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MINI-REVIEW

Novel drugs approved by the EMA, the FDA, and the MHRA in 2023: A year in review

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Abstract

In 2023, seventy novel drugs received market authorization for the first time in either Europe (by the EMA and the MHRA) or in the United States (by the FDA). Confirming a steady recent trend, more than half of these drugs target rare diseases or intractable forms of cancer. Thirty drugs are categorized as "first-in-class" (FIC), illustrating the quality of research and innovation that drives new chemical entity discovery and development. We succinctly describe the mechanism of action of most of these FIC drugs and discuss the therapeutic areas covered, as well as the chemical category to which these drugs belong. The 2023 novel drug list also demonstrates an unabated emphasis on polypeptides (recombinant proteins and antibodies), Advanced Therapy Medicinal Products (gene and cell therapies) and RNA therapeutics, including the first-ever approval of a CRISPR-Cas9-based gene-editing cell therapy.

KEYWORDS
drug development, EMA, FDA, MHRA, new drug approvals, regulatory

Abbreviations: 5-HT, 5-hyrdoxytryptamine; AAV, adeno-associated virus; Ab, antibody; Acc, accelerated approval; AKT, protein kinase B; ALK, anaplastic lymphoma kinase; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; APC, adenomatous polyposis coli; ASO, antisense oligonucleotide; AT1, angiotensin II type I receptor; ATP, adenosine triphosphate; Aβ, amyloid β; BCMA, B cell maturation antigen; Br, breakthrough; Cas9, CRISPR-associated protein 9; CD, cluster differentiation; CDI, Clostridioides difficile infections; CGRP, calcitonin gene-related peptide; CHAPLE, complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy; CHMP, Committee for Human Medicinal Products; CKD, chronic kidney disease; CMV, cytomegalovirus; COVID, coronavirus disease; CRISPR, clustered regularly interspaced palindromic repeats; CXCR4, C-X-C chemokine receptor type 4; DMD, Duchenne muscular dystrophy; DMF, dimethyl fumarate; DOR, duration of response; EMA, European Medicines Agency; ER, oestrogen receptor; ETA, endothelin-1 type A receptor; FDA, Food and Drug Administration; FIC, first-in-class; FT, fast-track; GABA-A, γ-aminobutyric acid receptor A; GFR, glomerular filtration rate; GPRC5D, receptor family C group 5 member D; Hb, haemoglobin; HER, erb-b2 receptor tyrosine kinase; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIF, hypoxia-inducible factor; HSV, herpes simplex virus; IgAN, immunoglobulin A nephropathy; IGF, insulin-like growth factor; JAK, Janus kinase; KEAP1, Kelch-like ECH-associated protein 1; LDHA, lactate dehydrogenase A; Mab, monoclonal antibody; MHRA, Medicines and Healthcare Products Regulatory Agency; MM, multiple myeloma; NF-κB, nuclear factor-kappa B; NK, neurokinin; NRF2, nuclear factor erythroid2-related factor 2; ORR, overall response rate; P2X3, purinergic 2X3 receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; PD-1, Programmed Cell Death Protein 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RAR, retinoic acid receptor; ROS, c-ros oncogene 1; RSV, respiratory syncytial virus; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SGLT, sodium–glucose cotransporter; SOD, superoxide dismutase; SOD, superoxide dismutase; T1D, type 1 diabetes; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; TRK A-C, neurotrophic receptor tyrosine kinase 1-3; VEGF(R), vascular endothelial growth factor (receptor).

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1 | INTRODUCTION

For healthcare professionals, researchers, teaching staff and students who seek a focused update on the innovative additions to the therapeutic arsenal, the *British Journal of Pharmacology* has decided to start an annual minireview series, containing a comprehensive and succinct list of all the novel drugs authorized in the past calendar year in the European Union by the European Medicines Agency (EMA) and European Commission, in the United States by the Food and Drug Administration (FDA), and in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency (MHRA).

We have compiled information using three main sources:

a. The official websites of the FDA, which are regularly updated with information on "Novel Drug Approvals" as they occur (https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023). These sites also provide updates on cellular and gene therapy products (https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products), as well as vaccines and other products (https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/2023-biological-license-application-approvals) approved by the Center for Biologics Evaluation and Research in 2023. Please note that blood and blood products as well as plasma derivatives are excluded from this list.
b. The monthly "Human Medicines Highlights" published by the EMA (https://www.ema.europa.eu/en/news-events/publications/newsletters#human-medicines-highlights-section). These highlights include a comprehensive list of all newly authorized products, including vaccines, along with links to the details of each new authorization.
c. The official website of the UK MHRA, which lists all marketing authorizations for various products (https://www.gov.uk/government/publications/marketing-authorisations-granted-in-2023).

We have included all novel drugs approved by these three agencies up to December 31st, 2023. We also accessed "The IUPHAR/BPS Guide to PHARMACOLOGY" (https://www.guidetopharmacology.org/), an informative go-to site to clarify the pharmacological mechanism of action of molecules based on indexed literature. The entire list of novel drugs approved in 2023 can be found in Table S1. Drugs that belong to different categories, such as small molecules, antibodies and proteins, and advanced therapy medicinal products (ATMP) and RNA are listed in Tables 1–3, respectively. Vaccines are shown in Table 4.

It is important to keep in mind that, at the EMA, the Committee for Human Medicinal Products (CHMP) may issue a "Positive Opinion" regarding a submission (which is a recommendation for authorization). This should not be confused as equivalent to the FDA's "Approval" process. The CHMP recommendation is to be followed by a favourable decision from the European Commission, which results in a legally binding Authorization that is equivalent to the FDA Approval. The MHRA decision to approve a marketing authorisation is a national decision, which may be made through an independent assessment (national procedure), collaborative assessment (Project Orbis and ACCESS procedure) or an assessment that is reliant on the decision of the EMA (European Commission Decision Reliance Procedure – ECDRP, available from 1/2021to 12/2023), replaced by International Recognition Procedure (IRP) from January 1st, 2024.

The inclusion and exclusion criteria for the construction of the 2023 list are shown in Box 1. To categorize the new drugs based on unmet need and mechanistic/therapeutic innovation, we considered that all three agencies have established procedures (listed in Box 2) for expedited approval (FDA), rolling review/conditional marketing authorization (MHRA) or accelerated authorization/conditional marketing authorization (EMA). Whether a drug underwent such a procedure is also shown in Table 1, which lists all the drugs.

In total, 70 novel drugs were approved in 2023 either by the EMA, the FDA or the MHRA (Figure 1). The number of drugs approved by each agency, as seen in Table S1, is different, with the FDA appearing to have first approved most of them. The discrepancy among the agencies does not mean that fewer novel drugs received a positive approval by the EMA or the MHRA. A significant number of the EMA- or MHRA-authorized products in 2023 had already received prior approval by the FDA and thus do not meet the inclusion criteria of the present mini-review. Alternatively, the EMA and the MHRA may have rejected/not authorized drugs that were approved by the FDA or decided to defer decision to a later date. Possible intrinsic (time) variations in the approval process or/and different priorities of the originator companies in requesting authorization by the three agencies may also contribute to gaps in approval time in the United States and the EU.

The new drugs cover unmet need in a broad variety of disorders and diseases (Figure 2), especially rare and poorly treated types of cancer or diseases for which the available options either do not exist or have limited therapeutic effectiveness (Table S1). For several rare diseases, a combination of criteria such as low prevalence (less than 1:1500 [US] or 1:2000 [EU, MHRA]), paucity, inadequacy or challenging development path of future treatments, or life-threatening nature of the disorder, has prompted the EMA, the FDA and MHRA to designate these conditions as well as the drugs aiming at them as "orphan." A substantial percentage of drugs approved in the past decade fall into this category and constitute a trend in the development of novel chemical entities. In 2023, twenty-four of the approved drugs were designated "orphan" by one or more agencies (listed in Box 3). Not surprisingly, many of them target rare diseases associated with genetic mutations and altered levels or activity of a mutated gene and the protein it encodes. In 2023, such diseases (approved drug in parentheses) include, for example, Duchene Muscular Dystrophy (**vamorolone**), Myasthenia gravis (**zilucoplan**, **rozanolixizumab**), excessive activity of lactate dehydrogenase (nedosiran), C55 protein deficiency (**pozelimab**), α-glucosidase deficiency (cipaglucosidase alfa, pegunigalsidase alfa), amyotrophic lateral sclerosis (ALS) with mutated superoxide dismutase 1 (tofersen), activated phosphoinositide 3-kinase delta syndrome (**leniolosib**), Rett syndrome (**trofinetide**), Friedrich's ataxia (**omaveloxolone**) or α-mannosidosis (velmanase alfa). The rest of the 2023 orphan drugs have been authorized for

TABLE 1 Small molecules.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Bexagliflozin	Brenzavvy	Improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise	**Sodium/glucose cotransporter 2** (SGLT2) inhibition	FDA		DOI: 10.1111/dom.15192
Capivasertib	Truqap	In combination with fulvestrant, for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/ PTEN-alterations	**Akt (protein kinase B, PKB) family** pan inhibition	FDA	P	DOI: 10.1056/NEJMoa2214131
Daprodustat	Jesduvroq	Anaemia caused by chronic kidney disease for adults on dialysis for at least four months	**Prolyl hydroxylases** inhibition	FDA		DOI: 10.1001/jamainternmed.2022.0605
Elacestrant	Orserdu	Oestrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy	**Estrogen receptors** degradation	FDA, EMA, MHRA	P, FT	DOI: 10.1200/JCO.22.00338
Etrasimod	Velsipity	Moderately to severely active ulcerative colitis in adults	**$S1P_1$ receptor** activation	FDA		DOI: 10.14309/01.ajg.0000859576.23012.a3 DOI: 10.1093/ecco-jcc/jjab016
Fezolinetant	Veozah	Moderate to severe hot flashes caused by menopause	**NK_3 receptor** antagonism	FDA, MHRA	P	DOI: 10.1016/S0140-6736(23)00085-5
Flotufolastat F 18	Posluma	Positron emission tomography imaging in certain patients with prostate cancer	Prostate-specific membrane antigen	FDA		

(Continues)

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Fruquintinib	Fruzaqla	Refractory, metastatic colorectal cancer	**VEGF (vascular endothelial growth factor) receptor family** inhibition	FDA	P	DOI: 10.21037/tcr-20-3539
Gefapixant	Lyfnua	Treatment of chronic unexplained cough or cough unresponsive to other medicines	**P2X3 receptor** antagonism	EMA, MHRA		DOI: 10.1183/16000617.0219-2022 DOI: 10.1007/s00408-023-00606-w
Gepirone	Exxua	Major depressive disorder	**5-HT$_{1A}$ receptor** activation	FDA		DOI: 10.4088/jcp.v69n040
Iptacopan	Fabhalta	Treatment of paroxysmal nocturnal haemoglobinuria	**complement factor B** inhibition	FDA		DOI: 10.1016/j.kint.2023.09.027
Ivosidenib	Tibsovo	Relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation	**isocitrate dehydrogenase (NADP$^+$) 1** inhibition	FDA, EMA, MHRA	P, Br	DOI: 10.1182/blood.2019002140
Leniolisib	Joenja	Activated phosphoinositide 3-kinase delta syndrome	**phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta** inhibition	FDA	Rare paediatric dis.,, P	DOI: 10.1016/j.jaci.2023.09.032
Lotilaner	Xdemvy	Demodex blepharitis	Antagonist of mite GABA chloride channel	FDA		DOI: 10.1016/j.ophtha.2023.05.030 DOI: 10.1097/ICO.0000000000003097
Momelotinib	Ojjaara	Intermediate or high-risk myelofibrosis in adults with anaemia	**Janus kinase 1**, **Janus kinase 2** & **activin A receptor type 1** inhibition	FDA		DOI: 10.1016/S0140-6736(22)02036-0 DOI: 10.1002/cam4.5799
Motixafortide	Aphexda	With filgrastim (G-CSF), to mobilize haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma	**CXCR4 chemokine receptor** antagonism	FDA		DOI: 10.1158/1078-0432.CCR-21-0929
Nirmatrelvir, ritonavir	Paxlovid	Mild-to-moderate COVID-19 in adults at high risk for progression to	**CoV 3C-like (main) protease** & **CYP3A4** inhibition	FDA, EMA		DOI: 10.1093/cid/ciac443

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
		severe COVID-19				
Nirogacestat	Ogsiveo	Progressing desmoid tumours requiring systemic treatment	γ-Secretase inhibition	FDA	P, FT, Br	DOI: 10.1056/NEJMoa2210140
Omaveloxolone	Skyclarys	Friedrich's ataxia	**Nuclear factor, erythroid 2 Like 2** (NRF2) pathway activation	FDA	P, FT, rare paediatric dis.	DOI: 10.1002/ana.25934
Palovarotene	Sohonos	To reduce the volume of new heterotopic ossification in adults and paediatric patients (aged 8 years and older for females and 10 years and older for males) with fibrodysplasia ossificans progressiva	**Retinoic acid receptor-γ** (NR1B3) activation	FDA	P, FT, Br	DOI: 10.1002/jbmr.4762
Perfluorhexyloctane	Miebo	Alleviate signs and symptoms of dry eye disease	Decreased tear evaporation	FDA		DOI: 10.37765/ajmc.2023.89464
Pirtobrutinib	Jaypirca	Relapsed or refractory mantle cell lymphoma in adults who have had at least two lines of systemic therapy, including a BTK inhibitor	**Bruton tyrosine kinase** inhibition	FDA, EMA	P, FT, Acc	DOI: 10.1056/NEJMoa230069
Quizartinib	Vanflyta	Newly diagnosed acute myeloid leukaemia that meets certain criteria	**fms related receptor tyrosine kinase 3** (FLT3) inhibition	FDA, EMA	P, FT	DOI: 10.1016/S0140-6736(23)00464-6
Repotrectinib	Augtyro	ROS1-positive nonsmall cell lung cancer	c-ros oncogene 1, receptor tyrosine kinase, **neurotrophic receptor tyrosine kinase 3** (trkC) & **ALK receptor tyrosine kinase** inhibition	FDA		DOI: 10.1158/1078-0432.CCR-19-2777
Rezafungin	Rezzayo	Candidemia and invasive candidiasis	Fungal 1,3-B-D-glucan synthase inhibition	FDA	P	DOI: 10.1016/S0140-6736(22)02324-8
Ritlecitinib	Litfulo	Severely patchy hair loss	**Janus kinase 3** & **Tec family** inhibition	FDA, EMA, MHRA	Br	DOI: 10.1016/S0140-6736(23)00222-2

(Continues)

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
						DOI: 10.1016/j.jaad.2022.11.005
Sotagliflozin	Inpefa	Heart failure (HFrEF AND HFpEF)	Sodium/glucose cotransporter 1 (SGLT1) & Sodium/glucose cotransporter 2 (SGLT2)inhibition	FDA		DOI: 10.1056/NEJMoa2030183
Sparsentan	Filspari	Proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression	ET_A receptor & AT_1 receptor antagonism	FDA	Acc	DOI: 10.1016/S0140-6736(23)02302-4
Sulbactam, durlobactam	Xacduro	Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Acinetobacter baumannii*-calcoaceticus complex	β lactam and β lactamase inhibitor combination	FDA	P, FT, qualified infectious disease product	DOI: 10.1016/S1473-3099(23)00184-6
Taurolidine, heparin	Defencath	Reduce the incidence of catheter-related bloodstream infections in adults with kidney failure receiving chronic haemodialysis through a central venous catheter	Antimicrobial plus anticoagulant	FDA	Limited population pathway for antibacterial and antifungal drugs (LPAD), qualified infectious disease product des., FT	DOI: 10.2215/CJN.0000000000000278
Triterpenes in dry extract from two species of birch bark	Filsuvez	Topical treatment of dystrophic and junctional wounds in epidermolysis bullosa		FDA, EMA		DOI: 10.1007/s40265-023-01935-z
Trofinetide	Daybue	Rett syndrome	Not fully determined, N-terminal tripeptide of IGF-1	FDA	P, FT	DOI: 10.1038/s41591-023-02398-1
Vadadustat	Vafseo	Symptomatic anaemia caused by CKD in people under dialysis	Prolyl hydroxylases inhibition	EMA, MHRA		DOI: 10.1093/ndt/gfad074
Vamorolone	Agamree	Duchenne muscular dystrophy	Glucocorticoid receptor (GR) activation	FDA	FT	DOI: 10.1371/journal.pmed.1003222

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Zavegepant	Zavzpret	Migraine	**CGRP receptor** antagonism	FDA		DOI:10.1016/S1474-4422(22)00517-8
Zilucoplan	Zilbrysq	Treatment of generalized myasthenia gravis in adults who are anti-acetylcholine receptor (AChR) antibody positive	**Complement C5** peptidase inhibition	FDA	P	DOI: 10.1016/S1474-4422(23)00080-7
Zuranolone	Zurzuvae	Postpartum depression	**$GABA_A$ receptor** positive allosteric modulation	FDA		DOI: 10.1038/s41386-023-01751-9 DOI: 10.1176/appi.ajp.20220785

FIC = first-in-class

Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track

treatment of intractable forms of cancer, typically unresponsive to current therapeutic options.

2 | "FIRST-IN-CLASS" (FIC) DRUGS

Ingenuity and innovation in pharmacology is best expressed by the successful clinical validation of novel molecular entities, which engage and modulate the function of their cognate therapeutic target(s) for the first time or fill a pathological functional void.

We therefore discuss briefly the most notable first-in-class and other noteworthy therapies (in 2023, there were 30 out of a total 70 novel drugs approved, listed in Box 4), defined as "drugs that modulate an as-yet unprecedented drug target or biological pathway" (Eder et al., 2014) or have a unique molecular mechanism of action. This category also includes drugs whose pharmacological profile only partially overlaps with that of previously approved drugs, for example, **momelotinib** and **lecanemab**. We succinctly describe the salient pharmacological characteristics of some noteworthy FICs and the main efficacy trial(s) that led to their approval. The brevity of this minireview does not allow a thorough discussion of possible advantageous characteristics of a novel drug relative to other drugs in its class, for example, a better adverse effect profile or a more user-friendly formulation (i.e., designation as "best-in-class").

3 | FIRST-IN-CLASS DRUGS BY THERAPEUTIC INDICATION AREAS

3.1 | Oncology

Multiple myeloma (MM) remains incurable, despite the wealth of treatments that have been developed in recent years targeting novel mechanisms, including anti-**CD38** antibodies, proteasome inhibitors or immunomodulatory agents. For patients with relapsed and refractory MM, despite having undergone treatment of all three of the above lines of therapy, three bispecific Abs have recently joined the MM arsenal (Firestone et al., 2023). **Teclistamab** is a humanized bispecific antibody directed against the **B cell maturation antigen** (BCMA) and **CD3e** receptors (approved by the FDA in 2022; Kang, 2022). Two more bispecific Abs followed on its heels this year. **Elranatamab** recognizes the same two antigens as teclistamab. **Talquetamab**, the first-in-class third Ab, approved in 2023, binds to G protein-coupled receptor family C group 5 member D (**GPRC5D**), an antigen expressed at low levels by normal human tissue but highly expressed on malignant plasma cells, at the same time engaging CD3e receptors, thus triggering T-cell–activated lysis of $GPRC5D^+$MM cells. The overall response rate (ORR) to elranatamab was 56%, but the duration of response (DOR), set at 12 months, was not reached during the trial, although the 6-month DOR and the 9-month DOR were 90% and 82%, respectively (Lesokhin et al., 2023). With talquetamab, the overall response rate (ORR) reached 73% and the DOR was 7.9 months (Chari et al., 2022). These results obtained Breakthrough Therapy and Accelerated Approval designations for both elranatamab and talquetamab, indicating the need for such innovation in MM. However, the shared frequent, serious or life-threatening adverse effects such as infections, fatal cytokine release syndrome and neurologic toxicity, require dosing for both via a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS), called the Tecvayli–Talvey REMS.

Repotrectinib is a novel, first-in-class oncological drug that addresses the puzzling problem of tumour refractoriness to treatment with tyrosine kinase inhibitors (TKIs) of **ALK**, **ROS1** and **TrkA-C receptors**, such as **crizotinib** and **entrectinib**, because solvent-front mutations secondary to rearrangements eventually confer resistance and are responsible for frequent relapse of the malignancies. For

example, 50% of crizotinib-resistant mutations, such as the frequent G2032R variant, are located in ROS1. Repotrectinib is a "next-generation" TKI, designed to effectively inhibit ROS1-G2032R as well as a variety of clinically important mutant kinase forms of ALK and TrkA-C, with IC_{50} values in the nM range. It therefore possesses a unique pharmacological profile (Drilon et al., 2018) responding to a dire unmet medical need. In a multicentre, open-label clinical trial (NCT03093116; Yun et al., 2020) in patients with locally advanced or metastatic $ROS1^{+}$non-small cell lung carcinoma, repotrectinib demonstrated an overall response rate of 79% in the kinase inhibitor-naïve group and of 38% in patients previously treated with a TKI, leading to its breakthrough and fast-track designation and approval in 2023.

The first-in-class pan AKT kinase inhibitor **capivasertib** was approved for use in breast cancer as a combination therapy with **fulvestrant**, an **oestrogen receptor** (ER) antagonist that also accelerates ER degradation (Osborne et al., 2004). Capivasertib is the first such **AKT kinase 1/2/3** antagonist to be approved by the FDA. The decisive phase III clinical trial (Turner et al., 2023) was conducted in patients with relapsed, progressive, ER^{+}/**HER2**$^{-}$ metastatic breast cancer, with tumours with or without alterations in AKT pathway-related proteins (**PIK3CA**, **AKT1** or **PTEN**). All patients were treated with fulvestrant and also received either placebo or capivasertib. Progression-free survival time in the capivasertib group was double compared with placebo (7.2 vs. 3.6 months), regardless of PIK3CA/AKT1/PTEN mutations. However, the FDA finally restricted its approval for use in patients that tested positive for one or more AKT pathway alterations, detected by an FDA-approved test.

Notch 1 overexpression and its proteolytic activation via γ-secretase, favour the proliferation and oncogenic growth of the soft tissue desmoid tumours (aggressive fibromatosis), underpinned by genetic mutations in genes encoding proteins of the Wnt–adenomatous polyposis coli (APC)/**β-catenin** pathway, such as *APC* and *CTNNB1*. These tumours are not metastatic but can cause significant damage of adjacent tissues, severe pain and adversely affect daily activity. No specific treatment exists and their management is problematic. While β/γ-secretase inhibitors in other fields, for example Alzheimer's disease, have not yet garnered approval (Imbimbo et al., 2023), the selective inhibition of γ-secretase by **nirogacestat** induced a significant objective response (41% vs. 8% with placebo) in adult patients with progressing desmoid tumours and almost doubled the number of patients that were event-free 2 years later (76% vs. 44% with placebo), however complete resolution was low (7% vs. 0% with placebo). Combined with low-grade adverse effects, this is both the first specific, systemic treatment that provides significant therapeutic benefit in this extremely rare tumour type (Gounder et al., 2023) as well as the first γ-secretase inhibitor to reach the clinic.

3.2 | Immune/inflammatory diseases

Bimekizumab is the first humanized monoclonal antibody to target simultaneously interleukin **IL-17A** and **IL-17F**, including **IL-17AF** heterodimers, thus offering a more complete inhibition of their deleterious effects in psoriasis than agents that target either cytokine alone. Bimekizumab has displayed efficacy and tolerability in 52-week trials (Reich et al., 2021; Ritchlin et al., 2023; Strober et al., 2023) in which it showed significant improvement on efficacy endpoints as compared with placebo, **adalimumab** and/or the IL-12/23 dual inhibitor, **ustekinumab**. In addition, a high proportion of patients who responded inadequately to adalimumab, ustekinumab and **secukinumab** and were switched to bimekizumab achieved significant skin plaque clearance (Kokolakis et al., 2022), thus securing its approval.

3.3 | Blood disorders

Two first-in-class **hypoxia-inducible factor prolyl hydroxylase** inhibitors (HIF-PHi) were authorized in 2023 by the EMA and the MHRA (**vadadustat**) and the FDA (**daprodustat**). These are also the first approved oral treatments for anaemia caused by chronic kidney disease for adults undergoing dialysis. They work by blocking the enzymes that degrade HIF-1α and HIF-2α, which are the critical inducers of erythropoiesis via **erythropoietin** production, and they thus stabilize both HIFs. Injectable erythropoietin and darbepoietin were the previously approved therapeutic options in the EU and the United States. However, small molecule oral HIF-PHi compounds have been approved for some years in both China and Japan. In clinical trials, both vadadustat and daprodustat have displayed efficacy and safety comparable to darbepoietin (Sarnak et al., 2023; Singh et al., 2022). There are important safety concerns pertaining to the use of erythropoietins in advanced kidney disease, linked to cardiovascular and thromboembolic events. These are equally evident with all the approved HIF-PHi compounds (Packer, 2023), including vadadustat and daprodustat (approx. in one in 10 patients), and have delayed their approval until this year and limited their authorization for use only by chronic kidney failure patients in dialysis. Daprodustat comes with an FDA-imposed black box warning for thrombotic vascular events, and similar language is employed for vadadustat by the EMA in the package leaflet. While the innovation and therapeutic progress that these drugs present in improving chronic kidney disease-linked anaemia and in maintaining a desired haemoglobin level is undisputed, ongoing clinical evaluation will further help us fully measure their therapeutic utility.

Several JAK inhibitors (JAKi) have been approved by both the FDA and the EMA in the past; however, JAKi are characterized by serious adverse effects including thrombosis, increases in cardiovascular sequelae and infections, leading the EMA in January 2023 to recommend measures to minimize the occurrence of these adverse effects (https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki). A first-in-class, novel JAK family inhibitor, momelotinib, was approved in 2023 by the FDA for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF caused by polycythaemia vera and essential thrombocythaemia, in adults with anaemia. Momelotinib has a unique pharmacological profile. In addition to **JAK1/2**, it can also inhibit **Activin A receptor type 1** (ACVR1). To this last action is

TABLE 2 Proteins/antibodies.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Bimekizumab	Bimzelx	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	**IL-17A** & **IL-17F**	FDA		DOI: 10.1016/S0140-6736(21)00125-2 DOI: 10.1136/ard-2023-224431 DOI: 10.1016/j.jaad.2023.04.063
Efbemalenograstim alfa	Ryzneuta	To decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated	**Granulocyte colony-stimulating factor receptor** activation	FDA		DOI: 10.1007/s00520-023-08176-6
Elranatamab	Elrexfio	Relapsed or refractory multiple myeloma who have received at least four prior lines of therapy	**CD3e** & **B cell maturation antigen** (BCMA)	FDA	P, Br, Acc	DOI: 10.1038/s41591-023-02528-9
Epcoritamab	Epkinly	Relapsed or refractory diffuse large B-cell lymphoma (not otherwise specified) and high-grade B-cell lymphoma after two or more lines of systemic therapy	**CD3e** & **CD20**	FDA, EMA, MHRA	P, Acc	DOI: 10.1111/cas.15996
Glofitamab	Columvi	Diffuse large B-cell lymphoma, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma after two or more lines of systemic therapy	**CD3e** & **CD20**	FDA, EMA, MHRA	P, FT, Acc	DOI: 10.1056/NEJMoa2206913
Lebrikizumab	Ebglyss	Moderate to severe atopic dermatitis in people over 12 years, unresponsive to topical treatment	**IL-13**	EMA		DOI: 10.1056/NEJMoa2206714
Lecanemab	Leqembi	Alzheimer's disease	**amyloid β**	FDA		DOI: 10.14283/jpad.2023.123
Mirikizumab	Omvoh	Ulcerative colitis	**IL-23A**	FDA, EMA, MHRA		DOI: 10.1124/jpet.122.001512
Nirsevimab	Beyfortus	Prevent respiratory syncytial virus (RSV) lower respiratory tract disease	RSV F-protein	FDA, EMA	FT	DOI: 10.1056/NEJMoa2110275

(Continues)

TABLE 2 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Pegzilarginase	Loargys	Treatment for arginase-1 deficiency	Arginine degradation	EMA, MHRA	O	DOI: 10.1002/jimd.12343
Prothrombin complex concentrate (human)	Balfaxar	Reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding or need for urgent surgery/invasive procedure	**Factor II** (prothrombin), **factor VII**, **factor IX** and **factor X**, as well as antithrombotic **protein C** and **protein S**	FDA		NCT04867837, NCT05523297
Retifanlimab	Zynyz	Metastatic or recurrent locally advanced Merkel cell carcinoma	**Programmed cell death 1 (cd279)**	FDA	P, FT	DOI: 10.3389/fonc.2022.935383
Rozanolixizumab	Rystiggo	Generalized myasthenia gravis in adults who are anti-acetylcholine receptor- or anti-muscle-specific tyrosine kinase antibody-positive	**Fc fragment of IgG receptor**	FDA	P	DOI: 10.1016/S1474-4422(23)00077-7
Talquetamab	Talvey	Adults with relapsed or refractory multiple myeloma who have received at least four prior therapies	**CD3e** & ***GPRC5D***	FDA, EMA, MHRA	P, Br, Acc	DOI: 10.1056/NEJMoa2204591
Tislelizumab	Tevimbra	Advanced, unresectable metastatic squamous oesophageal cancer, not responding to platinum-based medicines	**Programmed cell death 1 (CD279)**	EMA, MHRA		DOI: 10.1200/JCO.21.01926
Toripalimab	Loqtorzi	Recurrent or metastatic nasopharyngeal carcinoma when used together with or following other therapies	**Programmed cell death 1 (CD279)**	FDA	P, Br	DOI: 10.1200/JCO.20.02712

FIC = first-in-class

Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track

TABLE 3 Advanced therapy medicinal products (ATMP) and RNA.

Active ingredient	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial
Avacincaptad pegol	Izervay	Geographic atrophy secondary to age-related macular degeneration	Complement C5 inhibitor RNA aptamer	FDA		DOI: 10.1016/j.ophtha.2020.08.027 DOI: 10.1038/s41433-023-02497-w
Beremagene geperpavec	Vyjuvek	Treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.	HSV-1 collagen VIIA1	FDA	P, FT, regenerative medicine advanced therapy, rare Paediatric disease priority	DOI: 10.1056/NEJMoa2206663
Delandistrogene moxeparvovec	Elevidys	Treatment for children between 4 and 5 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene	AAVrh74-short dystrophin	FDA	Acc	DOI: 10.1002/ana.26755
Donislecel	Lantidra	Treatment of type 1 diabetes of adults unable to unable to approach target HbA1c because of current repeated episodes of severe hypoglycaemia despite intensive diabetes management and education	Allogeneic pancreatic islet cells	FDA		DOI: 10.7759/cureus.46912, NCT03791567
Eplontersen	Wainua	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults	Transthyretin-directed antisense oligonucleotide	FDA		NCT04136184
Exagamglogene autotemcel	Casgevy	Sickle cell disease of persons 12 years and older with recurrent vaso-occlusive crises	CRISPR/Cas9 technology-edited autologous haematopoietic stem cells to express HbF	FDA, MHRA	P, FT, regenerative medicine advanced therapy	DOI: 10.1056/NEJMoa2031054, NCT03745287
Lovotibeglogene autotemcel	Lyfgenia	Sickle cell disease of persons 12 years and older with recurrent vaso-occlusive crises	Lentiviral vector-modified autologous haematopoietic cells to express HbA^{T87Q}	FDA	P, FT, regenerative medicine advanced therapy	DOI: 10.1056/NEJMoa2117175
Nedosiran	Rivfloza	To lower urinary oxalate levels in patients 9 years and older with primary hyperoxaluria type 1 and relatively	Hepatic lactate dehydrogenase RNAi	FDA		NCT04042402 DOI: 10.1016/j.kint.2022.07.025

(Continues)

TABLE 3 (Continued)

Active ingredient	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial
		preserved kidney function				
Tofersen	Qalsody	Amyotrophic lateral sclerosis in adults who have a SOD1 gene mutation	Antisense oligo targeting mutant SOD1 mRNA	FDA	Acc	DOI: 10.1056/NEJMoa2204705
Valoctocogene roxaparvovec	Roctavian	Severe haemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU·dl^{-1}) without pre-existing antibodies to AAV 5	AAV5-**coagulation factor VIII** (deleted B domain)	FDA	P, Br, regenerative medicine advanced therapy	DOI: 10.1056/NEJMoa2211075
	Vowst	Prevention of recurrence of *Clostridioides difficile* (*C. difficile*) infection (CDI) in adults	Faecal microbiota, highly purified Firmicutes spores	FDA	P, Br	DOI: 10.1080/19490976.2023.2232137 DOI: 10.1093/cid/ciad639.

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Priority, Br = breakthrough, Acc = accelerated approval, FT = fast-track

attributed its ability, both preclinically (Asshoff et al., 2017) and in the clinic, to suppress blood **hepcidin** levels and to increase iron availability and markers of erythropoiesis, thus alleviating transfusion-requiring anaemia bouts (Oh et al., 2020); in contrast, other JAKi can either exacerbate or inadequately manage anaemia. In a phase III clinical trial leading to its approval (Verstovsek et al., 2023), momelotinib significantly improved clinical symptoms of MF, anaemia measures and spleen response, and displayed a favourable safety profile compared to **danazol**.

Haemophilia type A is an X-linked rare disease (1:5000) accounting for ~80% of all haemophilia cases and results from a congenital deficiency of functional **coagulation factor VIII**, leading to inadequate fibrin formation and protracted bleeding. Current treatments include exogenous factor VIII or **emicizumab**, but breakthrough bleeding necessitating transfusions still occur. In 2023, valoctocogene roxaparvovec (*Roctavian*) was approved as the first-in-class gene therapy for severe haemophilia type A. The gene encoding B-domain-deleted factor VIII protein was delivered via an AAV5 vector by a single infusion, allowing selective expression and production of factor VIII in hepatocytes. Four weeks later, the treatment decreased the rates of factor VIII concentrate use by patients by a remarkable 98.6%, of treatment-necessitating bleeding by 83.8% (Ozelo et al., 2022) and showed a sustained reduction of annualized bleeding rate 2 years post-treatment (Mahlangu et al., 2023).

Sickle cell disease (SCD) patients are burdened with haemolytic anaemia, vasculopathy and suffer from severely painful, debilitating vaso-occlusive events (VOE), all resulting in significantly reduced quality of life. Two novel, one-time-infusion, gene/cell therapies for SCD were approved by the FDA this year. Both involve the reintroduction in the patient of autologous cells, after their ex vivo manipulation to produce a form of haemoglobin (Hb), through two distinct methods. With lovotibeglogene autotemcel (*Lyfgenia*), CD34$^+$ haematopoietic stem cells obtained from the patient were transduced ex vivo to produce a mutant form of human β-globin (Hb β-A-T87Q) that "normalizes" erythrocyte shape ("anti-sickling Hb"), encoded by the replication-defective lentiviral vector BB305. The lentiviral integration aims at life-long, stable integration and expression. After successful engraftment (in all 35 patients), Hb β-A-T87Q was still being produced up to 36 months post-treatment and accounted for more than 40% of total Hb (Kanter et al., 2021). There was also a significant reduction of haemolysis and a complete resolution of severe VOE in all evaluated patients (vs. a median of 3.5 VOE/year prior to therapy). Of note, betibeglogene autotemcel (*Zynteglo*), a therapy approved for treatment of β-thalassemia by the FDA in 2022 and by the EMA in 2019 and since withdrawn by the latter, uses an identical vector (lentivirus and Hb gene sequence) as lovotibeglogene autotemcel, but the cells transduced by its protocol are different, due to different mobilization procedures for apheresis. So, the final gene-modified cells cannot be used alternatively in the two indications. Exagamglogene autotemcel (*Casgevy*), on the other hand, relies on the revolutionary CRISPR-Cas9 technology to edit the *BCL11A* erythroid-specific enhancer locus in autologous CD34$^+$ haematopoietic stem and progenitor cells to "reactivate" fetal haemoglobin gene expression and production, so that when transplanted back into the patient these cells produce fetal haemoglobin (HbF), at the same time exhibiting repressed expression of the sickle-cell Hb form. In preliminary results of the still ongoing phase 1/2/3 pivotal clinical trial (Frangoul et al., 2020; NCT03745287), 28/32 evaluated patients were VOE-free between months 6 and 18 post-therapy. A parallel trial is running in patients with β-thalassemia, with encouraging results, while the EMA panel has recommended

TABLE 4 Vaccines.

Active ingredient	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial
RSV A and RSV B prefusion proteins F	Abrysvo	Immunization of pregnant women or individuals 60 years of age and older	RSV	FDA, EMA, MHRA	P, FT, Acc	DOI: 10.1056/NEJMoa2216480
RSVPreF3 antigen	Arexvy	Prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older	RSV	FDA, EMA, MHRA	P, FT, Acc	DOI: 10.1056/NEJMoa2209604
	Cyfendus	Post-exposure prophylaxis of disease following suspected or confirmed exposure to *Bacillus anthracis* in persons 18 through 65 years of age when administered in conjunction with recommended antibacterial drugs	Anthrax	FDA		
VLA1553	Ixchiq	Prevention of disease in adults at increased risk of exposure to chikungunya virus	Live, weakened chikungunya virus	FDA	P, FT, Br	
	Penbraya	Prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W and Y in individuals 10 through 25 years of age	Pentavalent vaccine against meningococcal groups A, B, C, W and Y	FDA		
Dengue vaccine	Qdenga	Protection against dengue disease in persons aged 4 years and older	Attenuated versions of the 4 virus serotypes	EMA		

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it for a conditional marketing authorization (CMA) for both indications and the MHRA has already approved a CMA in both indications. This is the very first time that a therapy relying on CRISPR/Cas9 editing reaches clinical approval, creating a therapeutic landmark; however, patients will be monitored for >10 years for adverse effects including haematopoetic malignacies.

3.4 | Kidney, metabolic and endocrine disorders

A dual antagonist of **endothelin-1 type A receptor** (ET_A) and **angiotensin II type I** (AT_1) receptor, **sparsentan**, is a first-in-class single molecule with this unique pharmacological profile, approved by the FDA for the treatment of primary immunoglobulin A nephropathy (IgAN) in patients who are at risk of rapid disease progression, making it the first nonimmunosuppressive therapy approved for IgAN. The design of numerous "hybrid" dual inhibitors is actively pursued by medicinal chemists. Sparsentan was generated by successfully modifying a molecule which combines a chemical structure inspired by the AT_1 inhibitor **irbesartan** with a moiety known to convey ET receptor inhibition (doi.org/10.1021/jm058225d). A pivotal, two-year-long clinical trial comparing sparsentan with irbesartan demonstrated a slower rate of decline in estimated glomerular filtration rate (GFR) in the spansertan group, a sustained, significant reduction in proteinuria at 36 weeks with sparsentan (−40%) (vs. −4% in the irbesartan group) and a safety profile similar to that of irbesartan (Rovin et al., 2023).

Iptacopan is a first-in-class reversible, oral inhibitor of **complement factor B**, targeting the alternative pathway of complement. In a significant number of patients presenting paroxysmal nocturnal haemoglobinuria, therapies that target **complement C5** (either **eculizumab** or **ravulizumab**) effectively diminish haemolysis-related symptoms and need for transfusions, stabilize Hb levels, and are associated with an overall better quality of life. Some patients, however, remain anaemic and still need transfusions, despite receiving treatment with the C3 inhibitor pegcetacoplan (*Empaveli*). Of note, both anti-C5 therapies and pegcetacoplan are given by injection (Jang et al., 2022). Iptacopan is a small molecule complement factor B inhibitor that, in clinical trials (Zhang et al., 2024; NCT04820530),

BOX 1 Criteria used

Drug inclusion criteria:

1. The authorized drug is a new molecular entity or a new biological product, having never before received marketing approval by any of the three agencies and thus enters for the first time the market in either Europe or the United States.
2. If the product is a combination, it is either a novel combination of already approved drugs or at least one of its active ingredients is a novel compound that is approved for the first time.

Drug exclusion criteria:

1. The molecule is a new formulation of an already approved medicine.
2. It received authorization in 2023 for use in a new indication, whether in the same general field or in a different disease.
3. It is a generic or biosimilar version of a previously approved drug.
4. It is an updated version of an already approved vaccine (e.g., flu and Covid-19).

BOX 2 Expedited approval

EMA expedited approval:

a. Accelerated Authorization for innovative therapies of significant interest to the EU citizens and
b. Conditional Marketing Authorization for immediate market entry with continuing monitoring before regular approval.

MHRA expedited marketing authorization

a. 150-day assessment timeline for all high-quality full applications.
b. National conditional marketing authorization (CMA) to address unmet medical need in Great Britain, enabling immediate market entry with continuing monitoring before regular approval, and
c. Rolling review applications, allowing preassessment of a dossier, with the final phase of assessment through rolling review completed within 100 days.

FDA expedited approval:

a. Fast-track, dictated by unmet medical need, involving faster development process combined with rolling review.
b. Accelerated Approval, when a drug, based on surrogate endpoints of effectiveness, seems advantageous over existing therapeutic options; approval is granted on the strength of these surrogate or intermediate clinical endpoints.
c. Priority Review, where a drug, showing reliable evidence of improved effectiveness or safety, is allowed a shorter review time (6 months vs. 10 months), and
d. Breakthrough Therapy, when a drug shows significant improvement over available therapies based on a clinically significant endpoint; in this case, FDA commits rolling review process and guidance, enabling faster development of the product.

significantly decreased the urine protein-to-creatinine ratio, an effect maintained up to 6 months after the onset of treatment, lowered proteinuria and caused a sustained reduction in complement biomarkers (plasma Bb fragment, serum Wieslab markers, and urinary C5b-9), offering an additional option in this patient category.

Type 1 diabetes (T1D) patients have few options to manage the inability to produce **insulin**, relying mainly on injection of various forms of insulin and taking preprandial **pramlintide**. Those unable to control glycaemia through these treatments now have access to a revolutionary, first-in-class T1D cellular therapy. Donislecel (Alam et al., 2023; NCT03791567) is an allogeneic pancreatic islet preparation, necessitating immunosuppression to maintain the graft. Donislecel delivered insulin independence in eight of 10 patients who received it, meaning that they were able to maintain fasting glucose levels <140 mg·dl^{-1} more than three times per week and two-hour glucose postprandial values <180 mg·dl^{-1} more than four times per week. None of the patients outright rejected the graft up to 15-months post-therapy, while HbA1c ≤ 6.5% levels were reached by 19/21 in the absence of severe hypoglycaemic events, enabling them to finally reach euglycaemia.

A novel siRNA drug, nedosiran (*Revfloza*), was approved for treatment of primary hyperoxaluria (PH) type 1. PH types 1, 2 and 3 are rare diseases linked to defects in liver metabolic enzymes. In PH1 and 2, the defect lies in the inability of the liver to normally detoxify glyoxylate and thus, via its conversion by liver lactate dehydrogenase A (LDHA), excessive levels of oxalate are generated (Cochat & Rumsby, 2013). PH1 is the most common and devastating form of PH and can cause severe damage to the kidneys by the deposits of calcium oxalate, eventually leading to End-Stage Renal Disease. In the pivotal clinical trial on 35 PH1 patients (Baum et al., 2023), nedosiran siRNA, a first-in-class drug to target LDHA, given subcutaneously once monthly for 6 months, successfully targeted LDHA and displayed a sustained reduction in oxalate urinary excretion and in its plasma

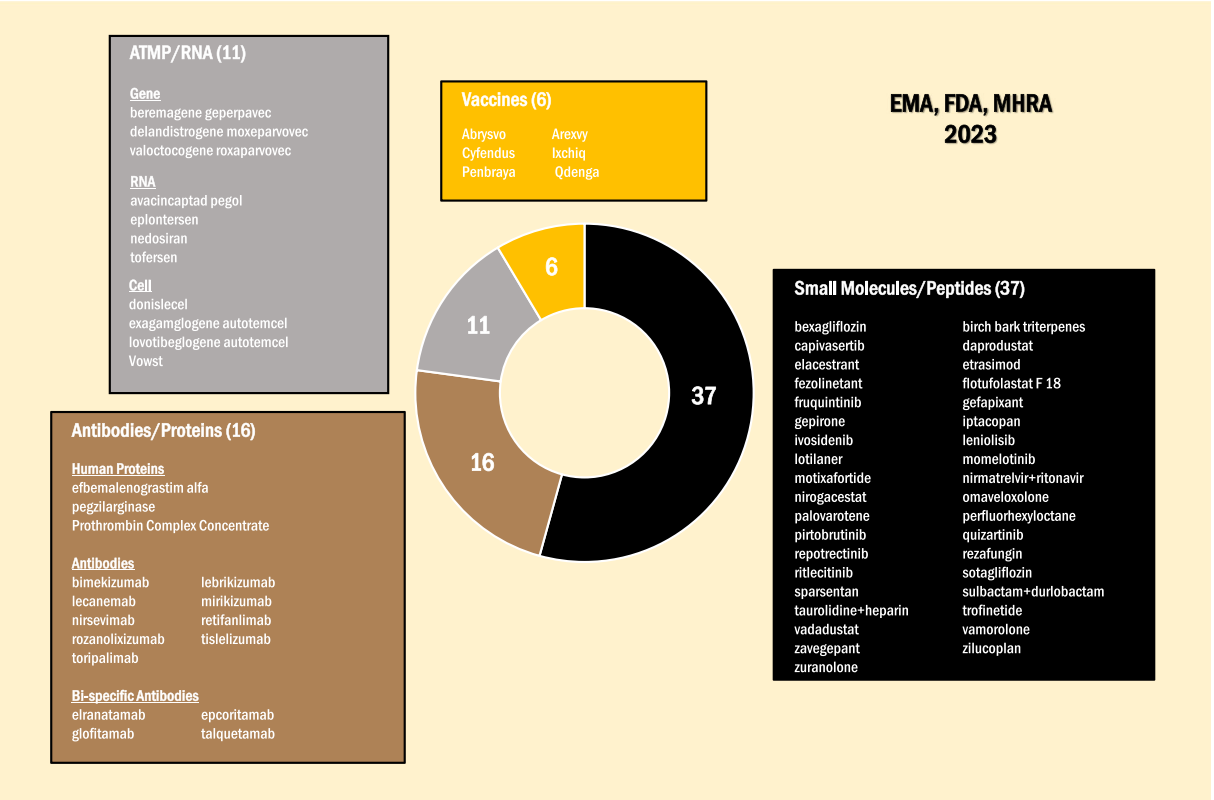

FIGURE 1 New drugs approved in 2023 by the European Medicines Agency (EMA), Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA), categorized by chemical/biological category.

levels. This led to approval of nedosiran to "lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2."

Another "first" is the approval of **fezolinetant** for women who experience menopausal hot flushes of medium or high severity, which can persist for years after menopause onset. The prevalence of hot flashes in perimenopausal and postmenopausal women is as high as 70%–80%, while a significant proportion (about 20%) report unbearable discomfort that can interfere with their daily activities (Stearns et al., 2002). Because many women who experience hot flushes also experience vaginal bleeding and have a medical history of thromboembolic disease, the current hormonal therapies are contraindicated. The only approved nonhormonal therapy in this indication (**paroxetine**, an anti-depressant SSRI) carries significant adverse effects. Fezolinetant, on the other hand, targets the overstimulation of the thermoregulatory centre in the hypothalamus. This is triggered by the declining levels of oestrogens at menopause, involves **kisspeptin–neurokinin B**–dynorphin (KNDy) neurons and depends on the excessive activity of the neuropeptide neurokinin B/**neurokinin 3 (NK_3) receptor** axis. Fezolinetant is a nonhormonal, selective, small molecule blocker of the NK_3 receptor in the hypothalamus and its innovative mode of action justified the priority review from the FDA. In the pivotal, 52-week-long clinical trial, it successfully reduced vasomotor symptoms manifesting as heat sensation, hot flushes and sweating, effects sustained through the length of the trial (DOI: 10.1016/S0140-6736(23)00085-5), while it displayed a mild toxicity profile.

3.5 | Infectious diseases

Two first-in-class, long-awaited Respiratory Syncytial Virus (RSV) vaccines were approved in quick succession by the EMA, the FDA and the MHRA in 2023, to prevent development of lower respiratory tract disease (LRTD). Approval applied to two sensitive populations viz. expecting mothers, providing protection to infants immediately after birth and the elderly persons aged 60 and older. RSV infection and its complications are the most frequent cause of acute LTRD and a leading cause of death in infants younger than 6 months (Li et al., 2022). Maternal vaccination, therefore, aims to effectively prevent infant hospitalization and mortality. Abrysvo is the first RSV vaccine to be authorized by the FDA for use during pregnancy, between 32 and 36 weeks of gestation. A one-shot i.m. injection of Abrysvo lowered the risk of LRTD by 34.7% and that of severe LRTD by 91.1% in infants within 90 days after birth, compared to placebo (Kampmann et al., 2023). Abrysvo was also approved in 2023 for prevention of LRTD in individuals 60 and older, who constitute a second population where RSV infection takes a disproportionate toll, showing 62% efficacy (Walsh et al., 2023). The second RSV vaccine, Arexvy, in the clinical trial that clinched its approval (Papi et al., 2023), significantly

FIGURE 2 New drugs approved in 2023 by the European Medicines Agency (EMA), Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA), by therapeutic area/category.

reduced the risk of developing RSV-associated LRTD by 82.6% in people 60 years old and older, regardless of RSV subtype or the presence of underlying coexisting conditions. For both vaccines, safety and serious adverse effect profiles were not statistically different than those of placebo.

The first-in-class combination of **nirmatrelvir** *and* **ritonavir**, known as paxlovid, finally received regular approval (converted from a conditional authorization) by both the EMA and the FDA, for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19. Nirmatrelvir is an inhibitor of the main viral protease but has poor pharmacokinetics, necessitating as a "booster" the co-administration of ritonavir, a drug normally used in the treatment of HIV infection, which is a strong inhibitor of the nirmatrelvir-metabolizing CYP enzymes. In a broad, randomized clinical trial (Najjar-Debbiny et al., 2023), paxlovid demonstrated its remarkable effectiveness (by approx. 90%) in reducing hospitalization

BOX 3 Orphan drugs (24)

Beremagene geperpavec	Prothrombin complex concentrate (human)
Delandistrogene moxeparvovec	Quizartinib
Epcoritamab	Retifanlimab
Exagamglogene autotemcel	Rozanolixizumab
Glofitamab	Talquetamab
Ivosidenib	Tofersen
Leniolisib	Toripalimab
Lovotibeglogene autotemcel	Trofinetide
Nedosiran	Valoctocogene roxaparvovec
Nirogacestat	Vamorolone
Omaveloxolone	Vowst
Pegzilarginase	Zilucoplan

BOX 4 First-in-class (30)

Abrysvo	Lotilaner
Arexvy	Lovotibeglogene autotemcel
Beremagene geperpavec	Momelotinib
Bimekizumab	Nedosiran
Capivasertib	Nirmatrelvir, ritonavir
Cyfendus	Nirogacestat
Daprodustat	Pegzilarginase
Delandistrogene moxeparvovec	Repotrectinib
Donislecel	Ritlecitinib
Exagamglogene autotemcel	Sparsentan
Fezolinetant	Talquetamab
Gefapixant	Tofersen
Iptacopan	Vadadustat
Ixchiq	Valoctocogene roxaparvovec
Lecanemab	Vamorolone

or death from any cause within 4 weeks in SARS-CoV2 infected individuals that had not been exposed to SARS-CoV2 previously and had not been vaccinated for COVID-19 and who were either 60 or older, regardless of prespecified risk factors for progression, or persons 18 and older who had prespecified risk factors for progression. Because ritonavir can alter the pharmacokinetics and possibly pharmacodynamics of other drugs that the patient may be taking, a thorough review and possible adjustment of these additional medications is recommended.

Clostridioides difficile infections (CDI) are characterized by a high relapse rate and constitute a particular threat associated with hospitalization. Therapies besides antibiotics comprise faecal transplantation, including the recently approved, rectally administered microbiota product named *Rebyota*. A related oral product, *Vowst*, was approved in 2023, as a three-day capsule treatment, containing live spores prepared from human faecal matter donated by appropriate individuals. The product works by outcompeting the disease-causing organism for growth. Up to 8 weeks after treatment, CDI recurrence in Vowst-treated participants was lower compared to placebo-treated participants (12.4% vs. 39.8%), demonstrating its capacity to significantly contain relapse of the infection (Jain et al., 2023).

3.6 | Nervous system disorders

After Bayer's abandonment of **eliapixant** during an ongoing phase II clinical trial due to an unfavourable risk–benefit balance (https://www.bayer.com/media/en-us/bayer-will-discontinue-phase-ii-development-candidate-eliapixant/), **gefapixant** is the first-in-class selective **P2X3 receptor** antagonist to gain EMA authorization, to treat refractory chronic cough or unexplained chronic cough (Chuang et al., 2023). Gefapixant is selective for the **ATP**-gated, trimeric ion channel receptors P2X3 and P2X2/3 (Richards et al., 2019). Blockade of its cognate receptors on respiratory afferent neurons modestly but significantly reduced the frequency of cough bouts per hour (by 61% vs. 55% reduction by placebo), while the only noteworthy drug-related adverse effect was a change in taste (ageusia, dysgeusia and hypogeusia; McGarvey et al., 2023).

Lecanemab has made a huge news splash in 2023, as it is the only **amyloid-β** (Aβ)-targeting antibody that has successfully shown a moderate but unequivocal clinical benefit, in delaying mental/cognitive decline in Alzheimer's disease patients (Cohen et al., 2023; van Dyck et al., 2022). In an 18-month-long trial, lecanemab treatment was started at an early stage of the disease and was able to reduce mental/cognitive decline, as measured by the cognitive CDR-SB score, by approximately 25% compared with placebo, from a decline of 1.66 with placebo to a decline of 1.21 with lecanemab (van Dyck et al., 2022). In addition, patients receiving lecanemab displayed 49% and 56% less decline, respectively, in the quality of life scores EQ-5D-5L and QOL-AD (Cohen et al., 2023). Lecanemab is characterized by high selectivity for soluble aggregated species of Aβ relatively to monomeric amyloid, having moderate selectivity over fibrillar amyloid. This selectivity profile is considered distinct from that of other anti-Aβ antibodies (hence our FIC designation) and is thought to provide an advantage, allowing lecanemab to selectively target the most pathogenic Aβ species (McDade et al., 2022; van Dyck et al., 2022), thus explaining its unique clinical efficacy. Unfortunately, severe adverse effects, including amyloid-related imaging abnormalities with oedema or effusions were significantly more likely in the lecanemab group (van Dyck et al., 2022), requiring very careful future monitoring of the patients receiving this therapy. Multiple ongoing studies will provide additional data on its long-term efficacy and toxicity.

3.7 | Other indications

Ritlecitinib was approved for treatment of severely patchy hair loss (King et al., 2023). It inhibits **Janus kinase 3** (JAK3) selectively by binding irreversibly to its Cys909 residue, while it can also inactivate members of the hepatocellular carcinoma (**TEC**) kinase family. In contrast, previously approved JAK inhibitors display no selectivity (**baricitinib** inhibits **JAK1,2&3**) or have more important inhibitory activity towards JAK1&2 (**upadacitinib**) or JAK2&3 (**tofacitinib**). The metabolic effects of these inhibitors, comprising upregulation of liver enzymes and **cholesterol**, as well as their haematological adverse effects (anaemia, thrombocytopenia) may be related to their nonselective profile (Ramírez-Marín & Tosti, 2022). Ritlecitinib did not elicit serious adverse effects in its parallel clinical trials for rheumatoid arthritis (Robinson et al., 2020) or nonsegmental vitiligo (Ezzedine et al., 2023), perhaps because of its unique pharmacological profile, and may overall be better tolerated than previously approved JAK family inhibitors.

3.8 | Rare/genetic diseases

Vamorolone (*Agamree*), approved for the treatment of the debilitating Duchenne Muscular Dystrophy (DMD) in young boys at least 2 years old, is considered an FIC, as the first approved "dissociative steroid": while, as is expected from steroid drugs, it displays anti-inflammatory activity via inhibition of NF-kB, a mechanism involved in the pathology of DMD, it fails to induce the characteristic steroidal gene expression-modulating activities. This is thought to be the basis of its inability, seen in preclinical studies, to elicit the classical steroidal bone morbidities and muscle atrophy. In addition, in contrast to many corticosteroids, which are agonists at the **mineralocorticoid receptor**, resulting in increases in water retention and blood pressure, vamorolone inhibits the mineralocorticoid receptor. In a pivotal 24-week study in which it was compared to **prednisone** (Guglieri et al., 2022), vamorolone demonstrated a favourable safety and tolerability profile relatively to the standard-of-care corticosteroid, which may be translated in a potentially better quality-of-life profile during the long-term treatment required to mitigate DMD symptoms.

Delandistrogene moxeparvovec (*Elevidys*) is a gene therapy approved for the treatment of DMD (Zaidman et al., 2023; NCT04626674). It consists of a rAAV rhesus isolate serotype 74 (rAAVrh74) vector, chosen for its tropism to the muscle and low prevalence of pre-existing immunity, expressing a recombinant micro-dystrophin protein (137 kDa vs. 427 kDa of the full-length) and is given as a single intravenous infusion. One year later, patients demonstrated stabilized or improved North Star Ambulatory Assessment total scores, while sustained expression of the recombinant mini-dystrophin was evident up to 2 years later (Mendell et al., 2023). Delandistrogene moxeparvovec received an accelerated approval based on the increased expression of the surrogate endpoint (expression of micro-dystrophin protein) observed in Elevidys-treated DMD individuals aged 4 to 5 years, allowing the FDA to conclude that these data are reasonably likely to predict clinical benefit in individuals, and thus warrant its approval.

Tofersen (*Qalsody*), administered intrathecally, aims at an ultra-small subset of ALS patients (less than 500 patients in the United States) harbouring a mutant form of superoxide dismutase 1 (SOD1), which misfolds and becomes toxic to neurons. It is a "first-in-class" anti-sense oligonucleotide targeting SOD1. Tofersen's accelerated approval was based on the lower levels of SOD1 in the patients' cerebrospinal fluid and on the reduction in their plasma of neurofilament light chains (NfL). The presence in the blood reflects axonal injury and neurodegeneration and which is therefore considered a reliable biomarker, predictive of the drug's effectiveness (Miller et al., 2022). The ongoing phase III trial may provide further data necessary for regular approval by the FDA.

Beremagene geperpavec (*B-VEC*) is a first-in-class gene-therapy approved for Dystrophic epidermolysis bullosa, a rare, genetic, blistering skin disease caused by mutations in *COL7A1*, which encodes type VII collagen (C7). B-VEC is a topical herpes simplex virus type 1 (HSV-1)-based gene therapy designed to deliver C7 (Guide et al., 2022), and therefore to restore levels of a "healthy" protein. At both 3 and 6 months post-treatment, exposure of primary wound pairs to B-VEC resulted in a remarkable ~70% complete wound healing (vs. ~22% with placebo), gaining approval with Orphan Drug, fast-track, Regenerative Medicine Advanced Therapy and Priority Review designations.

Velmanase alfa (*Lamzede*) is a first-in-class enzyme replacement therapy, reintroducing the α-mannosidase enzyme in individuals affected by this very rare genetic disease ($1/10^5$) called alpha-mannosidosis, which leads to dysfunction in lysosomal storage, resulting in the accumulation of mannose-rich oligosaccharides in many organ systems and tissues and wide-spreading, eventually debilitating symptoms. Up to now, eligible individuals could receive allogeneic haematopoietic stem cell transplantation, a risky intervention with variable results. In the pivotal 52-week trial, patients who received weekly infusions of valmenase for 52 weeks showed significantly improved overall mobility and muscle strength scores (Borgwardt et al., 2018), with better improvement scores observed when treatment is initiated in childhood (Guffon et al., 2023).

3.9 | Other noteworthy approvals

Three novel drugs targeting the C5 component of the complement system were approved in 2023. Because C5 is already targeted by an approved antibody drug (ravulizumab, in 2018), we cannot include them in the "first-in-class" category; however, we wanted to emphasize that each one uses a somewhat different mechanism to reduce C5 activity: pozelimab is a neutralizing antibody, zilucoplan is a peptide, while **avacincaptad** is an aptamer. Pozelimab is the first treatment ("first-in-disease") to be approved in CHAPLE disease, a very rare, life-threatening disease, that develops because the protein product of the mutated C55 gene cannot limit the activity of the complement system, which as a consequence becomes over-activated. This damages the integrity of vascular wall cells in blood and lymphatic vessels associated with the upper digestive tract and results in protein extravasation and enteropathy that can be fatal. In a necessarily very small clinical trial (10 patients), pozelimab stabilized serum albumin levels (a biomarker of disease) and

resulted in fewer hospitalizations (NCT04209634). Zilucoplan, on the other hand, is a first-in-class synthetic, macrocyclic peptide, which reduces the activation of the complement classical, alternative, or lectin pathways by blocking the generation of activated C5a and C5b from C5. It was authorized for use in generalized myasthenia gravis (Howard et al., 2023). The third C5 inhibitor, avacincaptad pegol, is a pegylated RNA aptamer, that also blocks the activation of complement C5. Because the complement pathway is considered to be implicated in the pathogenesis of age-related macular degeneration (AMD), avacincaptad was approved for topical treatment of geographic atrophy secondary to age-related macular degeneration (Jaffe et al., 2021; Patel et al., 2023). Of note, the complement pathway is implicated in the pathogenesis of a large array of immune and inflammatory disorders and genetic diseases (Morgan & Harris, 2015), so that complement-targeting drugs have either been approved or currently being investigated in additional complement-mediated diseases, and therefore more such approvals should be expected in the near future.

Omaveloxolone (*Skyclarys*) is the second approved compound to target the inducible transcription factor **nuclear factor erythroid 2-related factor 2** (NRF2) pathway. NRF2 has an overall protective role in conditions associated with oxidative stress and inflammation, because it regulates hundreds of genes encoding proteins controlling homeostatic functions. **Kelch-like ECH-associated protein 1** (KEAP1) associates with NRF2 and limits its activity; electrophilic molecules targeting cysteine 151 in KEAP1 can therefore act as "NRF2 activators." One such compound, **dimethyl fumarate** (DMF), has already been authorised for the treatment of remitting–relapsing multiple sclerosis and psoriasis. However, there is still some confusion as to the critical mechanism by which DMF is effective in these disease settings, because its anti-inflammatory effects in a preclinical model of MS (acute inflammatory experimental autoimmune encephalomyelitis) manifests in both NRF2-proficient and NRF2-deficient animals (Dinkova-Kostova & Copple, 2023). Of the KEAP1-targeting molecules currently under clinical investigation, the first one to secure FDA approval via fast-track, priority review and rare paediatric disease modality is omaveloxolone. It was designated an orphan drug by the FDA and the EMA, and has been approved only by the FDA. It is the first ever molecule to be approved for the alleviation of symptoms of Friedreich ataxia (Lynch et al., 2021), a rare, fatal, genetic neurogenerative disease, which also has additional cardiac and endocrine manifestations (Keita et al., 2022). Omaveloxolone improved the neurological function of the patients, was well tolerated and displayed a mild toxicity profile. Because the NRF2-KEAP1 pathway is deregulated in a number of diseases ranging from cancer to psoriasis, the outcome of current clinical trials with NRF2 activators, including omaveloxolone, will be of great interest in the next few years.

4 | OVERALL CONCLUSIONS

In 2023, there was a notable number of approvals of innovative drugs in both Europe and the United States, widening the spectrum of available therapeutics. The majority of these approved treatments were groundbreaking, focusing on rare diseases or challenging conditions with limited effective therapies available. However, it should be noted there were few approvals for additional drugs to treat, among others, mental disorders, cardiovascular diseases or chronic pain, all of which are conditions that affect large proportions of the world's population.

This year marked the introduction of the first-ever CRISPR-Cas9 gene modification cell therapy for severe sickle-cell anaemia, exagamglogene autotemcel (aka "exa-cel"). Additionally, the first anti-β-amyloid antibody, lecanemab, to show significant but modest improvements in slowing cognitive impairment in Alzheimer's disease was approved. Approvals for novel small noncoding oligonucleotide RNA therapeutics also continued throughout 2023.

Looking ahead to 2024, there is great anticipation, especially because final clinical evaluations for long-awaited therapies targeting diseases with significant global prevalence are nearing approval decisions by the end of the coming year. These include CRISPR-Cas9 PCSK9 base-editing for atherosclerosis, the long-term efficacy assessment of a novel malaria vaccine, and a CMV vector-based vaccine to prevent HIV infection.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021).

AUTHOR CONTRIBUTIONS

A. Papapetropoulos and S. Topouzis wrote the original draft; the rest of the authors reviewed and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

PF is the founder and CEO of Pharmahungary Group, a group of R&D companies holding patents on cardioprotective oligonucleotides and providing R&D services for drug development. Dr. Martemyanov is a consultant and a stakeholder at Evodenovo, Inc., and Blueshield Therapeutics, Inc., companies commercializing development of novel opioid therapeutic strategies and antidepressants. The other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

N/A-Review

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