novo achieved an operating profit of DKK 102.6 billion, up by 37% at actual exchange rates, and by 44% at constant rates for the year. The operating profit was 44.2% of sales, up from 42.3% the previous year. Research and development spending was DKK 32.4 billion, or 14% of sales, up from 13.6% in 2022.

Alys launches with capital

Alys Pharmaceuticals Inc, a new company with a preclinical pipeline of candidate drugs for immune-related disorders, was launched on 12 February with $100 million of capital. The company was co-founded by the venture capital group Medicxi and a group of six scientists specialising in immuno-dermatology. The scientific founders are based at institutions in the US, Germany and France and include Craig Mello, professor at the UMass Chan Medical School, US, and winner of a Nobel Prize in 2006 for the discovery of RNA interference.

Alys combines the assets of six companies which were in the Medicxi portfolio, but apparently were too small to have a market impact on their own. "We believe that bringing together several asset-centric companies with a phenomenal team will power up Alys to transform innovation in immuno-dermatology," said Francesco De Rubertis, partner at Medicxi, in a prepared statement. The Alys pipeline consists of 13 projects, some of which target diseases which are already being served by approved medications, like atopic dermatitis, and others, like mastocytosis, which are less well served. Mastocytosis is a disorder of abnormal mast cell proliferation. Uniquely, the 13 projects involve a wide variety of compound modalities.

Novo to acquire Catalent

Novo Nordisk A/S has announced plans to increase capacity for the supply of its medicines for diabetes and obesity in a staged transaction under which a subsidiary of its controlling shareholder, Novo Holdings A/S, will take over Catalent Inc, one of the world's largest contract manufacturing organisations (CMO). Announced on 5 February, the deal is expected to complete towards the end of 2024.

Under the agreement, Novo Holdings, which manages the assets of the Novo Nordisk Foundation, will acquire Catalent for $16.5 billion. In a second step, the holding company will sell three of Catalent's manufacturing sites to Novo Nordisk for an upfront payment of $11 billion. All three facilities – located in Italy, Belgium and the US – are fill-finish sites which sterilise and standardise the active ingredients of drugs and put them into containers for marketing.

The additional capacity is expected to meet market demand for Novo's obesity drug Wegovy (semaglutide), a glucagon-like peptide-1 (GLP-1) receptor agonist, which received US regulatory approval in 2021. Wegovy accounted for 13.5% of the company's sales of DKK 232.3 billion ($33.6 billion) in 2023. Demand for Wegovy exceeded supply last year forcing the company to reduce the supply of lower dose strengths of the drug. The planned increase in manufacturing capacity is one of the responses.

The three Catalent sites employ more than 3,000 people and have ongoing collaborations with Novo and other pharmaceutical companies. Eli Lilly and Co, which is competing with Novo on the diabetes and obesity markets, has contracts with at least one of the sites, according to the *Financial Times*. David Ricks, Lilly's chief executive, told the newspaper on 6 February that the Catalent deal should be looked at by antitrust authorities. In response to an email from *MedNous*, the company said that "once the deal is closed, Novo Nordisk will fully honour the current CMO contracts."

Earlybird closes new fund

Earlybird Venture Capital, one of Europe's larger investment groups, has raised €173 million in new capital for the Earlybird Health Fund, an instrument dedicated to the support of European companies across the healthcare sector. Announced on 14 February, the receipts will be used to invest in enterprises with technologies for digital health, diagnostics, medical devices and tools for research and development. Among participants in the new fund is British Patient Capital, a group that makes long-term investments in UK companies. According to Christine Hockley, managing director of the British fund, the Earlybird strategy will complement efforts already underway in the UK to energise innovation in the healthcare sector. A leading German health insurer, BARMER, is also an investor.

Earlybird has harnessed artificial intelligence to create a proprietary tool for identifying potential deals. Called Eagle Eye, the tool collects information from both start-ups and established companies to assess potential for new business deals and financing opportunities. "Eagle Eye will soon be the driver of a more effective, efficient, and inclusive deal sourcing and due diligence process for our investment teams, " said Christoph Massner, principal, in a prepared statement.

Founded in 1997, Earlybird Venture Capital has four funds each of which focus on different geographies and sectors. The Digital West Fund concentrates on digital technology opportunities in the Nordic region, UK, Belgium, the Netherlands, France and southern Europe. A complementary Digital East Fund focuses on early stage information technologies in eastern Europe and Turkey. The Health Fund is focused on Europe across all healthcare sectors and Earlybird-X provides capital to robotics and AI in early development.

Based in Germany, Earlybird Venture Capital has €2 billion under management across the four funds. It has been responsible for nine initial public share offerings and 32 trade sales.

Round-up of European biopharmaceutical company news

US-based **Biogen Inc** is to discontinue the development and commercialisation of Aduhelm (aducanumab), its monoclonal antibody treatment for Alzheimer's disease in order to direct resources towards newer treatment types. Developed with Eisai Co Ltd, Aduhelm was given an accelerated approval by the US Food and Drug Administration on 7 June 2021 on the basis of data showing a reduction of beta-amyloid plaque in patients. The approval was controversial because the results of clinical trials supporting the decision were contradictory. Moreover the FDA's own advisory committee opposed the authorisation. As a condition of the approval Biogen was required to conduct a follow-up trial to confirm the drug's efficacy. In a statement issued on 31 January, the company said it will stop the confirmatory trial, ENVISION, noting that the decision is not related to any safety or efficacy concerns. A key consideration was the likelihood that new potential treatments will be identified for Alzheimer's disease before the confirmatory study ends, it said. The company also disclosed that it had been unable to identify potential partners, or raise external financing for the project. Going forward, the company will focus on the development and commercialisation of Leqembi, an anti-amyloid beta treatment given full approval by the FDA on 6 July 2023. It will also continue development of a small molecule inhibitor of tau aggregation and an antisense oligonucleotide also targeting tau. Biogen in-licensed aducanumab from Neurimmune AG of Switzerland. The rights to the drug will return to the Swiss company.

Calliditas Therapeutics AB of **Sweden** received notice from the US Patent and Trademark Office on 13 February of the coming into force of a new patent for Tarpeyo, its lead product for primary immunoglobulin A nephropathy, a rare kidney disease. The patent covers a method of treating IgA nephropathy with a composition that includes Tarpeyo (budesonide) delayed release capsules. This is the company's second US patent for the product and provides product protection until 2043. Calliditas intends to file corresponding patent applications in other geographies including Europe and China. Tarpeyo was given an accelerated approval by the US Food and Drug Administration in 2021 and a full approval on 20 December 2023. The drug is the first fully FDA-approved product for IgAN based on a measure of kidney function.

Cumulus Oncology Ltd, an Edinburgh, **UK**, investment group, announced the launch of its second biotech company on 1 February, giving further evidence of its strategy to innovate in oncology. The new company, GIO Therapeutics AG is based in Basel, Switzerland and will develop pharmaceuticals targeting G protein-coupled receptors (GPCRs). GPCRs represent the largest family of cell surface receptors in the human genome, regulating physiological responses and acting as drug targets. Leading the new company as chief executive officer is Xavier Leroy, previously an executive at Domain Therapeutics SA, a French company which is also developing drugs targeting GPCRs. In a statement, Dr Leroy said that while GPCRs are well-known drug targets, their potential as cancer therapies is underutilised. Cumulus, which was founded in 2017, has created one other company. This is Nodus Oncology which is developing drugs addressing DNA damage response.

Syncona Ltd, a **UK** evergreen investment group, announced on 8 February that its portfolio company Autolus Therapeutics Plc is to collaborate with BioNTech SE of Germany to develop new therapies in oncology. The project will aim to advance both companies' CAR T cell therapy programmes towards commercialisation. These include BioNTech's cell therapy for solid tumours, BNT211, and Autolus' two CAR T cell therapy programmes, AUTO1/22, and AUTO6NG, for oncology indications. Under the terms of the agreement, BioNTech has agreed to purchase $200 million of Autolus' American Depositary Shares in a private placement. Following on from this, it will appoint a director to the UK company's board of directors. Under the terms of a licence and option agreement, BioNTech will make a $50 million cash payment to Autolus in exchange for royalties on the prospective sales of Autolus' lead product obecabtagene autoleucel, a CAR T cell therapy for adult B cell acute lymphoblastic leukaemia which is being reviewed by the US Food and Drug Administration. BioNTech also has an option to use Autolus' commercial and clinical site network and manufacturing facilities in the UK. BioNTech plans to have 10 or more ongoing potentially registrational clinical trials in its pipeline by the end of 2024.

UK-based **AstraZeneca Plc** completed the acquisition of the US biopharmaceutical company Icosavax Inc on 19 February giving it a late-stage vaccine candidate targeting the respiratory syncytial virus (RSV) and the human metapneumovirus. Both viruses cause severe respiratory infections and can lead to hospitalisations in adults 60 years of age and older. The vaccines are made from virus-like particles (VLPs) which are designed to resemble the structure of viruses with a high-density display of antigens. According to AstraZeneca, the VLP technology is expected to induce a stronger and more durable immune response than traditional vaccines. The value of the acquisition, including both upfront and contingent value rights payments, is $1.1 billion.

UK-based **GSK Plc** received a fast-track designation from the US Food and Drug Administration on 12 February for bepirovirsen, a treatment for chronic hepatitis B, a disease that is estimated to affect about 300 million people worldwide. Bepirovirsen is an antisense oligonucleotide which inhibits the replication of viral DNA in the body, thereby suppressing the level of hepatitis B surface antigen in the blood and stimulating an immune response. Products with fast-track designations from the FDA are eligible for an accelerated approval, if all regulatory criteria are met.

BlueRock licenses cell therapy

BlueRock Therapeutics LP has exercised an option and gained exclusive rights to a cell therapy derived from induced pluripotent stem cells (iPSC) for the treatment of primary photoreceptor diseases. The product, OpCT-001, was developed in collaboration with Fujifilm Cellular Dynamics Inc, a manufacturer of human iPSCs and iPSC-derived cells, and Opsis Therapeutics LLC.

The deal, announced on 23 January, involves an undisclosed licence fee paid by BlueRock to its partners. The partners are also eligible for further payments on the achievement of certain development and commercial milestones.

BlueRock, a wholly owned subsidiary of Bayer AG, plans to seek regulatory approval to start clinical development of OpCT-001 this year. Primary photoreceptor diseases are a subgroup of inherited retinal disorders that include retinitis pigmentosa and cone rod dystrophies. These diseases affect the structure and function of photoreceptor cells in the retina, leading to vision loss. As humans cannot regenerate photoreceptors, one approach is to replace them with a cellular therapy, according to Fujifilm. OpCT-001 is composed of allogeneic human iPSC derived photoreceptor cells which, once transplanted, are intended to help a patient recover vision by maturing into rods and cones in the retina. Rods are responsible for peripheral vision and cones, for central high acuity and colour vision.

Fast track for CAR therapy

An experimental chimeric antigen receptor (CAR) T cell therapy intended for the treatment of multiple sclerosis received a fast track designation from the US Food and Drug Administration on 19 January, indicating its potential to address a major medical need. The therapy is being developed by Kyverna Therapeutics Inc, a biotech company incorporated in 2018 and located in Emeryville, California, US.

According to the US National Library of Medicine, there are currently 11 disease-modifying treatments for multiple sclerosis approved for marketing in the US. These include antibody therapeutics and the cytokine interferon beta-1a.

As a cell therapy, Kyverna's product would be a new approach for treating the disease which has an estimated global prevalence of 1.8 million people.

The therapy, KYV-101, is an autologous product consisting of a patient's own T cells which have been engineered with a receptor targeting CD19, a protein expressed on the surface of malignant B cells. The first CAR T cell therapies were developed to treat leukaemia and lymphoma. Only recently have biotech companies started to investigate these same therapies for autoimmune diseases.

KYV-101's receptor was developed by the US National Institutes of Health and in-licensed by Kyverna. It has been designed to improve a patient's tolerance of the drug by altering the structure of the receptor's domains.

FDA comments on CAR T risks

Healthcare professionals are being advised to monitor patients and clinical trial participants who receive treatment for cancer with a chimeric antigen receptor (CAR) T cell therapy for the risk of secondary malignancies. In a commentary in *The New England Journal of Medicine* on 25 January 2024 Nicole Verdun and Peter Marks write that while secondary cancers from these medicines appear to be relatively rare, they need to be identified. Drs Verdun and Marks are both senior officials at the US Food and Drug Administration.

"Although CAR-T products have to date been associated with fewer cancers than products made with the previous generation of viruses used for gene therapy transduction, the potential for oncogenesis caused by genomic integration or other mechanisms still exists with the current generation of retroviral vectors," they write.

They go on to recommend that clinicians contact the drug's manufacturer if they observe a new cancer after treatment with a CAR T product and collect patient samples for testing.

CAR T cell therapy is an autologous product produced from a patient's own immune cells which are engineered to produce chimeric receptors that can recognise specific proteins, or antigens, on cancer cells. The engineering involves transducing the chimeric receptor into the T cells with a viral vector. Five of the six currently approved CAR T cell therapies use a lentiviral vector for transduction. The sixth uses a retroviral vector. The six therapies have been approved in the US to treat leukaemia, lymphoma and multiple myeloma.

Drs Verdun and Marks write that insertional oncogenesis is a risk with the current constructs and urged manufacturers to consider new strategies in the future. "Moving forward, particularly as the use of CAR T cells for indications outside haematology and oncology is considered, new strategies involving targeting insertion of the CAR construct to specific loci might help reduce the risk of cancers due to integration of the CAR construct at oncogenic loci within the genome," they write.

As of 31 December, the FDA had identified 22 cases of T cell cancers which occurred after treatment with a CAR T cell product. In 14 cases the cancers appeared within two years after treatment. On 19 January the agency issued a safety update to manufacturers requiring new product labelling for the therapies. It said the risk of T cell malignancies was applicable to all BCMA and CD19 directed genetically modified autologous T cell therapies.

Cellular Origins appoints COO

Cellular Origins, part of the technology consultants TTP, has appointed Peter Crossley as chief operating officer to support the company's cell and gene therapy manufacturing activities. Mr Crossley worked as a consultant at TTP for 17 years, playing a key role in developing its life science business. With a BEng in aerospace engineering from the University of Bristol, UK, Mr Crossley developed gas turbines at Rolls-Royce, before moving to R&D and technical management in consumer products at Dyson Ltd and Fisher & Paykel Ltd.

News Briefs

New cell therapy for melanoma

A cell therapy for melanoma, the first of its kind, was given an accelerated approval by the US Food and Drug Administration on 16 February for patients whose disease has progressed despite earlier treatment with a checkpoint inhibitor or a personalised cancer therapy. The therapy, Amtagvi (lifileucel), is a tumour infiltrating lymphocyte cell therapy (TIL) which consists of T cells that have been derived from a patient's own tumour. The safety and effectiveness of Amtagvi were evaluated in a multicentre, single-arm study in individuals with unresectable or metastatic melanoma. The patients had been previously treated with at least one systemic therapy, including a PD-1 blocking antibody, or an inhibitor of the BRAF protein if their disease was caused by a V600 mutation of the BRAF gene. The patients also may, or may not, have also received an inhibitor of the MEK protein. The main efficacy outcome measures were objective response rate and duration of response. The median time to initial response to lifileucel was 1.5 months. Among the 73 patients who received lifileucel within the recommended dosing range, 31.5% had an objective response rate. The median duration of response was not reached. A confirmatory trial is ongoing to verify Amtagvi's clinical benefit, the FDA said.

Hearing restored in 11-year old

An 11-year-old with profound hearing loss from birth experienced restored hearing within 30 days of receiving a gene therapy, the developer Akouos Inc reported on 23 January. Akouos is a subsidiary of Eli Lilly and Co. The product, AK-OTOF, is a dual adeno-associated viral vector-based therapy designed to restore auditory function by gene transfer. It is being tested in a Phase 1/2 trial in children with OTOF-mediated hearing loss. OTOF is a gene that encodes the otoferlin protein which is involved in inner hair cell vesicular transport. AK-OTOF has been given orphan drug designation and rare paediatric disease designation by the FDA and a positive opinion on orphan designation by the European Medicines Agency.

New financing for Sensorion

France-based Sensorion SA, which is developing therapies to prevent and treat hearing loss disorders, announced financing of €50.5 million on 9 February to support clinical development of a new product for hearing loss. Participating in the financing were Redmile Group, Sofinnova Partners and the US healthcare group Aquilo Capital. The product, SENS-401, is a small molecule drug designed to protect and preserve inner ear tissue. It is being studied in a Phase 2a trial for the prevention of residual hearing loss in patients scheduled for cochlear implantation. The same product is also being studied for the prevention of cisplatin-induced ototoxicity. The drug has received orphan designations in both the EU and the US.

On the Move

Transgene SA, a company developing virus-based immunotherapies to treat cancer, has appointed **James Wentworth** as chief business officer and member of the executive management team. The appointment comes as Transgene advances a therapeutic vaccine for HPV-positive cancers. Dr Wentworth, who will lead business, corporate development and partnering strategies, has over 15 years of business development and commercial experience in pharma and biotech companies. He joined Transgene from Adaptimmune Plc where he was director, business development and strategy. Dr Wentworth holds a BSc and a PhD in pharmacology from the University of Bristol, UK, and an MBA from the International Institute for Management Development (IMD) in Lausanne, Switzerland.

Joerg Moeller, an experienced pharma R&D executive and artificial intelligence (AI) advocate, has been appointed chief executive officer and executive board member of **BenevolentAI Ltd**. The company applies its AI platform to accelerate drug discovery. Dr Moeller was at Bayer AG for 20 years, culminating in the position of pharmaceutical research and development head of the company's pharmaceuticals division. His work at Bayer included external strategic AI collaborations. Most recently, Dr Moeller was head of global research and development, at LEO Pharma A/S. He currently is a board member of Secura Bio, a privately held US biotech company.

Osivax, a developer of broad-spectrum vaccines, has appointed **Nicola Groth** to its executive committee as chief medical officer. The appointment comes as the company advances its lead candidate influenza vaccine into Phase 2. Dr Groth is experienced in managing late-stage clinical trials and building registration packages for influenza vaccines. Prior to joining Osivax, she headed global safety evaluation and risk management at GlaxoSmithKline Vaccines and has also held strategic positions in vaccine development, epidemiology and medical affairs at Novartis Vaccines. Dr Groth is a doctor of medicine and holds a PhD in hygiene and preventive medicine from the University of Siena, Italy.

The Critical Path Institute (C-Path), a public-private partnership, has appointed **Klaus Romero** as chief executive officer and promoted **Cécile Ollivier** to vice president of global affairs. Dr Romero has worked over 16 years at C-Path in several positions supporting its initiatives in drug development. Ms Ollivier joined C-Path as managing director, Europe in April 2021. In her new role she will focus on international collaborations. She has more than 16 years' experience in the healthcare sector, making contributions to paediatric and rare disease drug development at organisations including the European Medicines Agency.

VectorY NV, a developer of vectorised antibody therapies to treat neurodegenerative diseases, has appointed **Khurem Farooq** as an independent board member. Mr Farooq is currently chief executive officer at Aiolos Bio whose acquisition by GSK was announced in January. Previously Farooq was CEO of Gyroscope, which was acquired by Novartis in 2021, and senior vice president of the immunology and ophthalmology business unit at Genentech, part of the Roche group. His appointment follows VectorY's $138 million Series A round announced in November 2023 to support clinical development of the company's lead programme for amyotrophic lateral sclerosis. Mr Farooq has a BSc in biological sciences from the University of Wolverhampton and an MBA from Aston University, both in the UK.

NMD Pharma A/S, which is developing clinical stage treatments for neuromuscular diseases, has appointed **Morten Bull** as general counsel and head of people and business services as it develops its late-stage clinical pipeline. Mr Bull had been general counsel on a consultancy basis since June 2023. Before joining NMD Pharma A/S, Mr Bull was executive director and global head of IP and R&D Legal at LEO Pharma A/S.

Enhanc3D Genomics has appointed **Daniel Turner** as chief scientific officer to help drive the company's development plans for its GenLink3D genomics platform and formation of commercial and academic partnerships. Dr Turner brings over 20 years of senior leadership in genetics, molecular biology, and sequencing research. He joined Enhanc3D Genomics from Oxford Nanopore Technologies Plc. He also was head of sequencing technology development at the Wellcome Trust Sanger Institute, UK. The appointment follows that of **Hazel Jones** as chief operating officer in November 2023.

Arndt Schottelius has been appointed as chief executive officer of **Maxion Therapeutics Ltd**, effective 1 March, in a planned succession process, where co-founder **John McCafferty** is transitioning from CEO to chief technology officer. Maxion is developing antibody-based drugs for ion channel and GPCR-driven diseases. Dr Schottelius is joining the company from Affimed NV where he was chief scientific officer. He has also held executive leadership positions at Kymab (acquired by Sanofi) and MorphoSys AG, soon to be acquired by Novartis.

EnteroBiotix Ltd, which has developed a platform for full-spectrum gut microbiome therapeutics, has appointed **James Barnes** as chief operating officer and **Chris Lea** as chief financial officer. Dr Barnes joins from BerGenBio ASA where he was COO and brings 18 years of experience in early and late phase drug development and business operations. Mr Lea was previously CFO of AIM-listed Cambridge Nutritional Sciences Plc as well as of two other AIM-listed companies, IndigoVision Group Plc and Superglass Holdings Plc.

Companies and universities in this issue

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