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MINI-REVIEW

Novel drugs approved by the EMA, the FDA and the MHRA in 2025: A year in review

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Abstract

In the 2025 novel drug mini-review, one can take a full measure of the ingenuity that underlies current drug design and development, despite the year's smaller harvest (46 novel drugs) compared to 2024 (53) and 2023 (70). 54% of the novel drugs are first-in-class (FIC). The emphasis on proteins/antibodies is maintained (~25% novel drugs in 2025), an industry trend that does not seem to abate. Fewer than half of the novel medicines address major or common disorders. Among the FIC drugs, it is worth mentioning the $Na_v1.8$ channel inhibitor suzetrigine, the first non-opioid approved to palliate acute pain; the first positive allosteric modulator of transient receptor potential melastatin 8 (TRPM8), acoltremon, that increases basal tear production in dry eye disease, a globally common disorder; lerodalcibep, a 'third generation' adnectin inhibitor of the protease Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) to treat elevated LDL-c; and zoliflodacin and gepotidacin, both innovatively targeting bacterial topoisomerases to treat uncomplicated urinary tract infections. Most of the approved medicines target unmet medical need areas and/or orphan indications (the latter alone accounting for 41% of the 2025 novel drugs) by applying imaginative approaches. These approaches include: the combination of *two* FIC drugs, the RAF/MEK clamp avutometinib paired with the FAK/Pyk2 inhibitor defactinib, to block more efficiently

Abbreviations: ADC, antibody–drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; APRIL, A Proliferation-Inducing Ligand; ASO, antisense oligonucleotide; BTK, Bruton's tyrosine kinase; CSU, Chronic spontaneous urticaria; DEB, dystrophic epidermolysis bullosa; DED, dry eye disease; DOR, duration of response; DPP1, dipeptidyl peptidase 1; EMA, European Medicines Agency; Fc, fragment crystallizable; FDA, U.S. Food and Drug Administration; FIC, first-in-class; FXII, coagulation factor XII; FXIIa, activated coagulation factor XII; HAE, hereditary angioedema; HER2, human epidermal growth factor receptor 2; HPV, human papillomavirus; IPF, idiopathic pulmonary fibrosis; IgA, immunoglobulin A; IgAN, IgA nephropathy; IgG, immunoglobulin G; KRAS, Kirsten rat sarcoma virus; LDL-c, low-density lipoprotein cholesterol; LGSOC, low-grade serous ovarian cancer; MASH, metabolic-associated steatohepatitis; MAb, monoclonal antibody; MHRA, Medicines and Healthcare Products Regulatory Agency; NPC, nasopharyngeal carcinoma; NSCLC, non–small cell lung cancer; NSP, neutrophil serine protease; ORR, objective response rate; OS, overall survival; PCSK9, proprotein convertase subtilisin/kexin type 9; PFS, progression-free survival; QOL, quality of life; RNAi, RNA interference; RRP, recurrent respiratory papillomatosis; TK2, Thymidine kinase 2; TK2d, Thymidine kinase 2 deficiency; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor; TRPM8, transient receptor potential melastatin 8; mtDNA, mitochondrial DNA; siRNA, small interfering RNA; uUTI, uncomplicated urinary tract infection; VMS, vasoomotor symptoms.

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the RAS–RAF–MEK–ERK/FAK oncogenic pathway in low-grade serous ovarian cancer; fitusiran, the first RNAi therapy for haemophilia, targeting for the first time the production of the natural anticoagulant anti-thrombin in the liver; and brensocatib, which attenuates the activation of downstream neutrophil proteases by inhibiting the protease DPP1, thereby preventing lung tissue destruction in bronchiectasis. The landscape of novel drugs approved in 2025 reveals that pharmaceutical innovation continues to advance through FIC mechanisms, sophisticated therapeutic approaches, and a strong focus on unmet medical need.

KEYWORDS
drug development, EMA, FDA, first-in-class, mechanism of action, MHRA, novel drug approvals

1 | INTRODUCTION

This is the third yearly mini-review aiming to cover, in a reader-friendly form, the exciting pharmacology of the novel drugs that were approved in the preceding calendar year by three major drug regulatory authorities. Forty-six (46) novel molecular entities (for inclusion/exclusion criteria, please see Box 1 and Papapetropoulos et al., 2024) were authorised by the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2025, fewer than those approved in 2023 (70) and in 2024 (53). It would be, as yet, too early to say whether the seemingly declining number in this brief 3-year period is representative of a longer-term trend. It should be noted that the novelty required for inclusion in our review obscures the fact that in the same period, previously approved drugs, with known safety characteristics, frequently obtain landmark extensions of their use and contribute significantly to the therapeutic arsenal. This is exemplified this year by two drugs reviewed in the section 'Other Notable Approvals'. In 2025, semaglutide joined a very restricted group of therapeutics with efficacy in metabolic-associated steatohepatitis (MASH); in addition, an oral (pill) form of semaglutide obtained FDA authorisation for use to reduce the risk of major adverse cardiovascular events (MACE) in high-risk diabetics and also for weight loss in overweight or obese non-diabetic patients. Another drug, aceclidine, approved decades ago for the treatment of glaucoma, was approved to treat presbyopia, a rare pharmacological option worth noting. A factor we also have to consider in looking at the above numbers is that one component of novelty is the capacity to target for the first time a molecular entity, something that is increasingly more difficult in 2025: after the 'big bang' in molecular biology and genetics in the 1990s and 2000s revealed many new targetable molecular pathogenic players, these have since been mined to a significant extent. As presented previously in Papapetropoulos et al. (2024) and Topouzis et al. (2025), there are specific sites and databases consulted for the elaboration of this mini-review, the criteria allowing inclusion of a newly approved medicine in the list of 'novel' drugs, as well as those that define 'first-in-class' (FIC) drugs.

One major measure of general advances in pharmacology is the ability to translate novel molecular concepts into clinically approved medicines, particularly those FIC drugs that achieve their therapeutic effect by targeting previously unaddressed pathological mechanisms or by modifying the function of a known target in a novel way. In this context, we briefly comment on a selection of such FIC therapeutic agents approved in 2025. Of the 46 novel medicines approved in 2025, 25 met these criteria (listed in Box 2; 54% of all 2025 novel drugs), encompassing compounds that intervene in molecular targets or pathways not previously exploited in drug development or that operate via unprecedented molecular modes of action (Eder et al., 2014). The latter criterion also applies to drugs that share only limited mechanistic similarity with earlier therapies, including the 2025 novel tyrosine kinase inhibitors we review herein. We

BOX 1 Criteria used.

Drug inclusion criteria:

1. The authorised 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 authorisation in the past year 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 First-in-class (25).

Acoltremon	Avutometinib and defactinib
Brensocatib	Donidalorsen
Dordaviprone	Doxecitine and doxribtimine
Elamipretide	Elinzanetant
Fitusiran	Garadacimab
Gepotidacin	Lerodalcibep
Nerandomilast	Penpulimab
Prademagene zamikeracel	Recombinant Chikungunya vaccine
Revakinagene taroretcel	Sevabertinib
Sibeprenlimab	Sunvozertinib
Suzetrigine	Telisotuzumab
Zoliflodacin	Zongertinib
Zopapogene imadenovec	

summarise the distinct pharmacological attributes of selected agents within the FIC group and highlight the pivotal clinical studies that formed the basis for their approval. Given the constrained scope of this mini-review, we do not explore in detail whether these agents offer advantages over existing treatments in terms of safety, tolerability or formulation, considerations often associated with 'best-in-class' status.

The past year (2025) has seen the clinical validation of novel targets, including selective **$Na_v1.8$ sodium channel** inhibition by the non-opioid analgesic suzetrigine and blockade of Factor XIIa by garadacimab for the management of hereditary angioedema. To modulate already exploited therapeutic targets, many new drugs also rely on a unique mode of interaction with, or modification of, a known, validated target, which differs from that of previously approved drugs and might differentiate their efficacy and/or toxicity. This year, such textbook examples are the prekallikrein mRNA-targeting antisense oligonucleotide (ASO) donidalorsen or the **PD-1** directed, low FcR-binding MAb, penpulimab.

Below we summarise the main characteristics, the pivotal clinical data and the unmet medical need that the 2025 FIC drugs address.

2 | FIRST-IN-CLASS (FIC) DRUGS OF 2025

2.1 | Oncology

2.1.1 | **Defactinib** + **avutometinib** combination

In any given year, it is rare that a combination of two novel drugs seeks and obtains marketing authorisation. In 2025, the combination of defactinib with avutomenib has been licensed by the FDA for the treatment of low-grade serous ovarian cancer (LGSOC), a rare gynaecologic cancer that accounts for <10% of epithelial ovarian cancer cases. LGSOC has a molecular, histologic and clinical profile distinct from the most common histological subtype, high-grade serous ovarian cancer (HGSOC) and is generally less sensitive than HGCOC to chemotherapy, which routinely follows primary resection (Banerjee, Van Nieuwenhuysen, et al., 2025; Grisham, Praiss, et al., 2025) while recurrence after treatment is highly probable. Because LGSOC is thought to be driven by mutations resulting in hyperactivation of the mitogen-activated protein kinase (**MAPK**) pathway (**RAS**–**RAF**–MEK–**ERK**), the most common of which are Kirsten rat sarcoma virus homologue (*KRAS*) mutations, MEK inhibitors (trametinib and binimetinib) have been clinically tested in this indication, but the overall response rates to them were very low, about 26% (trametinib) and 16% (binimetinib), a situation compounded by the drugs' toxicity that obliged many of the patients to discontinue therapy (Banerjee, Van Nieuwenhuysen, et al., 2025; Grisham, Praiss, et al., 2025).

Avutometinib is a FIC rapidly accelerated fibrosarcoma (RAF)/MEK clamp, which not only inhibits MEK but is also able to block the compensatory reactivation of MEK by upstream RAF that occurs with MEK inhibition alone (Gonzalez-Del Pino et al., 2021; Ishii et al., 2013) and forms dominant negative RAF–MEK complexes that prevent the phosphorylation of MEK by **A-Raf**, **B-Raf** and **C-Raf** (Ishii et al., 2013; Lito et al., 2014). However, even this, more efficient 'clamp' inhibition of the MAPK pathway by avutometinib leads to the parallel activation of focal adhesion kinase (**FAK**), a well-characterised key adaptive resistance mechanism to MAPK inhibition (Dawson et al., 2021; Lubrano et al., 2025). The intracellular tyrosine kinase FAK is a critical mediator of signal transduction downstream of integrins and growth factor receptors, which together drive cancer cell survival, proliferation and migration. Overall, FAK overexpression in many tumours correlates with poor prognosis (Lubrano et al., 2025). Notably, it has been shown, in the context of other tumour types and in tumours in which the RAS–RAF–MEK–ERK oncogenic signalling is also implicated, such as in melanoma, that therapeutic targeting by inhibitors of B-Raf or MEK leads to the adaptive activation of FAK, a response mechanistically linked with acquisition of resistance by the tumour (Lubrano et al., 2025; Pang et al., 2021). Defactinib is a FIC ATP-competitive inhibitor that selectively and potently (at nM concentrations) targets the kinase activity of both FAK and its closely related (60% homology) family member, Protein Tyrosine Kinase 2-beta (**Pyk2**), inhibiting phosphorylation of FAK at Tyr 397 (Kang et al., 2013).

Defactinib also has synergy with avutometinib in the context of other cancer types, such as NSCLC and ovarian cancer (Kang et al., 2013). Addition of defactinib to avutometinib in a preclinical model of LGSOC resulted in greater inhibition of tumour growth compared to avutometinib alone (McNamara et al., 2024) and provided the rationale of a Phase I study in this indication, in which combination of avutometinib with defactinib demonstrated promising efficacy and tolerability in LGSOC patients. The ensuing Phase II, open-label, multicentre trial in LGSOC (ENGOT-ov60/GOG-3052/RAMP 201; NCT04625270) was designed to assess the efficacy and safety of avutometinib + defactinib. The trial included 57 adult patients with recurrent LGSOC who had received at least one prior systemic therapy, including a platinum-based regimen, and harboured KRAS

mutations, determined upon biopsy testing. Patients were treated with the avutometinib + defactinib combination until disease progression or unacceptable toxicity were observed. The major efficacy outcome measure, objective response rate (ORR), in the KRAS-mutated cohort was an impressive 44%, while the duration of response (DOR) ranged between 3.3 and 31.1 months (Banerjee, Van Nieuwenhuysen, et al., 2025) and the median progression-free survival (PFS) was 22.0 months. The most frequent grade ≥3 treatment-related adverse events (AEs) were elevated creatine phosphokinase (24%), diarrhoea (8%) and anaemia (5%). Toxicity led to discontinuation of treatment by 10% of the patients. However, these results strongly supported the use of the avutometinib + defactinib combination as a potential standard of care for women with recurrent LGSOC and led to the design of a Phase III LGSOC study where the novel combination will be tested against the investigator's treatment of choice (Grisham, Monk, et al., 2025); it will therefore provide valuable data regarding possible advantages of this new treatment. The dual targeting by a RAF/MEK clamp inhibitor and a FAK inhibitor appears to be an attractive strategy in other solid tumours (Riordan et al., 2025; Yoshimura et al., 2024). In the near future, ongoing clinical studies will help oncologists determine whether this combination can be used as a tumour-agnostic therapeutic approach for patients with additional cancers with an overactivated RAS–RAF–MEK–ERK pathway.

2.1.2 | Dordaviprone

The presence of the Histone 3 (H3) K27M mutation (H3K27M) is a dominant negative gain-of-function mutation that leads to suppression of histone methyltransferase activity and a global reduction in trimethylation of H3 at residue 27 (H3 K27me3). When present in glioma, it is associated with dismal prognosis: 1-year OS rate of these patients is approximately 60%. The standard of care remains radiation therapy, due to the impossibility of resection without serious damage to the patient. H3K27M is seen in up to 70% of paediatric cases of diffuse intrinsic pontine glioma (DIPG) and in 60% of adult patients with diffuse midline glioma (DMG). H3 K27M-mutant DMG is classified by the World Health Organisation (WHO) as a distinct form of Grade IV glioma and is characterised by global loss of H3 K27 trimethylation (H3 K27me3-loss) (Arrillaga-Romany, Gardner, et al., 2024).

Few recently authorised drugs, if any, have a pharmacological profile that can match the unique nature of dordaviprone. Dordaviprone initially emerged as an inducer of TNF-Related Apoptosis-Inducing Ligand (TRAIL) that elicits death in cancer cells (Allen et al., 2024). Dordaviprone was later shown to induce endoplasmic reticulum stress response or integrated stress response in various cancer types, followed by ATF4 activation, expression of the death receptor **DR5** and finally tumour cell death (Kline et al., 2016; Ma et al., 2019). Dordaviprone was also identified as an allosteric activator of caseinolytic protease (**clpP**), a serine protease found in the mitochondrial matrix (Goncalves et al., 2025; Ishizawa et al., 2019) whose (hyper)activation can inhibit the mitochondrial electron transport chain (Nouri et al., 2020). Finally, dordaviprone was shown to also act as a competitive antagonist of **$D_{2/3}$ dopamine receptors**, whose activation has been described to support cancer-type dependent cell growth and survival (Kline et al., 2018; Ali et al., 2022; Kline et al., 2018). All these activities are compatible with an anti-cancer potential of dordaviprone. In initial clinical studies, it was established that oral administration of dordaviprone in cancer patients achieved good systemic distribution and levels, without any reports of dose-limiting toxicities (Odia et al., 2024). In a subsequent Phase II study in patients with glioblastoma, the only patient that achieved a durable, radiographic response to dordaviprone monotherapy incidentally harboured the H3 K27M mutation. This fortuitous observation led, ultimately, to the clinical trial and approval of dordaviprone in H3 K27me3 mutant glioma (Arrillaga-Romany, Gardner, et al., 2024).

The efficacy of dordaviprone monotherapy by mouth was evaluated in four non-randomised clinical trials (NCT02525692, NCT03295396, NCT03416530 and NCT05392374) or one expanded access protocol (NCT03134131) (Arrillaga-Romany, Gardner, et al., 2024), in 50 adult (n = 46) and paediatric (n = 4) patients with recurrent H3 K27M-mutant DMG, despite treatment with standard-of-care radiotherapy. Patients with diffuse intrinsic pontine glioma (DIPG), primary spinal tumours, atypical histologies or cerebrospinal fluid dissemination were excluded. The major efficacy outcome measure, ORR, was evaluated by blinded independent central review to reach 22%. A secondary outcome, DOR was 10.3 months. Among the 11 patients with objective responses, 73% had a DOR of ≥6 months and 27% had a DOR of ≥12 months. On the strength of the Phase II studies and the excellent toxicity profile (Odia et al., 2024) dordaviprone was granted approval, while a Phase III trial has been initiated and is on-going in newly diagnosed patients with H3 K27M-mutant DMG (NCT05580562; Arrillaga-Romany, Gardner, et al., 2024). Dordaviprone therefore offers a much-needed therapeutic option in this very challenging indication.

2.1.3 | Penpulimab

The engineering of the fragment crystallizable (Fc) region of therapeutic antibodies can modulate at will the anti-tumour cytotoxic effector mechanisms mediated by the MAb's Fc domain, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP) (van der Horst & Mutis, 2024). For example, in 2024, the Fc domain of the FIC zenocutuzumab was designed to confer increased clustering and enhanced ADCC (Topouzis et al., 2025). This year, penipulimab similarly demonstrates that the incorporation of a modified IgG1 instead of an IgG4 Fc domain may confer distinct advantages that differentiate this MAb from other licensed anti-programmed cell death-1 (PD-1) MAbs.

Immune Checkpoint Inhibitors (ICIs) such as PD-1 MAbs are relatively late additions to the oncology armamentarium. Among them, toripalimab, tislelizumab, and camrelizumab are humanised, IgG4-bearing MAbs and thus exhibit effector-binding capabilities, which can, however, reduce their desired antibody-mediated anti-

cancer efficacy (Xue et al., 2021). This might result in part from Fc binding to FcγRI^{+} macrophages, an effect that leads to MAb-mediated phagocytosis of PD-1^{+} T cells and thus ultimately compromises the drug's tumour cell-killing efficacy (Huang et al., 2022). Fc-mediated binding to FcγRs can also elicit the release of inflammatory cytokines and underlie immune-related adverse effects (irAEs) associated with the use of these IgG4-bearing MAbs. In fact, preclinical investigations have demonstrated that blockade of FcγRs prior to administration of anti-PD-1 MAb can prolong MAb binding to tumour-infiltrating CD8^{+} T cells and further increase the antibody's effect on tumour burden (Arlauckas et al., 2017; Dahan et al., 2015). Hence, the engineering and incorporation of a particular Fc domain can reduce antibody-dependent adverse effects and boost the desirable tumour-cell cytotoxic functions triggered by the MAb (Chen et al., 2024; Kinder et al., 2015).

Penpulimab, approved in 2025 for the treatment of nasopharyngeal carcinoma (NPC), is a human IgG1 MAb targeting PD-1 with a mutated Fc region that attenuates its Fc receptor- and complement-mediated effector function (Han et al., 2021), thereby reducing ADCC and complement-dependent cytotoxicity (CDC). By the same token, penpulimab is also expected to display mitigated immune-related adverse effects (Dahan et al., 2015). NPC is a distinct entity, differing from other head and neck cancers due to its biology, epidemiology, aetiology, histology, molecular pathogenesis and treatment response. Because of this, NPC was excluded from Phase III clinical trials which led to the approval of pembrolizumab or nivolumab for head and neck squamous cell carcinoma. For all these reasons, NPC is a very challenging oncology indication, with few treatment options and frequent recurrence leading to the patient's demise (Juarez-Vignon Whaley et al., 2023). Penpulimab was approved by the FDA as a first-line treatment of adults with recurrent or metastatic non-keratinizing NPC, together with cisplatin or carboplatin and gemcitabine, based on results from a randomised, double-blind trial in 291 patients (Zhong et al., 2024; NCT04974398). The primary efficacy endpoint was PFS and a key secondary therapeutic efficacy measure was overall survival (OS). Median PFS was 9.6 months in the penpulimab-treated group and 7.0 months in the placebo arm. Moreover, 31% and 11% of patients were alive and progression-free after 12 months of follow-up in the penpulimab and placebo arms, respectively (Zhong et al., 2024; NCT04974398), supporting penpulimab's efficacy in extending survival and stalling disease progress in NPC.

In addition, the FDA also licensed penpulimab as a single agent in metastatic non-keratinizing NPC with disease progression that occurs while on platinum-based chemotherapy or after undergoing two other prior lines of therapy, one of them platinum-based. In this second trial (Chen et al., 2024; NCT03866967), single-agent penpulimab was administered in 125 patients, until disease progression or unacceptable toxicity were observable, for a maximum of 24 months. The endpoints were ORR assessed radiologically, which reached 28%, while the second evaluation measure, median DOR was not reached, due to the evaluation cutoff date; however, at 9 months, a response was observable in 66.8% of the patients. The median PFS and OS were 3.6 and 22.8 months, respectively. In this trial, 7.6% of the patients experienced Grade 3 or higher immune-related adverse effects (irAEs).

In both clinical studies, immune-related adverse effects (irAEs) were deemed acceptable and manageable, and together with the encouraging clinical responses argued in favour of the approval of penpulimab in this challenging indication, which is characterised by lack of effective treatments. Of note, penpulimab is currently tested in multiple additional cancer settings, for example in the treatment of hepatocellular carcinoma (Han et al., 2021) or squamous non–small cell lung cancer (NSCLC) (Wang, Lv, et al., 2025). The ongoing trials and monitoring of penpulimab's clinical efficacy and adverse effects will confirm whether Fc engineering makes this anti-PD-1 MAb a best-in-class as well.

2.1.4 | Sunvozertinib, zongertinib and sevabertinib

The ≥100 small molecule receptor tyrosine kinase inhibitors (TKIs) that have been approved since the initial landmark approval of imatinib (reviewed in Tomuleasa et al., 2024) have drastically changed the therapeutic landscape in a variety of diseases, especially in oncology. This year, several more TKIs have been authorised, of which three are considered FIC because of their unique pharmacological profile. The first such FIC TKI to be approved in 2025 was sunvozertinib, followed by zongertinib and sevabertinib. Sunvozertinib is an irreversible inhibitor of the Epidermal Growth Factor Receptor (**EGFR**) with selectivity for several EGFR mutant forms of the receptor, including sensitizing (exon19del and L858R), T790M and exon 20 insertion mutations (ex20ins), with weak inhibitory activity against wild-type EGFR; in addition, sunvozertinib can also inhibit the kinase Bruton's Tyrosine Kinase (**BTK**) (Wang et al., 2022; Wang, Xu, et al., 2025). Sevabertinib is a reversible TKI of mutant EGFR and of mutant HER2 receptor (**ERBB2**), including HER2 ex20ins, point mutations and amplification of wild-type HER2 (Le et al., 2025; Siegel et al., 2025). Finally, zongertinib is a covalent, irreversible inhibitor of HER2 oncogenic mutants, including ex20ins, that notably spares the **EGFR** (Wilding et al., 2025; Heymach et al., 2025). All three new drugs are authorised for treatment of NSCLC harbouring oncogenic mutations in the EGFR or HER2 receptors, especially ex20ins in the transmembrane domain. The duplication of amino acids YVMA in exon 20 of HER2 is the most commonly found oncogenic mutation in NSCLC and is a portent of aggressive disease progression and of poor response to current therapies (Wilding et al., 2025). Oncogenic *EGFR*exon20ins mutations are seen in 0.3%–2.9% of all NSCLC cases and in 2%–5% of EGFR-mutant NSCLC cases (Oxnard et al., 2013; Yuan et al., 2025). The ADC trastuzumab deruxtecan is the only FDA-authorised HER2-directed treatment for *HER2*-mutant NSCLC, however, it is associated with serious AEs, such as interstitial lung disease. Pan-HER TKIs have shown overall limited therapeutic benefit in NSCLC with HER2 oncogenic mutations, while some of them, including afatinib, neratinib, poziotinib and pyrotinib, are associated with dose-limiting adverse effects, including diarrhoea and rash, attributed to their lack of selectivity and ability to also inhibit EGFR (Heymach et al., 2025; Siegel et al., 2025; Wilding

et al., 2025). Similarly, the efficacy of targeted therapies for NSCLC *EGFR*exon20ins mutations (~2% of NSCLC) is equally limited: The EGFR/MET bispecific MAb, amivantamab, shows an ORR of about 40%, while with mobocertinib, an EGFR TKI, ORR is only around 28%, and about half of the patients experience dose limiting ≥ Grade 3 treatment-related AEs, sometimes requiring therapy discontinuation (Wang et al., 2022). Overall, in NSCLC there is a pressing need for both more effective molecules selectively targeting EGFR or HER2 oncogenic exon20ins mutations, sparing wild-type EGFR and displaying an improved toxicity profile.

The pivotal trial for sunvozertinib (NCT03974022) was an open-label, dose randomisation trial, that enrolled 202 patients with locally advanced or metastatic NSCLC who, upon screening, showed that their tumours harboured EGFR ex20ins mutations, and whose disease progressed while on or after prior platinum-based chemotherapy. These patients received randomly 200 or 300 mg sunvozertinib, and after interim evaluation all received the higher dose, until disease progression or intolerable toxicity. In the finally evaluable patients, the confirmed ORR was 46% and the DOR was 11.1 months. Interestingly, higher ORRs were observed in patients with baseline brain metastasis (52.4% vs. 28.6%) or previous amivantamab treatment (41.7% vs. 25%), as well as longer DOR (13.8 vs. 11.1 months). The most common drug-related Grade ≥3 AEs were diarrhoea (18%), anaemia and elevated blood CPK, considered to be related to inhibition of wild-type EGFR and underlying disease status. (Yang et al., 2025). These results let to sunvozertinib's approval for the treatment of NSCLC patients with locally advanced or metastatic NSCLC progression despite ongoing or prior platinum-based chemotherapy, with EGFR ex20ins mutations, seen by an FDA-approved companion diagnostic test.

Zongertinib's efficacy was evaluated in patients with unresectable or metastatic, non-squamous NSCLC with HER2 (ERBB2) mutations, in a Phase Ia/Ib clinical trial (Heymach et al., 2025; NCT04886804). Primary analysis results from three cohorts treated with zongertinib were reported. In cohort 1, comprising 71 patients with HER2 tyrosine kinase domain (TKD) mutations who had received prior platinum-based chemotherapy but had not been treated with a HER2-targeted tyrosine kinase inhibitor or antibody–drug conjugate (ADC), ORR (the main endpoint) was 71%, with a median DOR and a median PFS of 14.1 and 12.4 months (secondary endpoints) at the cutoff date. In Cohort 5, that included 31 patients with HER2 TKD mutations that had previously been treated with an ADC, 48% of the patients showed a confirmed ORR. Finally, 30% of the 20 patients in Cohort 3, whose tumours carried HER2 mutations outside the TKD, had a confirmed ORR. Grade 3 or higher adverse effects occurred in 17%, 3% and 25% of the patients of Cohorts 1, 5 and 3 respectively, however, no zongertinib-related interstitial fibrosis (a mark of EGFR inhibition) was observed. The durable clinical benefit and manageable safety profile of zongertinib, with low levels of Grade 3 or higher drug-related AEs, including those related to EGFR inhibition (e.g., rash and diarrhoea), enabled its FDA approval for the treatment of unresectable or metastatic NSCLC harbouring HER2 TKD activating mutations, who have received prior systemic therapy. A companion diagnostic test was also approved by the FDA to detect susceptible mutations prior to initiating zongertinib therapy.

Sevabertinib, the third TKI approved for NSCLC, was evaluated in an open-label, three-cohort, Phase 1/2 study (dose-expansion and dose-extension phases, NCT05099172) that enrolled 209 patients with locally advanced or metastatic HER2-mutant NSCLC. The cohorts were defined based on prior treatment: the first cohort comprising 81 previously treated patients who had not received HER2-targeted therapy; a second, comprising 55 patients who had previously received HER2-directed ADCs; and a third, comprising 73 treatment-naïve patients. The primary endpoint, ORR, was achieved by 64%, 38% and 71% of the patients in the three groups, respectively. In addition, encouraging results were derived from the secondary endpoints: The median DOR was 9.2, 8.5 and 11.0 months in the first, second and third group, respectively, while the median PFS was 8.3 and 5.5 months for the first two groups, while the PFS data were not ready to be evaluated regarding the third. Grade 3 or higher drug-related AEs occurred in 31% of the patients. The most common AE was diarrhoea (84% to 91%), with Grade 3 or higher diarrhoea present in 5% to 23% of patients, and therapy-related AEs led to drug discontinuation in 3% of patients. No cases of interstitial lung disease were evidenced (Le et al., 2025). Sevabertinib is therefore effective in both previously treated and untreated patients and has a manageable toxicity profile, comparable to that of other HER2 inhibitors. This led to its authorisation for the treatment of locally advanced or metastatic, non-squamous NSCLC harbouring **HER2** (*ERBB2*) TKD-activating mutations, following detection by an FDA-approved companion diagnostic test.

These three novel TKIs offer valuable additional therapeutic options for patients with NSCLC harbouring EGFR or HER2 activating oncogenic mutations, whose disease progresses despite prior treatment. In the next few years, as more patients are treated with them, their efficacy will be compared to that of previously approved EGFR and HER2 TKIs. Furthermore, among the important questions that will be addressed by their continued clinical application, is how zongertinib and sevabertinib, the two HER2-directed TKIs, compare to each other in terms of efficacy and toxicity, and whether all three TKIs can be used at earlier stages of NSCLC, in combination with other EGFR or HER2 inhibitors (such as ADCs) or with platinum, before resistance to these standard-of-care therapies manifests.

2.1.5 | Telisotuzumab vedotin

NSCLC, the deadliest cancer type worldwide (https://www.who.int/news-room/fact-sheets/detail/lung-cancer), is a highly heterogenous entity, and our understanding of its molecular underpinnings has been greatly enhanced in recent years. Among the molecular mechanisms responsible for the initiation and growth of NSCLC are oncogenic genomic alterations in the *MET* proto-oncogene (*MET* amplification, c-Met mutations, fusions or overexpression). Such alterations are frequently present and are associated with increased likelihood of tumour growth, invasion and metastasis, underscoring the importance

of targeting these mechanisms as drivers of tumour development and growth. The development of new molecular mechanism-specific approaches comprises a variety of small molecule c-Met tyrosine kinase inhibitors that inhibit the activity of specific c-Met activated isoforms (see for example (Lee et al., 2025). These inhibitors are complemented by c-Met-directed MAbs and are frequently combined with immunotherapy. All these new mechanism-directed therapies are however characterised by the development of resistance by the cancer, hence the need for additional cytotoxic drugs that aim directly at tumour-expressed molecular targets to reduce tumour burden, independently of mutations that may modify the downstream signalling (Hendriks et al., 2023; Meyer et al., 2024; Syal et al., 2025). A significant percentage (25%–39%) of NSCLC patients have tumours that overexpress **c-Met**, in addition to harbouring *MET* genomic alterations, with c-Met overexpression being a negative prognostic factor for survival in early and advanced NSCLC (Camidge et al., 2024). However, there are no approved therapies that specifically target c-Met protein overexpression, such as ADCs, which deliver a payload that triggers either direct or immune-mediated tumour cell elimination simply dependent on the increased presence of the antigen/molecular target on the tumour cell surface. Indeed, the 2022 approval of the ADC trastuzumab deruxtecan for the treatment of *HER2*-mutant NSCLC was hailed as a significant advancement (Zanchetta et al., 2024).

In 2025, the FDA granted accelerated approval to the ADC drug telisotuzumab vedotin, a c-Met-directed antibody bearing the cytotoxic payload monomethyl auristatin E (MMAE), a microtubule inhibitor conjugate, for adults with locally advanced or metastatic, non-squamous NSCLC with high c-Met protein overexpression (≥50% of tumour cells with strong [3+] staining). The FDA also approved a companion diagnostic biomarker test, to determine c-Met overexpression and therapy susceptibility of the tumour. The approval of telisotuzumab was granted after the positive results in a Phase II clinical trial (NCT03539536; Camidge et al., 2024), which enrolled non-squamous wild-type epidermal growth factor receptor (*EGFR*) NSCLC patients with tumours which overexpressed the c-Met receptor, defined as ≥25% tumour cells with 3+ staining (either high: ≥50% 3+ or intermediate: ≥25% to <50%), who received the drug every 2 weeks. Of note, c-Met overexpression is present in about 25% in the EGFR wild-type-expressing population (Camidge et al., 2024). The ORR was 28.6% (34.6% in the c-Met high and 22.9% in c-Met intermediate groups). The median DOR was 8.3 months (9.0 months in the c-Met high and 7.2 months in the c-Met intermediate groups). The median OS (14.5 months) and median progression-free survival (PFS) (5.7 months) were comparable between high and intermediate c-Met patients. The most common treatment-related AEs were peripheral sensory neuropathy (30%), peripheral oedema (16%) and fatigue (14%). Considering the lack of selective therapies for c-Met protein-overexpressing NSCLC, the encouraging clinical responses and the manageable adverse effects, the FDA granted its approval to telisotuzumab, while an ongoing Phase III study (NCT04928846) will provide additional information, since the Phase II study did not comprise a comparator arm. Future studies will also define telisotuzumab's efficacy in patient subpopulations whose tumours, besides c-Met overexpression, also harbour genomic markers of *MET* activation.

3 | NEUROLOGY

3.1 | Suzetrigine

The management of severe pain has for decades been heavily reliant on **opioid receptor** agonists, an approach that has been burdened by safety concerns due to the high incidence of potentially life-threatening side effects (e.g., respiratory depression, constipation) as well as by the significant socioeconomic price exacted by patient addiction to opioids and the abuse of these drugs by the general population.

Suzetrigine, approved this year, is an analgesic targeting an altogether different mechanism, being a highly selective inhibitor of $Na_v1.8$ sodium channels (**$Na_v1.8$**). $Na_v1.8$ are channels highly expressed in primary pain-sensing C-fibre neurons and display limited expression in most other kinds of neurons (Bennett et al., 2019). Suzetrigine shows thousands fold-higher selectivity for $Na_v1.8$ versus all other Na_V subtypes. Suzetrigine binds allosterically to the protein's second voltage-sensing domain, stabilises the closed state of $Na_v1.8$ and reduces nociceptive signalling in primary human dorsal root ganglia sensory neurons. (Jones et al., 2023; Osteen et al., 2025; Vaelli et al., 2024; Yekkirala et al., 2017).

The efficacy of suzetrigine in reducing post-operative acute pain was evaluated in two randomised, double-blind, placebo-controlled trials. Suzetrigine was administered after abdominoplasty (NCT05558410, n = 1,118) or bunionectomy (NCT05553366, n = 1,073), both being standard acute pain surgical procedures for testing new analgesics, since both are associated with acute pain (for example, they were previously used for the approval of the first 'biased' opioid agonist, **oliceridine**, (Tan & Habib, 2021). For the primary endpoint, the time-weighted sum of the pain intensity difference in numeric pain rating scale from 0 to 48 h was measured, the least squares mean difference between suzetrigine and placebo was 48.4 after abdominoplasty and 29.3 after bunionectomy. Suzetrigine's analgesic effects were comparable to those of **hydrocodone bitartrate**/**acetaminophen** (paracetamol) combination tested in parallel. However, suzetrigine achieved a faster two-point or greater reduction in numerical pain rating scale than hydrocodone bitartrate/acetaminophen (at 2 h vs. 8 h, respectively). Finally, suzetrigine treatment resulted in manageable, mild-to-moderate adverse effects (Bertoch et al., 2025). Together with its absence of tolerance in preclinical models (Ali et al., 2025), peripherally acting suzetrigine offers a much-needed, landmark alternative to opioids in the management of acute pain. Future studies will better define its long-term effectiveness in various populations and different pain indications.

4 | HEART AND BLOOD DISORDERS

4.1 | Donidalorsen and garadacimab

Mutations in *SERPING1*, the gene encoding C1 esterase inhibitor, occur in approximately 1 in 50,000 individuals and cause a rare autosomal dominant disease, since they lead to either C1 inhibitor deficiency, resulting in hereditary angioedema (HEA) or to C1 inhibitor dysfunction, resulting in type II hereditary angioedema (HAE), and account for the majority (over 95%) of HAE cases. Type III HAE stems from increased activation of Factor XII, the first factor in the contact system, which ultimately also results in an overproduction of bradykinin, even, occasionally, in the presence of normal levels of C1 inhibitor. In all forms of hereditary angioedema (HEA) disease, a common consequence is uncontrolled activation of the **kallikrein**-kinin system and thus elevated levels and signalling of bradykinin via bradykinin **B2 receptors**, manifesting with increased vascular permeability, which results in angioedema. If the upper airways, especially the larynx, are involved and are swollen, there is an increased risk of life-threatening asphyxia (Ameratunga & Longhurst, 2024; Busse et al., 2021). When a HAE attack happens, one cannot predict its progression and anatomical spread. For this reason, it is recommended that patients carry with them on-demand treatments. In this situation, quick and timely administration is important. Several drugs have been approved to treat HAE: some are licensed for prophylaxis from HAE attacks and others are approved for rapid administration when an HAE episode occurs. Most current therapies, including C1 esterase inhibitors or bradykinin receptor antagonists, require subcutaneous or intravenous delivery, while only two among the total of 12 FDA-approved drugs for use in HAE are oral therapies (excluding symptomatic treatments such as corticosteroids, https://www.haea.org/pages/p/treatments). In 2025, the FDA approved the second such targeted oral treatment for HAE, sebetralstat, an inhibitor of plasma kallikrein (Riedl et al., 2024), making it the first oral therapy for on-demand treatment. However, since **berotralstat**, a drug with a similar molecular mode of action, was already approved in 2020 for prophylaxis from HAE attacks (Wedner et al., 2021), sebetralstat cannot be considered a FIC, and will not be reviewed here in detail.

All current medications used for prophylaxis in HAE are chronically administered, subcutaneous or intravenous treatments and include human plasma-derived or recombinant C1 inhibitor concentrates, an oligopeptide bradykinin receptor antagonist and an antibody kallikrein inhibitor. Despite the undeniable progress in HAE management that these treatments have produced, disease burden persists in many patients, obliging them to switch medications; an additional factor for switching is provided by the relatively frequent (every 2 weeks up to twice weekly) parenteral administration of the available therapeutic agents (Grumach et al., 2023; Mendivil et al., 2023). Overall, there is significant unmet need for more effective long-term prophylaxis in HAE. To address this need, two drugs were approved in 2025 for the prevention of HAE episodes, both FICs: donidalorsen and garadacimab.

Donidalorsen, approved this year by the FDA, is a 2′-*O*-methoxyethyl–modified antisense oligonucleotide (ASO) conjugated to a *N*-acetylgalactosamine ($GalNAc_3$) moiety. The ASO part of donidalorsen degrades plasma prekallikrein messenger RNA (mRNA) via ribonuclease H1, thereby reducing the levels and activity of kallikrein, the enzyme responsible for the overproduction of bradykinin in HAE. It is therefore a novel mode of prekallikrein targeting, different from direct enzyme inhibition. Furthermore, the ASO modification provided by the $GalNAc_3$ moiety greatly enhances the ASO's uptake by the liver, which is the main site of plasma prekallikrein expression and production, compared to the unconjugated ASO, allowing less frequent treatment and use of lower doses, and thus attempting to bypass the need for frequent parenteral delivery required by the HAE treatments approved before 2025 (Riedl, Bordone, et al., 2024).

Donidalorsen was evaluated in a 25-week, Phase III, double-blind, randomised trial in a total of 90 HAE patients, in which 22 patients received placebo, 45 received donidalorsen every 4 weeks (4-week group) and 23 were treated with donidalorsen every 8 weeks (8-week group). The primary endpoint was the time-normalised number of investigator-confirmed HAE attacks per 4 weeks (attack rate) during the 25-week treatment period. The least squares mean time-normalised attack rate was 0.44 in the 4-week group, 1.02 in the 8-week group and 2.26 in the placebo group. The mean attack rate from Week 1 to Week 25 was 81% lower in the every 4-week and 55% lower in the every 8-week donidalorsen group, compared to the placebo group. The median decrease of the attack rate from baseline was 90% in the 4-week donidalorsen group and 83% in the 8-week donidalorsen group, compared with 16% in the placebo group. HAE attacks are painful and debilitating, severely decreasing the patients' quality of life (QOL). Donidalorsen administered every 4 weeks resulted in an improvement in the least-squares mean total score for the change at week 25 on the Angioedema QOL Questionnaire (scores range from 0 to 100, with a score of 100 indicating the worst possible QOL) that was 18.6 points better than that with placebo. The AEs observed more frequently included topical erythema at the injection site, headache, and nasopharyngitis, while most adverse effects (98%) were mild or moderate in severity (Fijen et al., 2022; Riedl, Tachdjian, et al., 2024). Donidalorsen is therefore an effective and safe treatment to prevent HAE attacks, supporting its prophylactic use by HAE patients.

Garadacimab takes an entirely different mechanistic tack, unprecedented in HAE: it is an IgG4 monoclonal antibody that blocks the catalytic activity of FXIIa (Drulyte et al., 2024), the principal initiator of the plasma contact system, which is involved in host defence, coagulation and inflammation; garadacimab therefore targets this pathogenic component of HAE for the very first time. Hyperactivity of FXIIa leads to activation of prekallikrein and finally, increased bradykinin levels that characterise and underlie the pathophysiology of HAE (Cohn & Renné, 2024). This monoclonal antibody is a potent selective inhibitor of the activated form of FXII (FXIIa) versus the zymogen, via its binding to the beta-chain of FXIIa. Crystallography studies of the FXII beta chain-garadacimab complex have shown that garadacimab interacts with βFXIIa in a way very similar to that employed by other FXII inhibitors, such as benzamidine and C1 esterase inhibitor (Drulyte et al., 2024).

The pivotal clinical study that led to garadacimab's approval by the EMA, the FDA and the MHRA (Craig et al., 2023; NCT04656418)

was a 6-month-long, randomised, double-blind trial. The eligible Type I or type II HAE patients received monthly injections of either garadacimab or placebo. The primary endpoint, investigator-assessed number of HAE attacks per month, was reduced from 2.01 attacks per month in the 25 patients that received placebo, to 0.27 attacks per month in the 39 patients that were treated with garadacimab, a reduction of 87%. Similarly, the median number of HAE attacks per month was 0 in the garadacimab cohort and 1.35 in the placebo. The most common AEs related to garadacimab were upper-respiratory tract infections, nasopharyngitis, and headaches. Importantly, considering that this agent is a FXIIa inhibitor, there was no evidence of increased risk of bleeding or thromboembolic events (Craig et al., 2023; NCT04656418). Garadacimab's efficacy in this study, combined with its favourable safety profile and the once-a-month treatment dosing, support the use of garadacimab as a potential prophylactic therapy for the treatment of hereditary angioedema (HEA).

In a single year, therefore, three novel therapeutics (of which two are FIC) were added to the roster of HAE drugs, each interfering at different sites of the pathological cascade or using innovative pharmacological approaches of stemming the production of bradykinin, providing patients with valuable additional choices. It will be interesting to see how these new drugs compare with older ones in terms of long-term efficacy and whether stratified patients according to the HAE type respond differently to them.

4.2 | Fitusiran

Haemophilia A and B are congenital, X chromosome-linked bleeding disorders arising from deficiency of clotting Factor VIII (FVIII) or Factor IX (FIX), respectively. A common feature of both haemophila A and B is the reduced thrombin production and the ensuing increased risk of bleeding episodes (Chowdary et al., 2025; Kenet et al., 2024). Patients with a severe form of haemophilia (<1% of normal plasma factor activity) often present with spontaneous bleeding events, while those with moderate and mild deficiencies develop abnormally high bleeding after trauma or surgery. Current therapeutic management of haemophilia comprises both episodic care (e.g., for bleeding episodes and surgeries) as well as prophylactic agents to prevent bleeding attacks. Such therapies include small molecules such as the protease inhibitor aminocaproic acid, replacement therapy with plasma-derived or recombinant clotting factor concentrates, non-replacement therapies that increase thrombin generation, therapies that tamper with anticoagulant pathways and restore indirectly the clotting system balance (e.g., marstacimab) or gene therapies that enable normal clotting factor synthesis in vivo (Chowdary et al., 2025; https://www.cdc.gov/hemophilia/treatment/index.html; Topouzis et al., 2025). These treatments differ significantly in their approved use (prophylaxis or on-demand treatment, treatment of haemophilia A or B), in the mode and frequency of administration, the duration of their effect and finally in their adverse effects.

One more innovative agent has been added to these in 2025 by the FDA approval of fitusiran as routine prophylaxis therapy to prevent or reduce the frequency of bleeding episodes associated with haemophilia A or B. Fitusiran is an RNA interference (RNAi) therapy that has an unprecedented mechanism of action: it selectively targets and causes the degradation of antithrombin mRNA (encoded by *SERPINC1*), suppresses the production of this natural anticoagulant in the liver, increases levels of the critical clotting enzyme thrombin, and restores haemostasis in patients with haemophilia. The double-stranded siRNA is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) moiety to facilitate hepatic uptake (Young, Lenting, et al., 2023). Besides being the first drug that targets and inhibits prothrombin in haemophilia, fitusiran is also the first approved oligonucleotide therapy for haemophilia.

The efficacy and safety of fitusiran were determined in two multicentre, randomised clinical trials which recruited patients diagnosed with haemophilia A or B. In the first study, (NCT03417102; Young, Srivastava, et al., 2023) the 57 enrolled participants had developed inhibitory antibodies to FVIII or FIX in the clotting factor concentrate therapy, rendering it ineffective; to manage episodes of bleeding they had been on 'bypassing agents' including activated prothrombin complex concentrate or recombinant factor VIIa treatment on demand. 19 patients were kept on the bypassing agent on-demand and 38 received the monthly fitusiran prophylaxis, for 9 months. The calculated mean annualised bleeding rate was 1.7 in the fitusiran group, 90% lower than in the bypassing agents on-demand group (18.1 episodes), with 66% of the fitusiran cohort attaining zero bleeds in this time versus only 5% in the bypassing agents on-demand group, demonstrating the efficacy of fitusiran in preventing bleeding episodes in this particular patient group and therapeutic setting.

The second, 9 month-long study (NCT03417245; Srivastava et al., 2023), enrolled haemophilia A or B participants who (in contrast to the first trial) had not previously developed inhibitory antibodies to FVIII or FIX and who were under on-demand treatment with clotting factor concentrates. Of the 120 participants, 80 were assigned to the monthly fitusiran group and 40 continued with clotting factor concentrate. Randomisation took into account the frequency of bleeds in the previous 6 months and the type (A or B) of haemophilia. The estimated mean annualised bleeding rate was 90% lower in the fitusiran prophylaxis group (3.1 bleeds/year) than in the on-demand clotting factor concentrates group (31 bleeds/year). Only 5% of the participants who continued on the clotting factor concentrates had no bleeds requiring treatment, versus 51% of those in the fitusiran group.

Some (5%) of the participants who received a fixed monthly dose of fitusiran presented excessive clotting (thromboembolic) events. On this basis, the fixed dosing scheme was not approved. To limit the risk of bleeding or excessive blood clotting, the FDA also licensed a companion diagnostic test to monitor antithrombin activity, enabling it to be maintained within the target range by adjusting the dosing and frequency of fitusiran injections. In an extension study that investigated this (Young et al., 2025; NCT03754790), the variable-dosing approach proved efficacious (70% reduction in annualised bleeding rate compared to the on-demand clotting factor concentrates group). Therefore, an adjustable fitusiran dosing regimen based on such periodic

measurements of antithrombin activity and clotting ability was the FDA-approved treatment.

Fitusiran carries a boxed warning for thrombotic events and gallbladder disease, occasionally requiring gallbladder removal. Because of potential hepatic toxicity, periodic liver enzyme tests are also recommended for the first 6 months after starting the therapy or when the fitusiran dose is increased.

All in all, prophylaxis with fitusiran antithrombin RNAi greatly reduces bleeding rate in participants with haemophilia A or haemophilia B, with or without inhibitory antibodies to clotting concentrates, compared to on-demand clotting factor concentrates, with over 50% of the patients showing zero bleeds during the trials. Therefore, fitusiran prophylaxis significantly restores haemostatic efficacy in both haemophilia A and haemophilia B and is a potentially groundbreaking therapy in the management of haemophilia.

4.3 | Lerodalcibep

Low density lipoprotein-cholesterol (LDL-c) is a major risk factor in cardiovascular disease (CVD), whose role in the development of atherosclerosis has been demonstrated by numerous studies. Reduction of the LDL-c levels has been a mainstay of the therapeutic prevention and management of cardiovascular disease (CVD), since reduction of LDL levels is an eminently achievable goal—in combination with diet changes—by effective drug treatments, the most important of which are statins (Hadjiphilippou & Ray, 2019; Michos et al., 2019). Because many patients with cardiovascular disease (CVD), including those at high risk, do not achieve the targeted LDL-c level even on maximally tolerated statin regimen and the addition of ezetimibe, additional LDL-c-lowering agents have been developed to help them attain the recommended LDL-c levels. The most effective such drugs target proprotein convertase subtilisin/kexin type 9 (**PCSK9**), an enzyme which degrades hepatocyte LDL-c receptors and lowers the uptake of circulating LDL-c by the liver. Currently approved PCSK9-directed drugs work by either blocking the activity of circulating PCSK9 by neutralizing the protease (monoclonal antibodies evolocumab and alirocumab) or by reducing the hepatic PCSK9 synthesis and consequently its plasma levels (the PCSK9-directed siRNA inclisiran) (Raal et al., 2020).

The twice monthly frequency, subcutaneous delivery mode requiring, occasionally, multiple dosages in sequence, and the limited stability at room temperature of approved PCSK9-targeting therapeutics, can become problematic in treating patients. Therefore, a new mechanistic inhibitory approach is desirable, especially since small molecules cannot achieve effective blockade of the convertase. PCSK9 binds to the LDL receptor within its well conserved epidermal growth factor precursor homology domain-A (EGFA) at the cell surface (Kwon et al., 2008). Based on this knowledge, lerodalcibep was designed and developed as a novel alternative to monoclonal antibodies and the siRNA. It is a recombinant fusion protein that binds to and inhibits PCSK9, the first ever 'adnectin' to be approved. Initial screening of mRNA display libraries identified an 11-kDa anti-PCSK9-binding polypeptide, called an adnectin, derived from domain 10 of human fibronectin type III (amino acids 1-96); this constitutes a versatile scaffold that was further engineered to exhibit high-affinity (<1 nM) for human PCSK9 EGFA. This adnectin presents important advantages: it contains no disulfide bonds, is not glycosylated, is stable at room temperature and can be efficiently produced using bacterial or mammalian expression systems (Mitchell et al., 2014). It is expressed as a fusion protein, via peptidyl linker to human serum albumin (amino acids 103-687), that significantly extends its half-life.

Three clinical studies demonstrating lerodalcibep's efficacy and safety led to its FDA authorisation. In the first, a 24-week global Phase III trial, lerodalcibep was evaluated in 478 heterozygous familial hypercholesterolaemia (HeFH) patients for whom additional LDL-c–lowering treatment over maximally-tolerated statin was considered necessary. Patients were randomised 2:1 to monthly subcutaneous injections of either lerodalcibep or placebo. Lerodalcibep achieved the primary efficacy endpoint by reducing LDL-c, compared to placebo, by 58.6% at week 24 and by 65.0% at the mean of Weeks 22 and 24. Sixty-eight percent of patients in the lerodalcidep group achieved both an LDL-c reduction of ≥50% and the recommended European Society of Cardiology LDL-c targets, with the most frequent adverse effect being only mild injection-site reactions (Raal et al., 2023; LIBerate-HeFH).

In a second, 52-week, double-blind, randomised, placebo-controlled (2:1 monthly lerodacibep:placebo) trial (Klug et al., 2024; NCT04806893), lerodacibep was evaluated in 811 patients with cardiovascular disease (CVD) or who were at very high or high risk of CV events and for whom additional LDL-c–lowering treatment over maximally-tolerated statin was required, 9.6% of whom had familial hypercholesterolaemia. At week 52, the mean placebo-adjusted reduction in LDL-c with lerodalcibep was 56.2%, while 90% of the lerodacibep cohort achieved both a ≥50% reduction in LDL-c and the recommended LDL-c targets during the study.

Because lerodalcibep showed promising results in the familial hypercholesterolaemia (FaHC) participants, a third trial was designed, that enrolled homozygous FaHC patients and compared lerodacilbep (monthly subcutaneous [s.c.] injection) to evolocumab (monthly s.c. infusion). This was an international, Phase III, randomised, open-label, crossover, non-inferiority study consisting of two 24-week treatment periods separated by an 8-week washout. LDL-c levels were similar in the same patients with both lerodalcibep and evolocumab at Week 24, as was the percentage reduction in LDL-c (Raal et al., 2025; NCT04034485).

This ingeniously-designed, 'third generation' anti-PCSK9 drug, not only shows efficacy, combined with a statin, in lowering LDL-c to target levels in various populations at-risk of cardiovascular events, but also has a very good safety profile, is given by s.c. injection, while one of the PCSK9 MAbs, evolocumab, is administered by s.c. infusion or multiple s.c. injections, and can be stored at room temperature for at least a month. Based on all the above, the FDA approved lerodalcidep use as an LDL-c lowering agent in adults with hypercholesterolemia, including FaHC, and therefore it offers another therapeutic option, next to statins, anti-PCSK9 MAbs and siRNA, when aggressive LDL-c lowering is medically advisable.

5 | INFECTIOUS DISEASES

5.1 | Gepotidacin and zoliflodacin

In our mini-review on drugs approved in 2024 (Topouzis et al., 2025), we deplored the low number of new medicines approved as first-line treatments for infectious diseases. This year, the FDA approved two new drugs for one of the commonest type of bacterial infections, uncomplicated urinary tract infections (uUTIs). In March 2025, gepotidacin was authorised for the treatment of uUTIs in female adult and paediatric patients 12 years of age and older by susceptible bacteria. In December, the same agency approved gepotidacin and another novel drug, zoliflodacin, for the treatment of uncomplicated gonorrhoea in adults and paediatric patients 12 years and older. Both of these medicines target bacterial enzymes (gyrases), which are also targets of one of the most heavily (over)used classes of antibiotic for UTIs, the fluoroquinolones such as ciprofloxacin. However, in addition to having a very novel chemical structure, they both employ mechanisms that differ substantially from those of fluoroquinolones and from each other.

Gyrase and **topoisomerase IV** (**Topo IV**) are both closely related DNA topoisomerase type II enzymes that together topologically arrange bacterial DNA by unwinding the supercoil that has formed and then they effect transient double-stranded breaks in DNA followed by religation, in order to enable bacterial genome replication. DNA gyrase is a heterotetramer of two subunits, GyrA2-GyrB2 and topoisomerase IV (Topo IV) is a ParC2-ParE2 heterotetramer (Bradford et al., 2020).

Fluoroquinolones primarily target the GyrA subunit of DNA gyrase and the ParC subunit of topoisomerase IV. They form a chelation complex with a magnesium ion (Mg^{2+}) via which they interact with the GyrA subunit and stabilise the cleaved DNA-enzyme complex, leading to double-stranded DNA breaks and bacterial cell death.

Zoliflodacin differs from fluoroquinolones in important ways, because it targets and binds mainly to the GyrB subunit of DNA gyrase, without forming a metal ion bridge (Collins et al., 2024; Morgan et al., 2023). Notably, zoliflodacin not only stabilises the cleaved DNA-enzyme complex but also prevents the re-ligation of the cleaved DNA strands and thus the formation of fused circular DNA.

Finally, gepotidacin has also a unique mechanistic profile, since it interacts equally well with both gyrase and topoisomerase IV at similar concentrations and for this reason it is considered a unique dual-targeting molecule. Consequently, development of bacterial resistance to it would require concurrent mutations in both enzymes. Gepotidacin both induces and maintains single-stranded bacterial DNA breaks (Oviatt et al., 2025), disabling replication of bacterial DNA.

Epidemiological data show that more than half of all women will develop acute cystitis in their lifetime (i.e., uncomplicated urinary tract infections [uUTIs] not originating from an anatomical malformation/disorder), making them among the most frequent of all bacterial infections requiring oral treatment with antibiotics. The choice of available first-line medicines is often very limited, due among others to possible contraindications for prescription of a specific medicine (e.g., limited renal distribution or clearance by underperforming kidneys), increasing pathogen resistance rates and last, substantial risk of serious drug-induced toxicity, as is the case for fluoroquinolones (Hooton, 2012), indicating a significant unmet need for additional novel, effective antibiotics for uUTIs.

Gepotidacin was evaluated in two pivotal Phase III, double-blind, double-dummy, non-inferiority (10% margin) trials (Wagenlehner et al., 2024; NCT04020341 [EAGLE-2] and NCT04187144 [EAGLE-3]), enrolling together 3,136 female patients over 12 years old, presenting with symptoms of uUTI caused by nitrofurantoin-sensitive uropathogens, including clinically important drug-resistant phenotypes such as *Escherichia coli* (90% of the participants) and *Klebsiella pneumoniae* (~2%). Participants were randomly assigned to receive either gepotidacin or nitrofurantoin for 5 days. The primary endpoint was therapeutic response (success or failure) at test-of-cure (i.e., Days 10–13), by presence of nitrofurantoin-susceptible qualifying uropathogens (≥10^5 colony-forming units [CFU] per mL). Therapeutic success was defined as complete symptom resolution and reduction of qualifying uropathogens to <10^3 colony-forming units [CFU]/ml by the assigned antimicrobial treatment alone. In EAGLE-2, 50.6% of patients that had taken gepotidacin and 47.0% of patients on nitrofurantoin achieved therapeutic success. In EAGLE-3, 58.5% of patients on gepotidacin and 43.6% of patients on nitrofurantoin reached therapeutic success. Therefore, gepotidacin was either non-inferior (EAGLE-2) or superior (EAGLE-3) to the comparator drug, nitrofurantoin. The most common AE with gepotidacin was mild diarrhoea (seen in approximately 16% of patients), whereas the most common AE with nitrofurantoin was mild nausea (in 4% of patients). Gepotidacin is therefore an orally active, efficacious and well-tolerated new option against common uropathogens (Wagenlehner et al., 2024).

One such important uropathogen is *Neisseria gonorrhoeae*. It can cause significant morbidity and is associated with rapidly developing resistance to all available classes of antibiotics including ceftriaxone, fluoroquinolones and azithromycin, becoming a multidrug resistance organism (Luckey et al., 2025), making it a global public health priority. The World Health Organisation (WHO) estimates that it infected 82.4 million people in 2020.

In two Phase III, randomised, non-inferiority clinical trials, clinicians evaluated zoliflodacin (Luckey et al., 2025; NCT03959527) and gepotidacin (Ross et al., 2025; NCT04010539) in, respectively, 930 and 628 participants of either sex over 12 years old, with clinical symptoms suggesting uncomplicated urogenital gonorrhoea. Patients were treated with either a single oral dose of zoliflodacin (NCT03959527) or two oral doses of gepotidacin (NCT04010539). Both trials included an arm of patients treated with the (comparator) standard combination of intramuscular ceftriaxone plus oral azithromycin. The primary endpoint (determined by culture at Day 6), was percentage of participants with eradication of *N. gonorrhoeae*. In the first trial, microbiological success (eradication) was 90.9% with zoliflodacin versus 96.2% with the comparator, while in the second trial it was 92.6% for gepotidacin versus 91.2% with the ceftriaxone/azithromycin treatment. These efficacy data make both zoliflodacin and gepotidacin non-inferior to the ceftriaxone/azithromycin

combination for eradication of gonorrhoea. In addition, zoliflodacin caused mild to moderate severity AEs, the most frequent being headache, neutropenia and leukopenia (all ≤10%) (Luckey et al., 2025), while gepotidacin induced mainly mild or moderate gastrointestinal AEs (Ross et al., 2025).

On the strength of the drugs' efficacy and mild toxicity profile, the FDA granted approval to both zoliflodacin and gepotidacin, via Fast Track, Qualified Infectious Disease Product and Priority Review designations, for use in the uncomplicated urogenital gonorrhoea indication.

As described, these two novel drugs differ from fluoroquinolones and from each other in their respective molecular target(s), in the mechanism of binding to the bacterial DNA and in their ability to prevent relegation, consequently, they are expected to show distinct resistance profiles and no cross-resistance between themselves or with fluoroquinolones, hence the high significance of their approval.

5.2 | Vimkunya

Chikungunya virus is a single-stranded, positive RNA alphavirus, with recurrent outbreaks spreading with mosquito bites. Individuals infected with chikungunya virus develop fever and joint pain during the acute phase. Most patients recover within a week, but some develop chronic, disabling joint pain that can last months. A small proportion may develop severe acute disease, which progresses to multiorgan failure. Once considered confined to sub-Saharan Africa, such outbreaks have become more frequent and widespread in the last 20 years, with multiple outbreaks seen in 2025. Autochthonous transmission now exists in 119 countries and massive outbreaks are increasingly noted in more temperate regions, such as China, Italy and France. Chikungunya infections seem to develop into a growing, global public health risk, emphasizing the need of medical intervention tools that will enable the containment and prevention of chikungunya virus disease (Weaver & Lecuit, 2015; Venkatesan, 2025). A live attenuated chikungunya vaccine (Ixchiq) was approved in 2023 (Papapetropoulos et al., 2024). However, in August 2025, the FDA suspended the U.S. licence for Ixchiq, because of reports of serious cardiac and neurological AEs requiring hospitalisation. The FDA is currently conducting a more in-depth risk–benefit assessment that will inform its decision to maintain recommendation of Ixchiq for prevention of infection in specific high-risk populations and settings (https://www.cdc.gov/chikungunya/vaccines/index.html).

Some of the pressing need for a preventive medicine was addressed by this year's licensing by the EMA, the FDA and the MHRA of the FIC recombinant chikungunya vaccine, Vimkunya. The vaccine comprises the chikungunya Senegal West African strain 37,997 capsid recombinant protein (C) (that mediates membrane fusion with host cells) and envelope E1 and E2 glycoproteins (that mediate receptor binding), which are targets of antibodies during natural exposure to the virus. These are assembled to form a quasi-spherical, virus-like particle (VPL). Since there is a single chikungunya virus serotype, the development of antibodies in response to Vimkunya vaccination should provide cross-protection against subsequent infection from all strains of the virus (Richardson et al., 2025).

The results from two pivotal Phase III randomised, double-blind, placebo-control (adjuvant alone) trials supported the approval of Vimkunya. The first (Richardson et al., 2025; NCT05072080) enrolled 3258 healthy adolescents and adults aged 12–64 years and the second (Tindale et al., 2025; NCT05349617) 413 healthy individuals over 65. Participants received one intramuscular dose of either Vimkunya or placebo. In both trials, Vimkunya achieved the immunogenicity (seropositivity) in response to the vaccine.

In the first trial, the co-primary endpoints were (a) the difference in Chikungunya virus serum neutralizing antibody seroreponse rate (vaccine [97.8%] minus placebo [1.2%]) at Day 22, which was 96.6, and (b) the chikungunya virus serum neutralizing antibody geometric mean titre (GMT) at Day 22 for vaccine and placebo, which were 1,618 and 7.9, respectively (Richardson et al., 2025). In the second trial, performed in the over 65 years age group, the coprimary endpoints of immunological superiority of the vaccine were the chikungunya serum neutralizing antibody (SNA) titres were compared with placebo at 3 time-points and the geometric mean titre at Day 22. Vimkunya induced a protective seroresponse (SNA $NT_{80} \geq 100$), considered the presumptive seroprotective antibody response, in 82% of participants at Day 15, in 87% of participants at Day 22 and in 76% of participants at Day 183. The target related to the geometric mean titre at Day 22 was also met (Tindale et al., 2025).

Most Vimkunya-related AEs (such as fatigue and myalgia) were self-limiting, short in duration and Grade 1 or 2 in severity. Vimkunya, therefore, is able to induce a rapid and robust immune response in all age groups, which (in the over 65 years age group where it was studied) persists up to 6 months later. Together, these findings support the potential for Vimkunya to protect individuals from disease caused by chikungunya virus, and clinched an accelerated approval of this recombinant, FIC vaccine from the EMA, the FDA and the MHRA.

5.3 | Zopapogene imadenovec

Although preventive human papilloma virus (HPV) vaccination, wherever available, has dramatically reduced the incidence of recurrent respiratory papillomatosis (RRP), RRP still is present in unvaccinated individuals (with an estimated US prevalence of 27,000 cases and 1000 new cases a year) and manifests as a rare, neoplastic disorder caused by chronic infection with HPV Type 6 or 11. The development of persistent, non-cancerous papillomas throughout the larynx, trachea and lungs can cause significant airway obstruction, can lead to post-obstructive pneumonias and death, presents a 7% risk of dysplasia and malignant transformation and overall causes significant, debilitating morbidity and reduces QOL in RRP individuals. There are no approved systemic medical therapies for RRP and current management relies on repeated surgical ablation of papillomas (Norberg et al., 2025).

Study of clinical specimens from RRP patients revealed a deficit of active papilloma-infiltrating T lymphocytes specific for HPV6 or 11.

This provided the basis for the design of a vaccination approach, developed as zopapogene imadenovec, which consists of a gorilla adenovirus vector-based gene (immuno)therapy, expressing selected regions from HPV Types 6 and 11 proteins, capable of eliciting robust T-cell immunity specific to HPV6 or 11. In previous ex vivo studies, zopapogene imadenovec was shown to induce HPV antigen-specific responses in peripheral T lymphocytes from RRP patients with HPV6- or HPV11-driven disease or in healthy donors, including release of IFNγ, granzyme B and GM-CSF (Lee et al., 2021).

The pivotal trial that evaluated the efficacy and safety of zopapogene imadenovec was a single-centre, single-arm, Phase 1/2 trial (Norberg et al., 2025; NCT04724980). After initial surgical management of the disease, thirty-five RRP adult patients received adjuvant zopapogene imadenovec on days 1, 15, 43 and 85. The primary outcome measure was complete response rate, defined as the percentage of patients who did not require an intervention to control RRP in the 12 months after treatment, and was reached by 18 (51%) patients, with vaccine-related AEs being mostly mild (chills and fever). The median DOR (time to first required surgical intervention) was not yet reached after a median follow up of 22 months, showing durability of response to zopapogene imadenovec (Norberg et al., 2025). The persistence of zopapogene imadenovec's efficacy and mild adverse effect profile promises to significantly alleviate the morbidity and increase the QOL of patients with HPV6- or HPV11-associated RRP.

6 | IMMUNE/INFLAMMATION

6.1 | Brensocatib

Non-cystic fibrosis bronchiectasis (referred to as 'bronchiectasis' from here on) is a chronic lung disease characterised by a persistent, recurring cycle of infection, inflammation and damage of lung tissue. One major pathway causing structural damage is the release of neutrophil serine proteases (NSPs) by infiltrating, activated neutrophils. These proteases are stored within the neutrophil cytoplasmic granules and comprise the structurally similar neutrophil elastase, proteinase 3 and cathepsin G, and are synthesised as inactive zymogens during granulocyte development. Their proteolytic conversion to the active form is controlled by dipeptidyl peptidase 1 (**DPP1**, also known as **cathepsin C**), which removes an N-terminal dipeptide. Excessive tissue levels of activated NSPs, especially neutrophil elastase, in several inflammatory diseases, overwhelm natural defence mechanisms, such as α1-antitrypsin, and contribute critically to the pathology that stems from inflammatory damage and tissue matrix destruction. Bronchiectasis is such a disease where increased infiltration of activated neutrophils correlates with severity and frequency of exacerbations and with clinical progression (Basso et al., 2023; Chalmers et al., 2020).

Better awareness and advanced diagnosis have recently shown that bronchiectasis, previously thought of as a rare disease, is far more common, affecting ~250,000 individuals in the US alone. Most patients have a high burden of daily symptoms (chronic cough and sputum production). The unrelenting disease exacerbation decreases lung function and increases all-cause mortality (Choi et al., 2024). There is no consistent standard of care for bronchiectasis, compounded by a lack of targeted approaches to oppose inflammation or slow disease progression. Brensocatib was developed to remedy this void: it is a competitive, reversible small molecule inhibitor of the central player in NSP activation, DPP1, that has been shown to reduce the activity of NSPs including neutrophil elastase, cathepsin G and proteinase 3 in vitro (Doyle et al., 2016), as well as in the serum of healthy volunteers in vivo (Palmér et al., 2018).

Based on promising results from a 24-week Phase II trial (Chalmers et al., 2020; NCT03218917), brensocatib was further evaluated in a pivotal Phase III double blind, randomised study enrolling 1721 patients (Chalmers et al., 2025; NCT04594369). The primary endpoint, annualised rate of adjudicated pulmonary exacerbations over a 52-week period, was 1.29 in the placebo group and 1.03 in the brensocatib group, showing a 21% reduction by brensocatib. A secondary endpoint was FEV_1 at week 52: There was a decline by 62 ml in the placebo-treated patients and by 24 ml in the patients treated with the highest does (25 mg daily) of brensocatib, a 52% reduction. Aside a higher incidence of hyperkeratosis with brensocatib, there was no other notable difference in the AEs between placebo and brensocatib (Chalmers et al., 2025). No increased incidence of infection was seen between the treatments, a concern related to the depressed NSP activity in this population, that will be also addressed further when brensocatib is clinically used for longer periods of time.

Brensocatib, therefore, a small molecule that successfully targets DPP1 for the first time, provides significant clinical benefits by directly reducing inflammation in patients with bronchiectasis and offers some much-needed option in this indication. It will be interesting to see whether, in the future, brensocatib will also be tested in other indications where excessive neutrophil protease activation is a critical causative component.

6.2 | Nerandomilast

In addition to several non-selective phosphodiesterase 4 (**PDE4**) inhibitors approved for use in dermatological disorders (Carmona-Rocha et al., 2025) and in chronic obstructive pulmonary disease (COPD) (the dual PDE3/4 inhibitor ensinfentrine, Topouzis et al., 2025), a novel PDE4 inhibitor, nerandomilast, secured FDA approval in 2025 for treatment in idiopathic pulmonary fibrosis (IPF). IPF is a chronic, progressive, and fatal lung disease that is characterised by irreversible loss of lung function, poor prognosis and a severely reduced life expectancy (King et al., 2014; Richeldi et al., 2014).

Nerandomilast, in contrast to previously approved non-selective PDE4 inhibitors (rofumilast, apremilast, crisaborole and ensinfentrine), selectively inhibits the PDE4B isoenzyme which is highly expressed in lung macrophages and fibroblasts, over PDE4A, PDE4C or PDE4D (Herrmann et al., 2022), and by doing so it increases intracellular cAMP levels, downregulates the expression of pro-fibrotic growth factors and inflammatory cytokines that are pathologically overexpressed in IPF (such as tumour necrosis factor [TNF]-α, interleukin [IL]-1β and

IL-6) and, consequently, reduces fibroblast proliferation, myofibroblast differentiation and deposition of collagen. Nerandomilast therefore modulates a target at the crossroads of immune and fibrotic pathways and elicits both anti-inflammatory and anti-fibrotic effects (Ibrahim et al., 2025; Reininger et al., 2025). The approved standard-of-care options in IPF, such as nintedanib and pirfenidone, delay but do not arrest the decline in lung function and are burdened with serious adverse effects that can lead to the discontinuation of treatment (King et al., 2014; Richeldi et al., 2014).

In the one year-long, pivotal Phase III clinical trial (Richeldi et al., 2025; NCT05321069), the primary endpoint, mean absolute change from baseline in forced vital capacity (FVC) at week 52, was −114.7 ml in the 18-mg nerandomilast 18-mg group versus −183.5 ml in the placebo group, that is, an adjusted difference of 68.8 ml, combined to an acceptable tolerability profile, with diarrhoea reported in 41.3% of the 18-mg nerandomilast group. Nerandomilast was designated breakthrough therapy and is a noteworthy novel drug because it is the first new approved treatment in more than a decade (since 2014) for this progressive, unrelenting interstitial lung disease, with few and inadequate therapeutic options, and as such it offers new hope to IPF patients.

7 | KIDNEY/METABOLIC/ENDOCRINE

7.1 | Doxecitine + doxribtimine

The nuclear-encoded, mitochondrial enzyme thymidine kinase 2 (TK2) catalyses the conversion of deoxycytidine and thymidine nucleosides to their nucleoside monophosphates. Further phosphorylation gives rise to deoxynucleoside triphosphates, necessary for replication of mitochondrial DNA (mtDNA). The autosomal recessive deficiency of TK2 is characterised by severe myopathy and muscle weakness, correlating with defects of mitochondrial respiratory chain activity and low mtDNA copy number in muscle tissue, and by elevated creatine kinase. Since its original description in 2001, close to 120 patients associated with TK2 deficiency have been reported sporadically. Because of the ultra-rare nature of the disease, it has not been comprehensively described, while prognosis is extremely difficult, due to dependence on the age at onset, the rate of muscle weakness progression and the involvement of the nervous system; it is no surprise that planning of clinical studies in TK2 deficiency has been close to impossible (Ceballos et al., 2024; Garone et al., 2018). Supplementation with deoxynucleoside monophosphates and deoxynucleosides, bypassing the TK2 enzyme defect, has been given under open-label compassionate use in TK2 deficiency patients, with positive reports of clinical efficacy and a favourable side-effect profile (Berardo et al., 2022).

In 2025, the FDA approved a combination of doxecitine and doxribtimine (Kygevvi) to treat TK2 deficiency in adults and paediatric patients who start to show symptoms when they are 12 years old or younger. Doxecitine is a synthetic form of the naturally occurring pyrimidine deoxyribonucleoside deoxycytidine, while *doxribtimine is identical to deoxythymidine*. Kygevvi treatment results in a high systemic concentration of deoxycytidine and deoxythymidine that can be utilised by unaffected salvage pathways, restoring the synthesis of mitochondrial DNA (mtDNA) precursors, and thus the mitochondrial DNA replication and respiratory chain enzyme activities (Chow et al., 2025; Lopez-Gomez et al., 2017).

Due to the rarity of the disease and the compassionate nature of the proposed treatment, the efficacy and approval of Kygevvi in patients with TK2 deficiency with onset of symptoms before 12 years old, was based on data from one Phase II clinical study, two retrospective chart review studies, and an expanded access programme. The survival in patients treated with Kygevvi was compared with the survival in an untreated external control group composed of untreated patients from published literature and one of the retrospective studies in this drug development programme (https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-1st-drug-thymidine-kinase-2-deficiency-very-rare-mitochondrial-disease; Domínguez-González et al., 2025). Data collected by the retrospective study (initiated in 2018; NCT03701568) was derived from 38 Kygevvi-treated and 69 untreated patients, with matched clinical characteristics and a median age of TK2 deficiency symptom onset of 2.5 years. Analyses confirmed a 95% reduction in risk of death in the Kygevvi-treated patients compared with untreated patients. Before treatment, 71.1% of patients lost ≥1 motor milestone and 3.7% regained a milestone. During treatment, no patients lost milestones and 65.4% regained ≥1 milestone. Most (63%) of Kygevvi-related AEs were mild. Collectively, these data provide convincing evidence that pyrimidine nucleos(t)ide therapy is well tolerated, significantly reduces the risk of death, delays disease progression and stabilises or improves motor symptoms in patients with TK2 deficiency. In addition, as related by the FDA site (https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-1st-drug-thymidine-kinase-2-deficiency-very-rare-mitochondrial-disease), survival analysis for 78 matched pairs of treated and untreated patients showed there were three deaths (4%) in TK2 deficiency patients receiving Kygevvi compared with 28 deaths (36%) in the external control group. Mean survival time at 10 years was 9.6 years for the group receiving Kygevvi compared with 5.7 years in the control group. On the basis of this cumulative evidence, Kygevvi received Breakthrough Therapy Designation for this rare indication.

7.2 | Elamipretide

Elamipretide, licensed in 2025 for treatment of patients with Barth syndrome, is the second ever FDA-approved drug targeting a mitochondrial disorder, next to this year's doxecitine and doxribtimine combination (Kygevvi), authorised to treat TK2 deficiency (see above).

Barth syndrome is a rare, X-linked mitochondrial disease affecting primarily males, stemming from the expression of pathogenic variants of the tafazzin, an enzyme essential for cardiolipin synthesis, which trans-acylates immature monolysocardiolipin to mature cardiolipin (Sabbah, 2022; Dong et al., 2025). Barth syndrome manifests early in life, with cardiomyopathy, neutropenia, skeletal myopathy and developmental delay, and severely affects QOL and survival itself. In a

recent study, it was found that 25% of Barth syndrome patients required heart transplantation and many patients had feeding difficulties requiring gastrostomy tubes (Vishwanath et al., 2025).

Elamipretide is a tetrapeptide that enters cells, accumulates in the mitochondria and binds by electrostatic interactions to mitochondrial cardiolipin, a phospholipid critical for mitochondrial structure and electron transport chain function (Acehan et al., 2011; Joshi et al., 2012). Elamipretide, via its interaction with cardiolipin, has been reported to stabilise the mitochondrial membrane, to preserve cristae integrity, to prevent oxidative damage and generation of reactive oxygen species, and to maintain membrane potential and ATP production (Pharaoh et al., 2023; Sabbah et al., 2025; Tung et al., 2025). For some years, elamipretide has been in clinical investigation in a number of diseases associated with mitochondrial dysfunction, such as heart failure, neurodegenerative diseases, renal dysfunction and diabetes (Tung et al., 2025; Sabbah, 2022. In 2025, elamipretide was finally authorised for use in Barth syndrome under an FDA accelerated approval process. In this case, because elamipretide showed that it improved strength of the muscles used to straighten the leg at the knee in the treated patients, the FDA allowed earlier approval on this promise of patient benefit, since other options are inexistent or seriously lacking (https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-treatment-barth-syndrome). A post-approval randomised, double-blind, placebo-controlled trial is expected to follow, seeking to confirm that the changes seen on knee muscle strength translate into broader clinical benefit for the patient, in order to secure full approval of the drug.

7.3 | Elinzanetant

As we reported in our min-review of the 2023 drugs, fezolinetant, the FIC neurokinin 3 (**NK_3**) receptor antagonist, was approved to reduce postmenopausal hot flushes in women (Papapetropoulos et al., 2024). This year, the FDA authorised in the same indication another molecule, elinzanetant, which differs from fezolinetant because it is a dual NK_1/NK_3 receptor antagonist and therefore has a partially overlapping pharmacological profile. While the role of the **NK_3 receptor** (the main receptor for NK-B) is well described in the aetiology of hot flushes, the role of the primary ligand of the **NK_1 receptor**, substance P, is still not very clearly defined in this pathophysiological context, although it has been shown that infusion of substance P leads to face and neck flushing (Schaffalitzky De Muckadell et al., 1986) and that NK_1 receptor is overexpressed in the hypothalamic neurons of postmenopausal women (Sassarini & Anderson, 2024). NK_1 receptor blockade may add to that of NK_3 receptor blockade to reduce hot flushes, by suppressing vasodilatation, tempering heat-sensing neuronal activity and effectively reducing vasomotor symptoms. In addition, clinical data suggest that the antidepressant and sleep-promoting action of NK_1 receptor antagonism may offer additional benefit in this population (Ratti, Bettica, et al., 2013; Ratti, Carpenter, et al., 2013).

The efficacy and safety of elinzanetant were evaluated in two pivotal, 14-week-long Phase III randomised, placebo-controlled clinical studies (OASIS 1: NCT05042362, OASIS 2: NCT05099159; Pinkerton et al., 2024). These studies included postmenopausal women 40 to 65 years old. There were two primary endpoints: reduction of daily frequency of moderate to severe vasomotor symptoms (VMS) and severity of VMS. At 12 weeks, elinzanetant treatment had achieved a reduction by 3.3 VMS more than the placebo, from a baseline frequency of 13.4 a day. In addition, elinzanetant significantly improved VMS severity by 0.35 scale points more than placebo at week 12, from a baseline VMS severity of 2.6. Finally, elinzanetant also improved sleep disturbances and menopause-related QOL at week 12 and showed an overall favourable safety profile, the most frequent side effects being somnolence, fatigue, and headache. Elinzanetant efficacy and safety were further examined in a third, 52-week study (OASIS 3; Panay et al., 2025; NCT05030584), establishing it as a promising and safe treatment for moderate to severe VMS. We will have to wait a few years to compare the dual NK_3/NK_1 antagonist, elinzanetant, to the NK_3 antagonist, fezolinetant, in terms of long-term efficacy and be able to conclude on putative clinical advantages or differences in adverse effect between the two NK receptor antagonists.

7.4 | Sibeprenlimab

Accumulation of deposits of immunoglobulin A (IgA) in the kidneys causes chronic inflammation, impaired renal function and constitutes the most common type of primary glomerulonephritis, IgA nephropathy (IgAN), that will lead, in 20%–40% of cases, to end-stage kidney disease. Besides broader symptomatic management such as **angiotensin-converting enzyme** inhibitors and **angiotensin II receptor** antagonists, immunosuppressants such as corticosteroids and cyclophosphamide are used to slow disease progress. The FDA has approved three treatments for use in IgA nephropathy: budesonide (a corticosteroid), sparsentan (an endothelin type A receptor [**ET_A receptor**] antagonist) and iptacopan (a complement factor B inhibitor) (Papapetropoulos et al., 2024; Stamellou et al., 2023).

This year, the FDA approved a novel, humanised immunoglobulin G2 (IgG2) monoclonal antibody, sibeprenlimab, for use in IgAN, with a novel mode of action: it binds and neutralises a cytokine of the **TNF-α** family, called A Proliferation-Inducing Ligand (**APRIL**). APRIL signals through the Transmembrane Activator and calcium modulator and Cyclophilin ligand Interactor (**TACI**) and through the B-Cell Maturation Antigen (**BCMA**) receptors, which together control B-cell survival, maturation, proliferation and immunoglobulin class switching. The well-documented elevated levels of APRIL in patients with IgAN are thought to be a main driver for the 'four hit' disease onset and progression: B-cell dysregulation, class switching to IgA and survival of plasma cells that produce galactose-deficient IgA1 (Gd-IgA1) (Hit 1), production of autoantibodies against Gd-IgA1 (Hit 2), which are responsible for the formation of immune complexes

(Hit 3) which deposit in the glomeruli and ultimately, with the participation of the complement system, cause glomerular damage, tubulointerstitial fibrosis and loss of renal function (Hit 4) (Cheung et al., 2024; Mathur et al., 2023; Myette et al., 2019). Sibeprenlimab attenuates APRIL signalling via TACI and B-cell maturation antigen (BCMA) and reduces the production of the pathogenic Gd-IgA1. Sibeprenlimab therefore disrupts the pathogenic 'four hit' cascade at its root, displaying a unique pharmacological (APRIL neutralisation) and functional profile among all approved medicines and among all drugs used in IgAN.

To evaluate sibeprenlimab's efficacy and safety, 500 adults with biopsy-confirmed IgAN were enrolled in a Phase III, multicentre, double-blind, randomised, placebo-controlled trial (Perkovic et al., 2025; NCT05248646), and received either placebo or subcutaneous sibeprenlimab every 4 weeks. The pre-specified interim analysis at 9 months was based on data from 320 patients (152 and 168 in the sibeprenlimab and placebo groups, respectively). Participants on sibeprenlimab showed a significant 50.2% decrease in the 24-h urinary protein-to-creatinine ratio as compared with a 2.1% increase with placebo. This clinical endpoint correlated with a 95.8% reduction in the levels of APRIL and a 67.1% reduction in the levels of the pathogenic galactose-deficient IgA1 with sibeprenlimab treatment. The safety profile was similar between sibeprenlimab and placebo, including the incidence of serious AEs (3.5% with sibeprenlimab and 4.4% with placebo) (Perkovic et al., 2025). These interim results secured an accelerated, conditional approval of sibeprenlimab by the FDA; the continuation of approval is contingent on the analysis of the key secondary endpoint, the annualised slope of estimated glomerular filtration rate over 24 months, upon trial completion. Sibeprenlimab, therefore, offers a unique, innovative option in the management of IgAN, since it targets the pathogenic production of Gd-IgA1, which is understood as Hit 1 of the 'four hit' cascade.

8 | OTHER INDICATIONS

8.1 | Acoltremon

Dry eye disease (DED) is a common ocular disorder, defined as 'a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles' (Wolffsohn et al., 2025). Environmental stimuli, such as mechanical pressure, osmolarity or temperature, activate afferent nerves of the ocular surface in addition to trigeminal parasympathetic nerves innervating the nasal cavity, resulting in an efferent parasympathetic response that stimulates the lacrimal functional unit (LFU), consisting of meibomian glands, conjunctival goblet cells and lacrimal glands (Pattar et al., 2025; Wolffsohn et al., 2025). The triggering of this neural mechanism, especially the afferent ocular surface neurons, provides the basis for a new approach in treating DED, by targeting a member of the transient receptor potential (TRP) superfamily, TRP melastatin 8 (**TRPM8**). TRPM8 is an ion channel that transduces cold sensory stimuli in neurons in the cornea and upper eyelids and regulates basal tear production. Of note, genetic deletion of TRPM8 suppresses cold responsiveness and reduces basal tearing but does not affect nociceptor-mediated tearing (Parra et al., 2010). Acoltremon is a FIC TRPM8 positive allosteric modulator with an EC_{50} value about 2000 times lower than that of the agonist molecule menthol for the TRPM8 receptor (Beck et al., 2007; Bödding et al., 2007).

Acoltremon was evaluated in two identical randomised, multicentre, double-blind, vehicle-controlled Phase III studies (Pattar et al., 2025; NCT05285644; NCT05360966), in a total of 931 adults with a DED diagnosis. Participants were treated with either acoltremon eye drops or placebo (vehicle) for 90 days. In the first of the two studies, 42.6% of the acoltremon-treated participants achieved the primary endpoint, a 10 mm or greater increase in unanesthetized Schirmer test (UST) score on Day 14, versus only 8.2% of those in the vehicle group. In the second study the respective numbers were 53.2% versus 14.4%. Reduction in the key secondary endpoint, global Symptom Assessment iN Dry Eye (SANDE) score on Day 28, was also significantly better in the alcotremon group, as was tear production through the 90-day trial period (frequently observable from Day 1). These data provide solid evidence that the FIC acoltremon increases basal tear production and lowers DED symptoms (Pattar et al., 2025), offering a novel approach to patients with DED, besides the current anti-inflammatory molecules, **nicotinic receptor** agonists, or tear evaporation inhibitors, which are associated with multiple adverse effects (Tong et al., 2025).

8.2 | Prademagene zamikerace

In Papapetropoulos et al. (2024), we reported the FIC beremagene geperpavec, a gene-therapy approach approved for dystrophic epidermolysis bullosa (DEB), a rare, genetic, blistering skin disease that is characterised by abnormal shearing of the epidermis from the dermis with the slightest insult, predisposing to infection, sepsis, and development of aggressive cutaneous squamous cell carcinomas. The disease is caused by mutations in *COL7A1*, which encodes type VII collagen. Beremagene geperpavec delivered a correct template of *COL7A1* via an adenovirus vector that re-established the expression of the healthy protein topically at the wound(s).

This year the FDA approved prademagene zamikeracel, a more complex approach to restoring skin integrity and function in DEB. Prademagene zamikeracel is a cell- and gene-based Advanced Therapy Medicinal Product (ATMP): it consists of a cellular sheet of primary, autologous (patient-derived) keratinocytes, which are cultured, transduced with a retrovirus expressing the full-length human *COL7A1* gene and then transferred on a petrolatum gauze and applied to the patient's wounds. In contrast to beremagene geperpavec, prademagene zamikeracel is therefore a strictly personalised therapy.

A 24-week long, Phase III trial (Tang et al., 2025; NCT04227106) was conducted with 11 patients who had a

confirmed clinical and genetic diagnosis of recessive DEB (RDEB), at least two chronic wounds >20 cm^2, had no evidence of an immune response to type VII collagen, and expressed the amino-terminal NC1 fragment of COL7A1. In all, 43 randomised intra-patient wound pairs with matched characteristics were treated with either prademagene zamikeracel or standard of care 1:1. The primary endpoints analysed at week 24 were the proportion of wounds with ≥50% healing, and pain reduction from baseline in the intention-to-treat population of all patients. At week 24, 35 (81%) of 43 wounds treated with prademagene zamikeracel displayed ≥50% healing vs only 7 (16%) of the 43 control wounds. The mean change in wound pain from baseline was −3.07 with prademagene zamikeracel and −0.90 in controls (mean pairwise difference: −2.23). Prademagene zamikeracel treatment was not associated with serious AEs. The promising risk–benefit profile of prademagene zamikeracel in this necessarily small cohort, combined with evidence from a Phase I/IIa trial showing wound healing and reduction of pain and itch after prademagene zamikeracel treatment for up to 8 years (So et al., 2022), supports the therapy's potential to decrease the burden of chronic, large wounds and the associated pain and reduction of QOL in RDEB patients.

8.3 | Revakinagene taroretcel

Another innovative, transduced cell and gene-based therapy was approved by the FDA in 2025: revakinagene taroretcel, for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

Idiopathic macular telangiectasia type 2 (MacTel) is a rare neurodegenerative retinal disorder, manifesting by reduced macular pigment, a characteristic angiographic pattern and a localised clinical presentation that affects the temporal perifovea. The result is progressive visual impairment due to the destruction of the retina, marked by damage to both the photoreceptors and the retinal pigment epithelial cells. Current treatment relies on intravitreal injections of anti-vascular endothelial growth factor (**VEGF**) agents for end-stage neovascular complications.

Müller glial cells support survival and health of photoreceptors by providing a supporting environment that includes neuroprotective cytokines. Ciliary neurotrophic factor (**CNTF**) shifts Müller glial cells to a neuroprotective phenotype and promotes the survival of photoreceptor neurons, preventing photoreceptor-cell loss (LaVail et al., 1992; Ntentakis et al., 2025). In preclinical models of the disease, exogenous CNTF has been shown to limit the signs of neurodegeneration (Chew et al., 2025). To circumvent the short half-life of the CNTF protein that would require frequent injections during (the necessarily) chronic therapy, a long-term delivery method has been developed: revakinagene taroretcel, an intraocular implant, surgically placed into the vitreous cavity, that contains the human retinal pigment epithelial cell line NTC-201-6A, transduced to express recombinant human CNTF. The semipermeable membrane enclosing the cells permits nutrient and oxygen exchange to the cells and prevents intraocular inflammation and rejection by the host immune system. Of note, retrospective analysis (from NCT00063765, NCT00447993, NCT00447980, NCT01530659, NCT03319849, and NCT00447954) suggests that a single implantation of revakinagene taroretcel provides sustained, bioactive CNTF for more than a decade (Chew et al., 2025; Kauper et al., 2025; Ntentakis et al., 2025).

The efficacy and safety of the encapsulated cell therapy (ECT) revakinagene taroretcel in patients with idiopathic macular telangiectasia type 2 (MacTel) was evaluated in two pivotal, randomised sham-controlled Phase III trials (Chew et al., 2025; NCT03316300; NCT03319849). The primary endpoint was rate of change in ellipsoid zone area (EZA) (photoreceptor) loss over 24 months (mm^2/24 months). Secondary outcomes were changes in retinal sensitivity, reading speed, and National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) scores (range, 0 to 100; 100 = better function). Safety evaluation focused on treatment-emergent serious AEs, (among which delayed dark adaptation and miosis).

Adjusted rates of change of ellipsoid zone area (EZA) loss were respectively 0.075 and 0.166 mm^2/24 months in the first trial for implant-treated (n = 58) versus sham-treated (n = 57) patients. In the second trial, the respective numbers were 0.111 (n = 59) and 0.160 mm^2/24 months (n = 54). Miosis, not observed in the sham-treated patients, was experienced by 16% of participants receiving revakinagene taroretcel, and delayed dark adaptation was observed in 20% of the encapsulated cell therapy (ECT)-treated patients versus 1% in the sham group (Chew et al., 2025). The significant reduction in ellipsoid zone area (EZA) loss by revakinagene taroretcel, compared with the sham procedure, is a highly promising, proof-of-concept clinical endpoint, which enabled the FDA approval of this first and only FDA-approved treatment in idiopathic macular telangiectasia type 2 (MacTel). However, given the ability of the implanted encapsulated cell therapy (ECT) to secrete CNTF goes on for years (Kauper et al., 2025), longer trials need to be conducted in order to assess better both the long-term efficacy as well as the safety of this cell-based device.

9 | OTHER NOTABLE APPROVALS

Some drugs approved for treatment in a specific indication in 2025 cannot be considered FIC or even novel based on the criteria we set in Box 1 and in Papapetropoulos et al. (2024), but received approvals worth noting from one (or more) agency/agencies. Their authorisation is expected to significantly impact the management of a common or major disorder affecting a large proportion of individuals globally. We very briefly review below three of these drugs whose approval in 2025 we consider noteworthy.

9.1 | Aceclidine

The **muscarinic receptor** agonist aceclidine (Zhu et al., 2006) has been approved for glaucoma for a few decades already (Romano, 1970).

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)
Aceclidine	Vizz	To treat presbyopia	Selective muscarinic receptor agonist	FDA		Aslam et al., 2025; NCT05728944
Acoltremon	Tryptyr	To treat the signs and symptoms of dry eye disease	Positive allosteric modulator of the transient receptor potential melastatin 8 (TRPM8) thermoreceptor channel	FDA		Pattar et al., 2025
Atrasentan	Vanrafia	To reduce proteinuria in adults with primary immunoglobulin A nephropathy	Endothelin A receptor antagonist	FDA	Acc	Heerspink et al., 2025
Avutometinib and defactinib	Avmapki Fakzynja co-pack	To treat KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC)	Avutometinib: RAF/MEK1 ('clamp' inhibition); defactinib: Focal adhesion kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2) inhibition	FDA	P, Acc, breakthrough therapy	Banerjee, Van Nieuwenhuysen, et al., 2025 Banerjee, Krebs, et al., 2025 NCT04625270; NCT06072781; NCT04625270
Brensocatib	Brinsupri	To treat non-cystic fibrosis bronchiectasis	Competitive, reversible inhibitor of neutrophil dipeptidyl peptidase 1 (DPP1)	FDA		Chalmers et al., 2025
Delgocitinib	Anzupgo	To treat chronic hand eczema	Pan Janus kinase (JAK) inhibitor inhibition of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)	EMA, FDA		Giménez-Arnau, Pinter, et al., 2025
Dordaviprone	Modeyso	To treat diffuse midline glioma harbouring an H3 K27M mutation	Activator of the mitochondrial caseinolytic protease P (ClpP), dopamine $D_{2/3}$ receptor selective antagonist	FDA	P, FT, rare paediatric disease designation	Arrillaga-Romany et al., 2024a; Arrillaga-Romany, Gardner, et al., 2024; Odia et al., 2024
Doxecitine and doxribtimine	Kygevvi	To treat thymidine kinase 2 deficiency	Deoxycytidine and thymidine combination to supplement their deficiency	FDA	P, breakthrough therapy and rare paediatric disease designations	Domínguez-González et al., 2025; NCT03701568; NCT03845712; NCT05017818; NCT06590493
Elamipretide	Forzinity	To improve muscle strength in patients with Barth syndrome	Cardiolipin binder that improves mitochondrial function	FDA	P, FT, Acc, rare paediatric disease designation	Thompson et al., 2024; Gwaltney et al., 2025
Elinzanetant	Lynkuet	To treat moderate-to-severe vasomotor symptoms due to menopause	Selective, dual neurokinin 1 (NK-1) and 3 (NK-3) receptor antagonist	FDA, MHRA		Pinkerton et al., 2024
Etripamil	Cardamyst	To treat episodes of paroxysmal supraventricular tachycardia	L-type calcium channel blocker	FDA		Stambler et al., 2023

TABLE 1 (Continued)

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Gepotidacin	Blujepa	To treat uncomplicated urinary tract infections, including onorrhea	Inhibition of both bacterial DNA gyrase and topoisomerase IV	FDA, MHRA	P, FT, qualified infectious disease product	Wagenlehner et al., 2024; Ross et al., 2025
Imlunestrant	Inluriyo	To treat ER^+, $EGFR2^-$, ER1-mutated advanced or metastatic breast cancer	Binds to and induces degradation of ERα	FDA	FT	Jhaveri et al., 2025
Mirdametinib	Gomekli	To treat neurofibromatosis type 1 with non-resectable symptomatic plexiform neurofibromas	Selective, non-competitive inhibitor of MEK1/2	FDA, EMA, MHRA	P, FT	Moertel et al., 2025; NCT03962543
Nerandomilast	Jascayd	To treat idiopathic pulmonary fibrosis	Phosphodiesterase 4B (PDE4B) selective inhibitor	FDA	P, breakthrough therapy	Maher et al., 2025; Richeldi et al., 2025
Paltusotine	Palsonify	To treat acromegaly	Somatostatin receptor 2 (SST2) agonist	FDA		Gadelha et al., 2024; Luo et al., 2025; Gadelha et al., 2023
Remibrutinib	Rhapsido	To treat chronic spontaneous urticaria	Inhibition of the Bruton's tyrosine kinase (BTK)	FDA		Metz et al., 2025
Rilzabrutinib	Wayrilz	To treat persistent or chronic immune thrombocytopenia	Reversible inhibition of the Bruton's tyrosine kinase (BTK)	FDA		Kuter et al., 2025; Kuter et al., 2023
Sebetralstat	Ekterly	To treat acute attacks of hereditary angioedema	Competitive, reversible inhibitor of plasma kallikrein	EMA, FDA, MHRA	FT	Farkas et al., 2025; Riedl et al., 2024
Sepiapterin	Sephience	To treat hyperphenylalaninemia in patients with sepiapterin-responsive phenylketonuria	Precursor of tetrahydropterin (BH4), the phenylalanine hydroxylase (PAH) co-factor, thus increasing PAH activity	EMA, FDA		Muntau et al., 2024
Sevabertinib	Hyrnuo	To treat locally non-squamous non-small cell lung cancer	Reversible dual inhibitor of HER2 (ERBB2) receptor kinase with activating mutations and of epidermal growth factor receptor (EGFR)	FDA	P, Acc, breakthrough therapy	Le et al., 2025
Sunvozertinib	Zegfrovy	To treat NSCLC with epidermal growth factor receptor exon 20 insertion mutations	Irreversible, selective tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) exon 20 insertion mutants	FDA	P, Acc, breakthrough therapy	Yang et al., 2025
Suzetrigine	Journavx	To treat moderate to severe acute pain	Selective NaV1.8 channel (SCN10A) allosteric inhibitor	FDA	P, FT, breakthrough therapy	Bertoch et al., 2025
Taletrectinib	Ibtrozi	To treat ROS1-positive non-small cell lung cancer (NSCLC)	Inhibitor of ROS1 tyrosine kinase	FDA	PT, breakthrough designation	Nagasaka et al., 2023; Li et al., 2024; Pérol et al., 2025
Vimseltinib	Romvimza	Treatment of symptomatic tenosynovial giant cell tumour	Colony-stimulating factor 1 receptor (CSF1R) kinase inhibitor	FDA, EMA		Gelderblom et al., 2024

(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)
Ziftomenib	Komzifti	To treat elapsed or refractory acute myeloid leukaemia with a susceptible nucleophosmin 1 mutation	Selective menin inhibitor disrupting formation of the menin-KMT2A complex	FDA	PT, breakthrough	Wang et al., 2025
Zoliflodacin	Nuzolvence	To treat uncomplicated urogenital gonorrhoea due to *Neisseria gonorrhoeae*	Blocks ligation of the cleaved covalent complex of DNA gyrase with double-stranded broken DNA to form fused circular DNA	FDA	P, FT, qualified infectious disease product	Luckey et al., 2025
Zongertinib	Hernexeos	To treat non-squamous non-small cell lung cancer	Irreversible inhibitor selective for HER2 (ERBB2) tyrosine kinase mutants, including exon 20 insertions	FDA	P, FT, Acc, breakthrough therapy	Heymach et al., 2025; Heymach, Opdam, et al., 2025
siRNAs/ASO						
Donidalorsen	Dawnzera	To prevent attacks of hereditary angioedema	Prekallikrein-directed antisense oligonucleotide (ASO)	FDA		Fijen et al., 2022; Riedl, Tachdjian, et al., 2024
Fitusiran	Qfitlia	To prevent or reduce the frequency of bleeding episodes in haemophilia A or B	siRNA targeting and causing the degradation of antithrombin mRNA	FDA	FT	Young, Lenting, et al., 2023; Kenet et al., 2024; Young, Srivastava, et al., 2023; Srivastava et al., 2023
Plozasiran	Redemplo	To reduce triglycerides in adults with familial chylomicronemia syndrome	siRNA targeting apolipoprotein C-III	FDA		Watts et al., 2025; Ballantyne et al., 2025
FIC = first-in-class						

Abbreviations: Acc = accelerated approval; Br = breakthrough; FT = fast-track; P = priority.

This year, the FDA approved this miotic drug as a non-invasive, non-surgical corrective agent for presbyopia (Aslam et al., 2025; NCT05728944). Besides surgery/invasive methods and varifocal glasses and contact lenses, only two pharmacological approaches to presbyopia have been evaluated over the years: softening of lens which has hardened with age, to better accommodate adaptation to short distances, and miotic agents, such as pilocarpine (Orman & Benozzi, 2023), which was approved for correction of presbyopia in 2021 (Orman & Benozzi, 2023). Acelidine is therefore the second muscarinic agonist approved for the same indication. No head-to-head study with the two miotic drugs has been conducted, so it will be interesting to compare efficacy and side effects in long-term use, since it seems that they are different enough (Aslam et al., 2025) to bias use by patients.

9.2 | Remibrutinib

The approved Bruton's Tyrosine Kinase inhibitors (BTKi's) ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib and rilzabrutinib are licensed for the management of haematological disorders such as Waldenström's Macroglobulinaemia, Immune Thrombocytopenia and various forms of haematological malignancies, as well as for graft-versus-host-disease (GVHD) (Cool et al., 2024; Rozkiewicz et al., 2023).

Chronic spontaneous urticaria (CSU) is a disorder present in approximately 1% of the general population worldwide, is defined by persistent presence of symptoms for more than 6 weeks, and significantly impairs patients' QOL. More than 50% of autoimmune subtypes (endotypes) of urticaria are caused by IgE and/or IgG antibodies activating mast cells and between 40% and 60% can present with concurrent angioedema. **Histamine H_1 receptor** antagonists remain the major first line treatments, however 50% of patients remain symptomatic, whereas second-line therapies like omalizumab (an IgE-binding MAb) have not been found to induce long-term remission (Giménez-Arnau, Szalewski, et al., 2025). The novel drug remibrutinib is the first BTKi to be authorised in CSU, to treat patients who remain symptomatic despite second generation H_1 receptor antagonist treatment (Kolkhir et al., 2024; Chhiba & Saini, 2025). BTK is expressed in mast cells, basophils, B cells, macrophages and thrombocytes, and is a

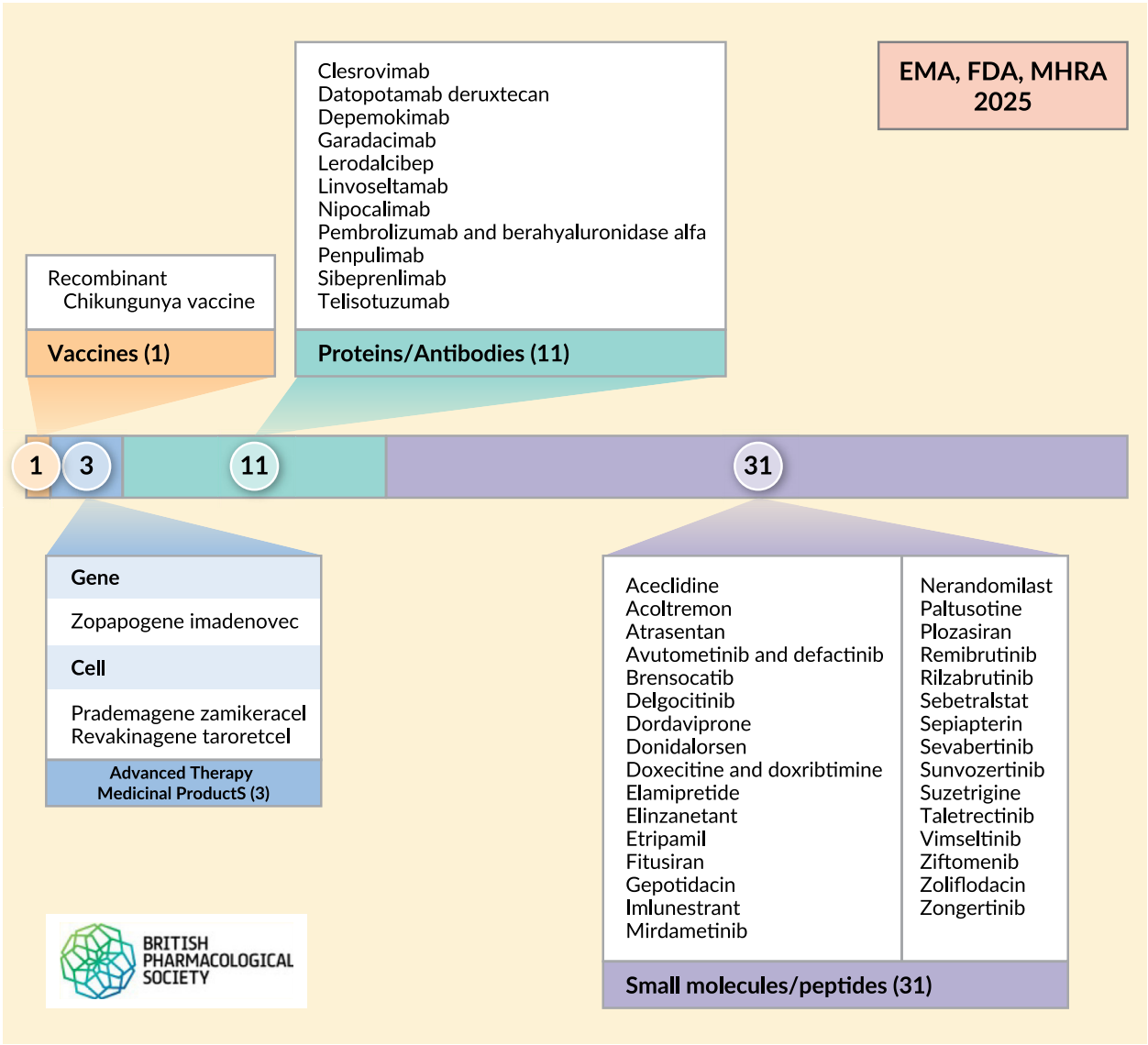

FIGURE 1 New drugs approved in 2025 by the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA) categorised by chemical/biological category.

critical signalling mediator upon engagement of Fc epsilon receptor-1 (FcεR1) by IgE, an event which in CSU results in the release of pro-inflammatory mediators (Bernstein et al., 2024), making BTK a logical therapeutic target in CSU.

In two clinical 52-week Phase III trials (Giménez-Arnau, Szalewski, et al., 2025; NCT05030311; NCT05032157), 613 patients were assigned to remibrutinib and 312 to placebo. The first 24 weeks were conducted following a double-blind protocol, whereas the next 28 weeks followed an open-label treatment. The primary end point was change from baseline in weekly Urticaria Activity Score (UAS) at week 52. At week 52, patients randomised to remibrutinib showed a significant change from baseline in weekly Urticaria Activity Score (UAS) of −23, with similar responses observed in patients who were switched from placebo to remibrutinib at week 24 (notably, with observable effect from week 1). The majority of treatment-associated AEs were mild or moderate in severity (Giménez-Arnau, Szalewski, et al., 2025). The sustained efficacy, rapid onset and the favourable safety profile and tolerability of remibrutinib in these patients supports the use of this BTKi in CSU, providing a valuable additional therapeutic when H_1 receptor antagonists cease to provide respite.

9.3 | Semaglutide

Proving beyond doubt that **GLP-1 receptor** agonists have surpassed every expectation in clinical medicine with their pleiotropic actions, semaglutide's use has been extended to three related indications, all in the cardiometabolic field.

In 2025, the FDA approved injectable semaglutide for the treatment of metabolic-associated steatohepatitis (MASH, also known as nonalcoholic steatohepatitis/NASH) in adults with moderate-to-advanced fibrosis. There is a strong association between MASH

TABLE 2 Proteins and antibodies.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/ mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Clesrovimab	Enflonsia	To prevent respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season	MAb directed to RSV fusion protein	FDA		Zar et al., 2025
Datopotamab deruxtecan	Datroway	To treat unresectable or metastatic, HR-positive, HER2-negative breast cancer	Topoisomerase inhibitor-conjugated, TROP2-directed MAb	FDA, EMA		Bardia et al., 2025
Depemokimab	Exdensur	To treat severe asthma characterized by an eosinophilic phenotype	Ultra-long acting antagonist of interleukin-5 (IL-5)	FDA, MHRA		Jackson et al., 2024; Gill et al., 2025; NCT04719832; NCT04718103
Garadacimab	Andembry	To prevent attacks of hereditary angioedema	MAb against activated Factor XII	EMA, FDA, MHRA		Craig et al., 2023; Craig et al., 2024; Craig et al., 2022; Guilarte et al., 2025
Lerodalcibep	Lerochol	To reduce low-density lipoprotein cholesterol	Anti–proprotein convertase subtilisin/ kexin type 9 (PCSK9) small binding protein	FDA		Klug et al., 2024; Raal et al., 2025 Raal et al., 2023
Linvoseltamab	Lynozyfic	To treat relapsed or refractory multiple myeloma	Bi-specific MAb recognizing B-cell maturation antigen (BCMA) on multiple myeloma cells and CD3 on T cells	EMA, FDA	FT, P, Acc	Bumma et al., 2024
Nipocalimab	Imaavy	To treat generalized myasthenia gravis (gMG) in persons positive for anti-AChR and anti-MuSK antibodies	Neonatal fc receptor (FcRn) blocker	FDA	PT, breakthrough therapy	Antozzi et al., 2025
Pembrolizumab and berahyaluronidase alfa	Keytruda Qlex	To treat solid tumour indications approved for the intravenous formulation of pembrolizumab	Perahyaluronidase alfa enhances dispersion and permeation of co-administered anti-PD-1 MAb	FDA		Felip et al., 2025
Penpulimab	Penpulimab	Treatment of recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC)	Targets programmed cell death-1 (PD-1) and lacks fc gamma receptor (FcγR) binding activity	FDA	FT, breakthrough	Zhong et al., 2024; Chen et al., 2024
Sibeprenlimab	Voyxact	To reduce proteinuria in primary immunoglobulin A nephropathy	Neutralizes APRIL (A PRoliferation-inducing ligand) activity	FDA	Acc, proof of clinical benefit awaited	Perkovic et al., 2025
Telisotuzumab	Emrelis	To treat c-met overexpressing non-squamous non-small cell lung cancer (NSCLC)	c-met-directed ab, conjugeted to the microtubule inhibitor cytotoxic payload monomethyl auristatin E (MMAE)	FDA	P, Acc, breakthrough therapy	Camidge et al., 2024

FIC = first-in-class

Abbreviations: Acc = accelerated approval; AChR = acetylcholine receptor; Br = breakthrough; FT = fast-track; MAb = monoclonal antibody; MuSK = muscle-specific kinase; P = priority; RSV = respiratory syncytial virus.

and excessive body weight and metabolic syndrome, with 80% of patients with MASH being overweight or obese, 72% dyslipidaemic, and 44% diagnosed with Type 2 diabetes (Diehl & Day, 2017). For this reason, use in MASH of an anti-diabetic drug that significantly reduces body weight, such as semaglutide, makes perfect sense. Semaglutide's efficacy was demonstrated in one ongoing, 240-week-long Phase III trial (Sanyal et al., 2025; NCT04822181) with participants continuing to receive their lipid-lowering, glucose-management and weight-loss medications. The planned interim analysis at week 72 showed that resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the 534 patients in the semaglutide group and in only 34.3% of the 266 patients in the placebo group. In addition, the inverse measure, a decrease in liver fibrosis without worsening of steatohepatitis, was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group (Sanyal et al., 2025). This approval, coming on the heels of resmetirom, an agonist of thyroid hormone receptor-β, approved in 2024 (Topouzis et al., 2025), offers additional, valuable options in the therapeutic management of MASH.

An oral route form for semaglutide has been approved for the treatment of diabetes for several years, after a feat of pharmaceutical technology formulated the drug in a tablet form with sodium N-(8-[2-hydroxybenzoyl] amino-caprylate, a molecule that both enhances absorption and reduces the GLP-1 agonist's degradation (Gatto et al., 2025). This year, the FDA also approved oral semaglutide for 'reducing the risk of major adverse cardiovascular events such as cardiovascular (CV) death, heart attack, or stroke in adults with type 2 diabetes who are at high risk for these events, whether they've had a prior CV event or not (primary and secondary prevention)'. The FDA also approved oral semaglutide for weight loss (https://www.prnewswire.com/news-releases/fda-approves-novo-nordisks-wegovy-pill-the-first-and-only-oral-glp-1-for-weight-loss-in-adults-302648344.html), based on a Phase III trial, in which semaglutide reduced body weight in overweight or obese participants with no diabetes by 13.6% compared to a reduction of 2.1% by placebo (Wharton et al., 2025). Since use of GLP-1 agonists, including oral semaglutide (Badve et al., 2025; Gatto et al., 2025; Husain et al., 2019) has been shown to significantly reduce the risk of adverse cardiovascular events in diabetes patients (McGuire et al., 2025), the approval of semaglutide in pill form, more patient-friendly than injection, can be a transformative treatment in reducing the increasing global burden of metabolic and CVD.

10 | OVERALL CONCLUSIONS

A brief glance at the metrics shows that the newly approved drugs display both points of convergence and divergence when set against the 2023 and 2024 data.

TABLE 3 Advanced therapy medicinal products (ATMP).

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Prademagene zamikeracel	Zevaskyn	Treatment of recessive dystrophic epidermolysis bullosa (RDEB)	Topically applied sheet of autologous cells expressing the *COL7A1* gene	FDA		Tang et al., 2025
Revakinagene taroretcel	Encelto	Treatment of idiopathic macular telangiectasia type 2	Intraocular implant of rhCNTF-expressing allogeneic retinal cells	FDA		Chew et al., 2025; NCT03316300; NCT03319849
Zopapogene imadenovec	Papzimeos	Treatment of recurrent respiratory papillomatosis	Gorilla adenovirus vector platform (GC46) expressing a fusion antigen composed of selected regions from HPV types 6 and 11 proteins	FDA	P, breakthrough therapy	Norberg et al., 2025
FIC = first-in-class						

Abbreviations: Acc = accelerated approval; Br = breakthrough; FT = fast-track; P = priority.

TABLE 4 Vaccines.

Active ingredient/s	Proprietary name	Approved therapeutic use	Molecular target/mode of action	Approving agency	Approval type	Pivotal clinical trial(s)
Recombinant chikungunya vaccine	Vimkunya	Prevention of disease caused by chikungunya virus	Recombinant chikungunya proteins assembled in virus-like particles (VLPs)	EMA, FDA, MHRA	P, Acc	Richardson et al., 2025; Tindale et al., 2025
FIC = first-in-class						

Abbreviations:Acc = accelerated approval; Br = breakthrough; FT = fast-track; P = priority.

BOX 3 Orphan drugs (19).

Avutometinib and defactinib	Donidalorsen
Dordaviprone	Doxecitine and doxribtimine
Elamipretide	Fitusiran
Garadacimab	Linvoseltamab
Mirdametinib	Penpulimab
Prademagene zamikeracel	Revakinagene taroretcel
Sebetralstat	Sepiapterin
Sevabertinib	Taletrectinib
Vimseltinib	Ziftomenib
Zopapogene imadenovec	

The most notable difference lies in the overall number of newly approved medicines, which declined to 46 in 2025, down from 53 in 2024 and even more compared to a soaring 70 in 2023. In the Introduction, we attempted to offer reasons that underlie this observation. On the other hand, maintained trends are the predominance of small molecules, including RNAi therapeutics (67%; Table 1, Figure 1), followed by a high percentage of novel drugs that are proteins/antibodies: 24% in 2025 (Table 2, Figure 1), compared with 28% in 2024 and 23% in 2023. We attribute this constantly high proportion (compared to percentages 10 or 20 years ago) to two main factors: (a) It is very hard or sometimes impossible to modify certain targets by small molecules, making the development of protein therapeutics targeting them a must, and (b) the protein engineering technology, especially that of antibodies, has matured and is now able to produce very innovative products, for example, bi-specific polypeptides or MAbs

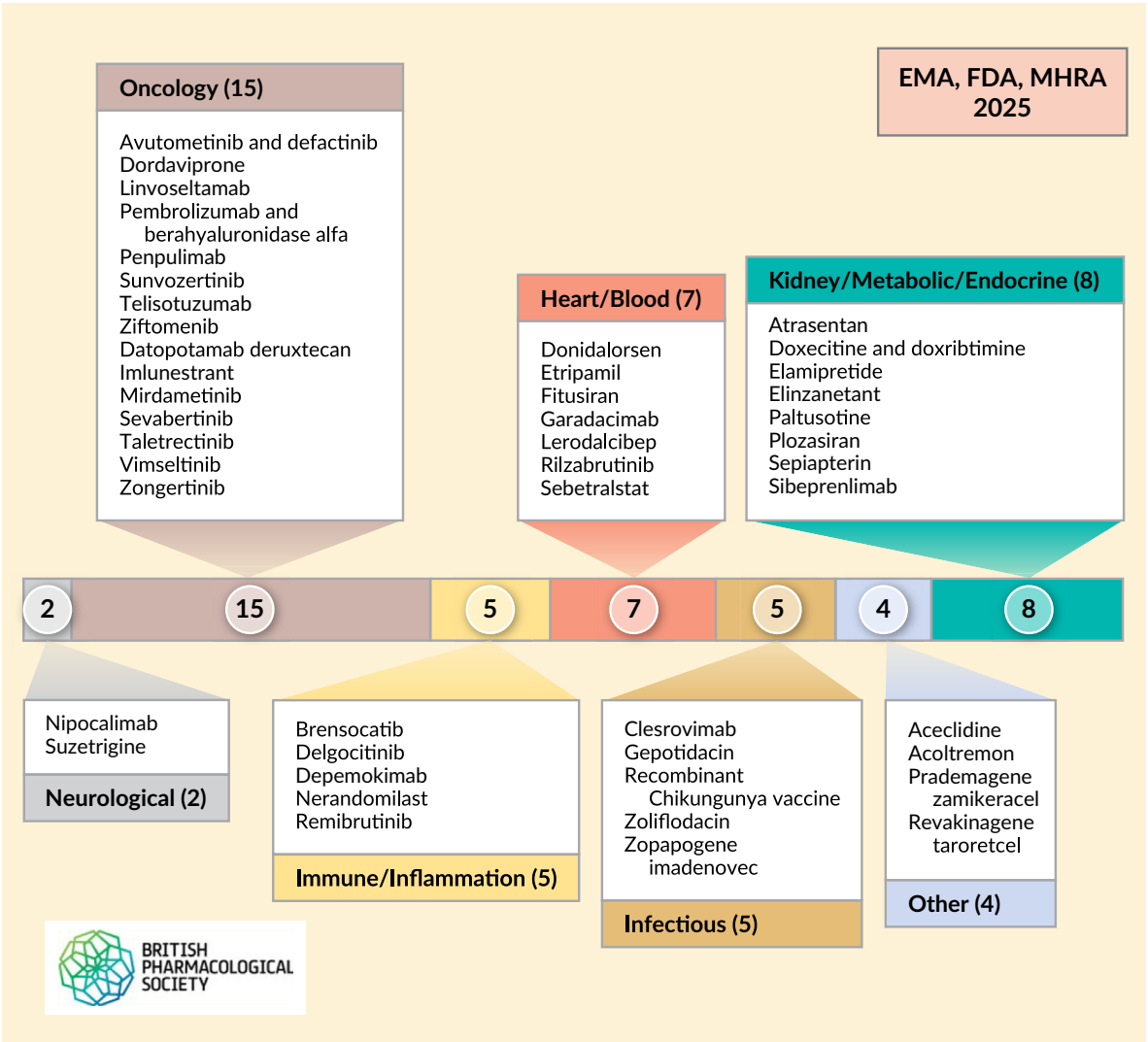

FIGURE 2 New drugs approved in 2025 by the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA) by therapeutic area/category.

bearing a rationally engineered Fc domain. Also, in keeping with recent trends, 2025 has seen the approval of three novel RNA-therapeutics (Table 1 and Figure 1), and three Advanced Therapy Medicinal Products (ATMPs) (Table 3 and Figure 1) and one new vaccine (Table 4 and Figure 1). Again, this year, a substantial proportion of the novel agents are intended for relatively small patient populations, reflected by the designation of approximately 41% (19 of 46) of the 2025 approvals for 'orphan' indications (very similar to 40% in 2024; listed in Box 3). This seems to be an industry strategy based both on unmet medical needs associated with 'niche' diseases and on the opportunity to introduce and validate innovative approaches and drugs first in orphan indications, and later use them to treat more significant patient populations.

In keeping with 2023 and 2024 (Papapetropoulos et al., 2024; Topouzis et al., 2025), oncology drugs again constitute the largest group (Figure 2): 15 out of 46 drugs approved in 2025, vs 16 out of 70 drugs in 2023 and 16 out of 53 novel drugs in 2024.

The 2025 harvest may be smaller, but the innovation and ingenuity in pharmacology and drug design cannot be missed – quite the contrary. In this respect, some interesting approvals in 2025 include the following:

- Dordaviprone, a molecule with a wildly diverse pharmacological profile: inducer of TRAIL and of integrated stress response, allosteric agonist of the mitochondrial caseinolytic protease and antagonist of $D_{2/3}$ dopamine receptors. These characteristics contribute to the highly unconventional anti-cancer potential of dordaviprone and make it a putative 'agnostic' therapeutic.
- A unique combination of *two* FICs, a RAF/MEK clamp, avutometinib, paired with a FAK/Pyk2 inhibitor, defactinib, to more efficiently block than either molecule alone the RAS–RAF–MEK–ERK/FAK oncogenic pathway in low-grade serous ovarian cancer. Since other solid tumours are driven by this signalling mechanism, this combination is also a putative 'agnostic' drug.
- A potent non-opioid analgesic, suzetrigine, a selective inhibitor of $Na_v1.8$ sodium channels, offers new hope in global efforts to limit and replace opioid use.
- The first Factor XIIa inhibitor, garadacimab, which blocks this upstream initiator of the prekallikrein/bradykinin production, and which takes a totally different tack in the treatment of hereditary angioedema (HEA) from other, also 2025-approved molecules such as the liver prekallikrein ASO donidalorsen and the prekallikrein inhibitor, sebetralstat. This diversity in targeting of a single pathway exemplifies the innovation potential of pharmacology.
- Fitusiran, the first RNAi therapy of haemophilia, targeting for the first time the production of the natural anticoagulant antithrombin in the liver.
- The first adnectin (small −11 kDa in this case- fragment of a polypeptide), lerodalcibep, identified by screening of an mRNA library, which was further affinity-engineered to inhibit the LDL receptor degrading enzyme, PCSK9. Notably, lerodalcibep provides a proof-of-concept for this ingenious approach to (future) drug identification and design.
- The first DPP1 protease inhibitor, brensocatib that attenuates the activation of downstream neutrophil proteases by DPP1, preventing tissue destruction in bronchiectasis and, perhaps, in the future, in other indications where pathogenic activation of neutrophil proteases is a causative driver.
- The first recombinant chikungunya virus vaccine, Vimkunya, for the treatment of a globally spreading infectious threat.
- The first inhibitor of the cytokine APRIL, sibeprenlimab, that attenuates the pathogenic B-cell maturation, proliferation and immunoglobulin class switching mediated by the APRIL receptors TACI and B-cell maturation antigen (BCMA) in IgA nephropathy.
- The first positive allosteric modulator of the channel Transient Receptor Potential Melastatin 8 (TRPM8), acoltremon, that increases basal tear production in dry eye disease, a globally common disorder.
- The first specific treatment for recurrent respiratory papillomatosis, zopapogene imadenovec, an adenovirus vaccine expressing HPV6 and HPV11 protein antigens, which elicits robust T-cell immunity specific to HPV6 or 11 and severely limits the need for repeated surgical intervention.

10.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/26 (Alexander, Cidlowski, Gibb, et al., 2025; Alexander, Davenport, Kelly, et al., 2025; Alexander, Fabbro, Gibb, et al., 2025; Alexander, Fabbro, Peach, et al., 2025; Alexander, Gibb, Kelly, et al., 2025; Alexander, Striessnig, Gibb, et al., 2025).

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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

P. F. is the founder and CEO of Pharmahungary Group, a group of R&D companies developing cardioprotective therapies and holding patents on cardioprotective molecules.

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