Recent developments of HDAC inhibitors: Emerging indications and novel molecules

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The histone deacetylase (HDAC) enzymes, a class of epigenetic regulators, are historically well established as attractive therapeutic targets. During investigation of trends within clinical trials, we have identified a high number of clinical trials involving HDAC inhibitors, prompting us to further evaluate the current status of this class of therapeutic agents. In total, we have identified 32 agents with HDAC-inhibiting properties, of which 29 were found to interact with the HDAC enzymes as their primary therapeutic target. In this review, we provide an overview of the clinical drug development highlighting the recent advances and provide analysis of specific trials and, where applicable, chemical structures. We found haematologic neoplasms continue to represent the majority of clinical indications for this class of drugs; however, it is clear that there is an ongoing trend towards diversification. Therapies for non-oncology indications including HIV infection, muscular dystrophies, inflammatory diseases as well as neurodegenerative diseases such as Alzheimer’s disease, frontotemporal dementia and Friedreich’s ataxia are achieving promising clinical progress. Combinatory regimens are proving to be useful to improve responsiveness among FDA-approved agents; however, it often results in increased treatment-related toxicities. This analysis suggests that the indication field is broadening through a high number of clinical trials while several fields of preclinical development are also promising.

KEYWORDS
belinostat, epigenetics, HDAC inhibition, panobinostat, romidepsin, vorinostat

INTRODUCTION

Epigenetic modifications, a range of heritable changes in the genome that occur without changes in the DNA sequence, can alter DNA accessibility, chromatin structure and subsequently regulate gene expression patterns. Encompassing three major mechanisms, DNA methylation, histone modifications and nucleosome positioning, these modifications are enzymatically reversible and play numerous roles in human physiology and pathophysiology1,2; it is not surprising that epigenetic modifications had been a subject of significant interest as potential therapeutics.3 To date, DNA methylation and two types of histone modification, methylation and acetylation, have achieved relatively high success; all of the epigenetic modulators currently approved by the Food and Drug Administration (FDA) target these mechanisms.4 In this review, we focus on histone acetylation, a major post-translational modification (PTM) with significant relevance in a wide range of physiological and pathophysiological processes.

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The mechanism of histone acetylation involves covalent addition of an acetyl moiety to the lysine ε-amino group on the histone protein tails, and is mediated by the counteracting action of two enzymes, the histone acetyltransferases (HATs) and histone deacetylases (HDACs).\(^5\) Originally identified as a PTM in histones,\(^6\) acetylation has subsequently been identified as a commonly occurring PTM in a wide range of non-histone proteins.\(^7\) Biologically, protein lysine acetylation results in the neutralization of the positive charge of the ε-amino group and has been identified to be involved in the regulation of a wide range of processes, such as gene transcription, protein folding or cytoskeleton organization.\(^7,8\) Dysregulation of the mechanism is also linked to a number of pathologies, including cancer and neurologic, immune, metabolic and inflammatory diseases, further highlighting its therapeutic potential.\(^9\) Throughout the past 30 years, modulating HDACs has been of particular interest to the scientific community,\(^10\) leading to five FDA-approved drugs that target HDACs and a growing number of agents in development.

During our investigation of trends within clinical trials,\(^11\) we noticed a relatively high number of studies involving both novel and established HDAC inhibitors, prompting us to further investigate this interesting class of therapeutic agents. Therefore, the aim of this review is to provide a comprehensive overview of the current trends in HDAC inhibitors research and clinical uses.

## HDAC ENZYMES OVERVIEW

The HDAC enzymes are highly evolutionarily conserved proteins that are also found in plants, animals and fungi.\(^14\) Overall, these enzymes are grouped into two main families, the classical HDAC family (arginase/deacetylase superfamily) and the Sir2 regulatory family (deoxyhypusine synthase-like NAD/FAD-binding domain superfamily).\(^15\) In humans, 18 HDAC enzymes are currently known which are grouped into four classes based on their homology with yeast proteins: the Class 1 Rpd3-like proteins, the Class 2 Hda1-like proteins, the Class 3 Sir2-like proteins and the Class 4 proteins.\(^15,16\) Class 1 consists of HDACs \(^1,\) \(^2,\) \(^3\) and \(^8\); Class 2 is sub-classified into Class 2a (HDACs \(^4,\) \(^5,\) \(^7,\) \(^9\)) and Class 2b (HDACs \(^6\) and \(^10\)); Class 3 is also referred to as sirtuins (SIRT), and consists of SIRT \(^1,\) \(^2,\) \(^3,\) \(^4,\) \(^5,\) \(^6\) and \(^7\); and Class 4 is represented by HDAC11. Figure 1 provides a schematic depiction of the classical HDAC enzymes (Classes 1, 2 and 4) which are the molecular targets for FDA-approved and investigative agents in clinical development included in our dataset.

Members of the Class 1 HDACs are characterized by ubiquitous tissue expression patterns and nuclear localization (HDACs \(^1,\) \(^2,\) \(^3\))\(^20\) while HDAC8 is smooth muscle-specific and characterized by nuclear and cytoplasmic localization.\(^21\) The HDACs \(^1,\) \(^2\) and \(^3\) are present within large multiprotein complexes; HDACs \(^1\) and \(^2\) are co-expressed in several major multiprotein co-repressor complexes, including Sin3, NuRD, CoREST, MiDAC and MIER family,\(^22\) while HDAC3 is a catalytic subunit of SMRT and N-CoR complexes.\(^23\) All three isoforms are major nuclear deacetylases. Distinct from the other Class 1 isoforms, HDAC8 functions independently of multiprotein complexes and is generally characterized by a higher catalytic efficiency against the acetyl lysine substrates, as compared to the acetyl lysine.\(^24,25\)

The Class 2 enzymes are expressed in a more tissue-specific pattern. The Class 2a isoforms HDAC 4 and 5 are expressed in the brain, heart and skeletal muscles;\(^26\) HDAC7 is expressed in the heart, lungs, placenta, pancreas, skeletal muscles and thymus;\(^27,28\) and HDAC9 is expressed mainly in the brain and skeletal muscle,\(^29\) while the Class 2b member HDAC6 is expressed in the heart, skeletal muscles and brain,\(^26\) and HDAC10 is expressed in the liver, spleen and kidney.\(^30\) The Class 2 enzymes are able to “shuttle” between the nucleus and cytoplasm in response to certain cellular signals owing to the presence of a nuclear localization signal, a nuclear export signal, or via co-localization together with other proteins or HDACs.\(^20\) The subclass is characterized by a reduced catalytic activity and no natural

![FIGURE 1 Schematic structure of classical HDAC enzymes](image)

**Key:**
- Class 1 deacetylase domain
- Class 2a deacetylase domain
- PAZ domain
- 14-3-3 binding site
- Class 4 deacetylase domain
- Class 2b deacetylase domain
- MEF2 binding site
- Coiled-coil motif

Gregoretti et al.\(^16\)
substrate had been described as of yet; it is presumed that the Class 2a deacetylase activity is dependent on binding with the HDAC-multiprotein complexes, such as HDAC3-SMRT/N-CoR. Among the Class 2b enzymes, HDAC6 is distinct for its predominantly cytoplasmic localization, presence of two functionally independent catalytic domains and the ubiquitin-binding zinc finger domain. In addition to being a major histone deacetylase, its substrates include several cytoplasmic non-histone proteins, such as α-tubulin, cortactin, Ku70 and HSP90. HDAC10 is localized in the nucleus and cytoplasm, and functions as a transcriptional repressor, acting as a robust acetyl polyamine hydrolase.

The only Class 4 enzyme, HDAC11, is expressed in the brain, heart, kidneys, testis, as well as in the skeletal muscles and has nuclear localization. It is notable for a high fatty-acid acylase catalytic efficiency. It is suggested that the HDAC11 internal pocket is related to HDAC8.

The HDAC enzymes have also been shown to possess a varying degree of catalytic reactivity towards acetylated lysine: only HDACs 1, 2, 3 and 6 have been shown to act as observable lysine deacetylases in vitro, while the Class 2a isozymes, HDAC8 and HDAC11 only deacetylate trifluoroacetyl lysine. A summary on the biological functions of classical HDACs, as well as the impact of associated knockout phenotypes, is presented in Table 1.

The aberrant expression of all the classical HDAC enzymes is most notably linked with cancer and typically associated with advanced disease and poor patient outcomes. However, there is evidence that the Class 1 proteins HDAC1, HDAC2, HDAC3 and HDAC8 have potential tumour-suppressor roles; the three enzymes have been described to be involved in maintaining genomic stability and the experimental data from animal models have shown loss-of-function mutants to result in tumorigenesis. In neuropathology, HDAC2 is linked to synaptic count and plasticity, along with dendritic spine density, and is reported to be a possible target in Alzheimer’s disease (AD). HDAC6 is another notable isozyme that is associated with a wide variety of processes involved in neurodegeneration. A recent in vitro/in vivo study additionally suggests HDAC3 to be a potential target that is linked to brain-derived neurotrophic factor (BDNF) and hyperphosphorylated τ-protein levels. Other documented HDAC involvement in human pathology includes viral silencing induction, particularly in HIV infection, diabetes, and immune-mediated diseases, notably chronic obstructive pulmonary disease.

Such an array of therapeutic possibilities involving the HDACs contributes to the growing interest in exploiting these enzymes as drug targets. In fact, it was the discovery of the naturally occurring HDAC inhibitors trichostatin A (TSA) and trapoxin A/B that preceded the elucidation of the biology of individual HDACs. In the next section, we will provide an introduction to the HDAC inhibitors as a class of therapeutic agents, as well as discuss a brief methodology of the dataset used in our study.

### TABLE 1 Biological functions of the classical HDAC enzymes. This table presents a summary of the biological functions of classical HDAC enzymes. The Physiological implications column presents some of the known involvement of HDACs in physiology. The Knockout phenotype column is cited as per Yoshida et al.

| HDAC class | HDAC isozyme | Physiological implications | Knockout phenotype |
|------------|--------------|---------------------------|--------------------|
| Class 1    | HDAC1        | Embryonic development, neuronal differentiation | Embryonic lethality due to severe proliferative defect |
|            | HDAC2        | Embryonic development, neuronal differentiation | Perinatal lethality due to severe cardiac defects |
|            | HDAC3        | Embryonic development, circadian rhythms energy metabolism, neuronal function and bone remodelling | Embryolic lethality |
|            | HDAC8        | Energy homeostasis, muscle contraction, microtubule integrity | Perinatal lethality due to skull instability |
| Class 2    | HDAC4        | Chondrocyte differentiation | Postnatal day 10 death, premature ossification of developing bones |
|            | HDAC5        | Chondrocyte differentiation, osteocyte mechanotransduction | Cardiac deficiency |
|            | HDAC6        | Neuronal differentiation | Viable, no visible pathology |
|            | HDAC7        | Cardiac remodelling, neuroprotection, endochondral ossification | Embryonic lethality due to dilatation and rupture of blood vessels |
|            | HDAC9        | Cardiac gene expression, vascular calcification | Cardiac deficiency |
|            | HDAC10       | Immunoregulation | Viable |
| Class 4    | HDAC11       | Immunoregulation, muscle metabolism, myoblast differentiation | Viable |
Inhibitory activities in selected HDAC inhibitor classes. This table presents the inhibitory activities (IC50) of the clinically established classes of HDAC inhibitors, summarized as per Ho et al.10

| HDAC class | HDAC isozyme | Vorinostat | Tucidinostat | Romidepsin | Panobinostat | Belinostat |
|------------|--------------|------------|--------------|------------|--------------|------------|
| Class 1    | HDAC1        | 60 nM      | 0.1 μM       | 1 nM       | 3 nM         | 26 nM      |
|            | HDAC2        | 42 nM      | 0.2 μM       | 1 nM       | 2 nM         | 22 nM      |
|            | HDAC3        | 36 nM      | 0.1 μM       | 1 nM       | 2 nM         | 19 nM      |
|            | HDAC8        | 173 nM     | 0.7 μM       | >1000 nM   | 22 nM        | 22 nM      |
| Class 2    | HDAC4        | 20 nM      | >10 μM       | 647 nM     | 1 nM         | 15 nM      |
|            | HDAC5        | 36 nM      | >10 μM       | >1000 nM   | 1 nM         | 25 nM      |
|            | HDAC6        | 29 nM      | >10 μM       | 226 nM     | 1 nM         | 10 nM      |
|            | HDAC7        | 129 nM     | >10 μM       | >1000 nM   | 2 nM         | 51 nM      |
|            | HDAC9        | 49 nM      | >10 μM       | >1000 nM   | 1 nM         | 24 nM      |
|            | HDAC10       | 60 nM      | 0.1 μM       | 1 nM       | 31 nM        | 59 nM      |
| Class 4    | HDAC11       | 31 nM      | 0.4 μM       | 0.3 nM     | 4 nM         | 27 nM      |

HDAC inhibitors act by inducing hyperacetylation in histone and non-histone proteins in cells and subsequently impact a wide range of effects in tumour and non-tumour cells. In cancer, hyperacetylation of histones alters the expression of epigenetically repressed genes in tumour cells, resulting in the induction of cell cycle arrest, apoptosis, senescence, differentiation and immunogenicity, as well as in the inhibition of angiogenesis.9 The hyperacetylation of the non-histone proteins, such as transcriptional factors and chaperone proteins, is also believed to be of importance. One example is hyperacetylation of the tumour-suppressing transcriptional factor p53, which results in its enhanced transcriptional activity, altering target gene expression and leading to tumour suppression.9,55 Hyperacetylation of the chaperone protein HSP90 can lead to the release and subsequent degradation of various oncogenic client proteins.55 HDAC inhibitors have also been shown to downregulate MYC expression in some solid tumours and leukaemia.9

In our dataset, we have identified 32 unique HDAC inhibitors. Of these, five agents are clinically established HDAC inhibitors, 11 are investigational HDAC inhibitors of the hydroxamic acid class, 11 are investigational molecules of non-hydroxamate nature and two are uncategorized investigational molecules. Additionally, we include three clinically established molecules with HDAC inhibitory activity reported as one of their mechanisms of action. Figure 2 illustrates the number of approved and investigational agents that target each HDAC protein, as well as the phylogenetic relationship between the classical HDACs. The data was extracted from updated versions of our previously published analyses on drug–target interactions of both US FDA-approved agents as well as agents in clinical development.11–13 These studies were originally based on information from the Drugs in Clinical Trials Database (discontinued) from CenterWatch80 and the DrugBank database81 and spans from 1983 to 2019. The targets, mechanisms of action, and indications were manually assessed using published studies and public databases including Drugs@FDA,82 EMA (European Medicines Agency) Medicines83 and NICE (National Institute of Health and Care Excellence) Technology appraisal guidance databases.84 US clinical trial information was

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**TABLE 2** Inhibitory activities in selected HDAC inhibitor classes. This table presents the inhibitory activities (IC50) of the clinically established classes of HDAC inhibitors, summarized as per Ho et al.10
obtained from the National Institute of Health Clinical Trials. Where applicable, EU clinical trial information, identified through the EMA EU Clinical Trials Register, was additionally included.

In the coming sections we will discuss the current status of the clinical use of and research into HDAC inhibitors. For approved agents, we will focus on the efficacy, safety and the impact on quality-of-life, as well as the pharmacogenetic aspects associated with their use. A comprehensive summary of the investigative agents in relation to their potential uses and highlighting relevant pre-clinical and/or clinical supporting evidence will also be presented.

4 | APPROVED HDAC INHIBITORS

In total, five agents with confirmed HDAC-mediated mechanism of action for treatment of different indications have been approved as of 2020: vorinostat, belinostat, romidepsin, tucidinostat and panobinostat (Table 3). The chemical structures of the currently approved agents are shown in Figure 3 (hydroxamic acid agents) and Figure 4 (non-hydroxamic acid agents). So far, the most clinically successful indications are haematological neoplasms, represented by T-cell lymphomas and multiple myeloma (MM). The first clinically successful HDAC inhibitor was the hydroxamic acid derivative SAHA, also known as vorinostat (Zolinza®). It is an orally available pan-HDAC inhibitor, approved by the FDA in 2006 for treatment of cutaneous T-cell lymphoma (CTCL). Other approved agents of the hydroxamate class are belinostat (Beleodaq®), an intravenous pan-HDAC inhibitor approved by the FDA for peripheral T-cell lymphoma (PTCL) in 2014, and panobinostat (Farydak®), another orally active pan-HDAC inhibitor approved by the FDA (2015) and EMA (2015) for MM. The non-hydroxamic benzamides class includes tucidinostat (Epidaza®), also referred to as chidamide, which is an orally active Class 1 and 2-specific agent that was approved by China’s National Medical Products Administration in 2014 for use in PTCL and in 2019 for use in postmenopausal advanced breast cancer patients in combination with exemestane, a steroidal aromatase inhibitor. Romidepsin (Istodax®), an intravenous cyclic depsipeptide, is also specific to Classes 1 and 2 and was approved by the FDA in 2009 for CTCL and in 2011 for PTCL.

4.1 | HDAC inhibitors in cutaneous T-cell lymphoma

CTCL is a type of primary cutaneous lymphoma, a heterogeneous group of non-Hodgkin lymphomas presenting in the skin with no evidence of extracutaneous disease at the time of diagnosis. Mycosis fungoides (MF) and Sézary syndrome (SS) are the classic types of
CTCL; MF is the most common subtype, while SS is a rare, leukaemic form of the disease.89 The prognosis in early-stage disease is generally positive with skin-directed treatment options being the most preferable option90; however, the impact of available treatment options on survival in advanced disease is still poor. Below we list results from important clinical studies of the two FDA-approved agents vorinostat and romidepsin in terms of efficacy, safety and quality-of-life assessment.

Vorinostat is identified in 18 clinical trials in ClinicalTrials.gov for treatment of CTCL and here we discuss five of the key studies. The original approval of vorinostat was based on the results of a pivotal phase 2b multicentre open-label trial91 investigating the efficacy and safety of the drug taken as 400 mg in 74 patients who had received at least two prior therapies (\(n = 74\)). This study was initiated after a phase 2 study92 that investigated the efficacy and safety of 400 mg and 300 mg daily regimens in patients with CTCL that were refractory/intolerant to at least one treatment (\(n = 33\)). The pivotal study showed predominantly partial response with only a single patient responding fully. The overall response was 29.7% with an estimated median duration of 5.5 months, while 48% of the patients achieved a stable disease state. In patients with advanced disease (IIb, III, IVa and IVb; \(n = 61\)), the response was 29.5% with an estimated duration of 6 months. Patients with SS (\(n = 30\)) have shown an overall response of 33.3%, lasting 5.5 months. Quality-of-life assessment showed pruritus relief in 32.3% of patients with moderate baseline itching (\(\geq 3\) score) and in 43.3% with severe baseline itching (7–10 score). Among the responding patients (\(n = 21\)), 47.8% showed improvement. A post-hoc analysis of the subset of long-term users (\(\geq 2\) years; \(n = 6\)) from the pivotal study showed 83.3% overall responsiveness with a single stage IIb MF patient responsive to vorinostat for > 4 years.93 The safety profile showed predominantly mild (grade 1–2) adverse effects (AE), typically including gastrointestinal, haematologic and constitutional disturbances. The most common AEs overall were diarrhoea (48.6%; all grade 1–2), fatigue (45.9%; 5.4% grade 3–4), nausea (43.2%; 4.1% grade 3–4), anorexia (25.7%; 2.7% grade 3–4), dysgeusia (24.3%; all grade 1–2), thrombocytopenia (21.6%; 5.4% grade 3–4) and weight decrease (20.3%; 1.4% grade 3–4). Thromboembolic events (5.4%), particularly

### Table 3

| Generic name | Trade name | Chemical class | Enzyme specificity | Approved indication | Efficacy profile | Safety profile |
|--------------|------------|----------------|-------------------|--------------------|-----------------|---------------|
| Vorinostat   | **Zolinza** | Hydroxamic acid | Pan-HDAC          | CTCL monotherapy   | 29.7% OR, 1.8 months TTR, \(\geq 6.2\) months DOR, 4.9 months TTP | Grade 1–2 GI, constitutional and haematological AEs; potentially fatal thromboembolic events, risk of cardiac abnormalities |

| Romidepsin   | **Istodax** | Cyclic depsipeptide | Class 1           | CTCL monotherapy   | 34% OR, 2 months TTR, 15 months DOR, 8 months TTP 25% OR, 1.8 months TTR, 16.6 months DOR | Grade 1–2 GI, constitutional and haematological AEs, tumour lysis syndrome, risk of cardiac abnormalities |

| Belinostat   | **Beleodaq** | Hydroxamic acid | Pan-HDAC          | PTCL monotherapy   | 25.8% OR, 5.6 months TTR, 8.4 months DOR | Grade 1–2 GI, constitutional and haematological AEs, tumour lysis syndrome, hepatic failure, risk of cardiac abnormalities |

| Tucidinostat | **Epidaza** | Benzamide       | Class 1 and 2     | PTCL monotherapy   | 29% OR, 1.4 months TTR, 9.9 months DOR | Grade 1–2 GI, constitutional and haematological AEs, risk of cardiac and hepatic abnormalities |

| Panobinostat | **Farydak** | Hydroxamic acid | Pan-HDAC          | MM (in combination with dexamethasone and bortezomib) | 58.5% OR, 12 months PFS | Severe diarrhoea, GI, constitutional, haematologic AEs, risk of cardiac abnormalities |

AE, adverse effect; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; GI, gastrointestinal; HDAC, histone deacetylase; MM, multiple myeloma; OR, objective response; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; TTP, time to progression; TTR, time-to-response
pulmonary embolism (4%), were observed as the most common life-threatening events. In addition, a pharmacogenetic study in Asian women with breast cancer has showed that the UGT2B17*2 genotype results in reduced vorinostat metabolism, leading to higher clinical benefit rate and longer median progression-free survival, but also more serious adverse events, as compared to patients with the wild-type alleles.94

Post-approval assessment of vorinostat included a retrospective cohort study (n = 15) showing overall responsiveness as 33% with partial response being the best result.95 Stable disease was observed in many of the patients (40%). Out of patients with advanced disease (IIib; n = 13), 33% reached stable state and 27% responded. This study included a 300 mg once daily regimen (n = 8) as well as the established dose of 400 mg once daily (n = 7). These results show that more than twice as many of the patients achieved stable disease state in the 400 mg daily group in comparison to the 300 mg daily cohort (57% vs 25%). The safety profile showed a lack of thromboembolic events, a higher rate of renal failure and a smaller risk of infectious complications as compared to the pivotal trial population.

Additionally, vorinostat has been evaluated in combination with the retinoid X receptor agonist bexarotene (n = 23),96 with 26% overall response rate, while 65% achieved stable disease state. Quality-of-life assessment in this study showed that 30% of the patients achieved clinically significant pruritus relief. In terms of safety, the regimen was found to be additionally associated with hypothyroidism (35%; no grade 3–4), hypertriglyceridaemia (30%; 13% grade 3), leucopenia (17%; 4% grade 3), neutropenia (17%; 13% grade 3), hypercholesterolaemia (17%; no grade 3–4) and lymphopenia (13%; 4% grade 3). Diarrhoea, the most common AE, was associated with vorinostat single-agent use (48.6%) and only noted in 13% of patients.

Six of the important clinical studies that investigate romidepsin for treatment of CTCL are presented below, including several combination regimens. The CTCL approval was based on the results of a multicentre, international, single-arm, open-label, pivotal phase 2 study97 in patients with early-to-advanced disease stage who had received one or more prior systemic therapies (n = 96). The study was initiated after a preliminary phase 2 multi-institutional study98 in patients who had received two or more prior cytotoxic regimens and any number of other therapeutic regimens (n = 96). The study was initiated after a preliminary phase 2 multi-institutional study98 in patients who had received two or more prior cytotoxic regimens and any number of other therapeutic regimens (n = 96). The overall response in the pivotal trial was found to be 34%, most of which was partial (28%); 6% responded completely and 47% reached stable disease state. The most responsive stage of the disease was observed to be IIb (n = 21) and the overall response rate in this category was 43%, of which 10% reached complete response. The median duration of response was 15 months, with the time to achieve it varying from 2 to 4 months. The cumulative responsiveness among the advanced disease patients (IIb, III and IVa; n = 68) was 38%. Pruritus assessment was performed based on the 100-mm visual analogue score (VAS). Improvement was reported in 92% of the patients with moderate to severe baseline pruritus (VAS ≥ 30–70 mm; n = 65), while 43% showed clinically meaningful improvement (i.e., a ≥30 mm decrease in VAS or complete pruritus resolution for two consecutive cycles). The safety profile of the drug showed mild toxicities; the most common AEs were nausea (56%; 2% grade 3), fatigue and other asthenic conditions (44%; 6% grade 3),
vomiting (26%; 1% grade 3), anorexia (20%), diarrhoea (14%; 1% grade 4), headache (14%), ageusia (13%) and dysgeusia (11%). The common haematologic reactions included thrombocytopenia (11%) and anaemia (10%; 2% grade 3). Additionally, romidepsin was found to be associated with the life-threatening tumour lysis syndrome (2%). Pharmacogenetically, the drug was found to be impacted by variants in the ABCB1 gene that leads to a possible trend in reduced clearance and less severe QTc prolongation in patients with increased ABCB1 expression.

We identified three post-approval retrospective studies of romidepsin, including two studies assessing the effectiveness and safety in the real-world setting and a long-term use assessment involving a dose-sparing regimen option. The first two studies showed 36% (n = 14) and 25% (n = 11) overall response rate, with partial responses in both studies. No SS or advanced stage-specific data was reported in any of the studies, however. The long-term use assessment study (n = 47) investigated the drug given as a 14 mg/m² infusion administered every other week, every month or every 6 weeks. No statistically significant differences in efficacy and safety from the baseline standard regimen were reported, with response shown to be 61% (n = 38; MF and SS) overall and 42% in patients reaching partial response.

Additionally, we identified a number of investigational studies involving romidepsin as a part of combinatorial regimens in CTCL, for example romidepsin in combination with an anthracycline such as liposomal doxorubicin (n = 23; nCTCL = 10). The addition of liposomal doxorubicin showed 70% overall responsiveness with 60% achieving partial response and 20% achieving stable disease state. The median duration of response was 5 months and the time to reach the response was 2 months. In the advanced disease subset, only IIb (n = 2) and IVa (n = 4) patients were represented which showed responsiveness of 63%. Safety profiles were evaluated for both the CTCL and PTCL cohorts and showed common toxicities to include thrombocytopenia (65%; 17% grade 3–4), anaemia (57%; 13% grade 3–4), neutropenia (26%; 9% grade 3–4), fatigue, nausea (both 48%; 4% grade 3–4), vomiting (35%; all grade 1–2), anorexia (30%; all grade 1–2), blood alkaline phosphatase increase (17%; all grade 1–2), dysgeusia, infections, hyperglycaemia and thrombosis (all four 13%; all grade 1–2); in the CTCL cohort, neutropenia was not reported. Several other combinations of agents are currently under consideration as well, including romidepsin in combination with brentuximab vedotin (phase 1; NCT02616965) and a four-drug combination including romidepsin with 5-azacitidine, lenalidomide and dexamethasone (RAdR; phase 1; NCT04447027).

To summarize, the currently CTCL-approved HDAC inhibitors have so far shown a generally positive efficacy and safety profile in both clinical trial and real-world populations. Overall, HDAC inhibitors are recommended to be used in advanced-disease patients prior to initiating systemic chemotherapy. Compared to romidepsin, vorinostat may be preferable from the patient perspective as it is orally active, although a recent review suggests that both drugs are suitable for most patients. A recent cost-effectiveness analysis has shown both vorinostat and romidepsin to provide less overall response as compared to methotrexate or interferon alpha (the most cost-effective options) for a higher mean price. The evidence on combinatorial regimens is not yet mature enough to draw a definite conclusion but encourages further evaluation.

4.2 HDAC inhibitors in peripheral T-cell lymphoma

PTCL is a heterogeneous group of T-cell or natural killer-cell-derived non-Hodgkin lymphomas that are typically associated with poor prognosis. The most common subtypes of the disease are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and ALK-negative anaplastic large cell lymphoma. Currently, there are three approved agents for treatment of PTCL: romidepsin, belinostat and tucidinostat. Below we discuss several of the salient studies that have contributed to each of their approvals including their efficacy and safety.

The approval of romidepsin for PTCL was based on a pivotal open-label, phase 2 study of patients with relapsed/refractory PTCL (n = 130) after prior systemic therapy and supported by a small-scale trial (n = 47) on patients with PTCL. The pivotal study showed 25% overall responsiveness (15% complete responses) and stable disease was reported in 25% of patients. The median time to response was 1.8 months overall with 3.7 months to reach complete response while the median duration of response was 16.6 months. In AITL patients, the overall response was 30%, of which 19% was complete. The safety profile showed comparable AEs to those previously reported in the CTCL trial; however, use of romidepsin in patients with PTCL was shown to additionally include neutropenia (30%; 20% grade 3–4) and leukopenia (12%; 6% grade 3–4).

The post-approval assessment includes two previously mentioned retrospective studies. The overall responses vary from 15.8% (all complete; n = 19) to 33%, of which 12.5% were complete (n = 42). The duration of response was 13 months, while the overall and progression-free survival values were 7.1 and 2.2 months, respectively. According to Zinzani et al, the most responsive subtypes are PTCL-NOS and anaplastic large cell lymphoma.

It is noteworthy that romidepsin has been involved in a large number of investigational studies as part of combinatorial regimens for treatment of PTCL. In the past 10 years, romidepsin has been evaluated in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (the CHOP regimen), gemcitabine, ptalatrexate, ifosfamide, carboplatin and etoposide, bendamustine, gemcitabine, dexamethasone and cisplatin, 5-azacytidine and liposomal doxorubicin. Table 4 summarizes the clinical evidence to date. Furthermore, romidepsin as a part of combination therapies is currently in many active clinical trials including the previously mentioned RAdR regimen, as well on carfilzomib (phase 1/2; NCT03141203), ixazomib (phase 1/2; NCT03547700), CHOEP-21 regimen (phase 1/2; NCT02223208), lenalidomide (phase 2; NCT02232516), and pembrolizumab (phase 1/2; NCT03278782).
For belinostat, the FDA approval was based on the results of an open-label, single-arm, non-randomized international phase 2 trial in patients with PTCL \( (n = 129) \). This trial was initiated after a phase 2 open label, multicentre study in patients with PTCL or CTCL who failed ≥1 prior systemic therapy. The approved regimen showed 25.8% overall response rate with partial response being more common than full (15% vs. 10.8%) while stable disease was noted in 15%. The response lasted 13.6 months, with the median time to response 5.6 weeks and the median time to progression 2 months. The median overall survival was 8 months and the median progression-free survival was 1.6 months. Among PTCL subtypes, patients with AITL \( (n = 22) \) showed 45.5% overall response while the response rate for patients with PTCL-NOS \( (n = 77) \) was 23.4%. The common AEs were reported to include nausea (41.9%; 1% grade 3–4), fatigue (37.2%; 5% grade 3–4), pyrexia (34.9%; 2% grade 3–4), vomiting (29%; 1% grade 3–4), constipation (23%; 1% grade 3–4), diarrhoea (23%; 2% grade 3–4), dyspnoea (22%; 6% grade 3–4), rash (20%; 1% grade 3–4) and peripheral oedema (20%; grade 1–2). Haematologic toxicities were reported to include anaemia (32%; 11% grade 3–4), neutropenia (34%; 15% grade 3–4), thrombocytopenia (25%; 17% grade 3–4), transaminase increase (11%).

| Combinatory regimen | CT phase | Number of patients | Efficacy profile | Safety profile |
|---------------------|----------|--------------------|------------------|----------------|
| Romidepsin and CHOP | Phase 1b/2 | 37 (35 assessed for efficacy) | 68.57% OR (51% CR, 26% PR), 26% PD, 21.3 months PFS | Grade 3–4 neutropenia (89%) and thrombocytopenia (78%), febrile neutropenia (14%), physical health deterioration (14%), lung infection (11%), vomiting (8%); acute cardiac toxicity (≥8.1%) |
| Romidepsin and gemcitabine | Phase 2 | 20 | 30% OR (15% CR and PR), 65% PD, 12 months DOR, 2.5 months PFS | Grade 3–4 thrombocytopenia (60%), neutropenia (50%), anaemia (20%) and transaminase increase (15%); nausea & vomiting (50%) |
| Romidepsin and pralatrexate | Phase 1 | 29 (23 assessed for efficacy) | 71% OR (TCL); PTCL patients all reached CR (17%), 4.4 months PFS | Grade 4 thrombocytopenia (14%), neutropenia (10%), sepsis (7%), fever, pneumonia (both 3%); grade 3 anaemia (29%), oral mucositis, thrombocytopenia (both 14%), neutropenia (10%) |
| Romidepsin and ICE | Phase 1 | 18 | 93% OR (80% CR, 13% PR), 10 months PFS | Grade 3–4 thrombocytopenia (83%), anaemia (50%), neutropenia (44%), fatigue (33%), nausea & vomiting (33%), infections (28%), dyspnoea (17%), transaminase increase (11%) |
| Romidepsin and bendamustine | N/A, case series | 7 | 42% OR (28.5% CR, 14.28% PR), 7 months PFS | Grade 4 thrombocytopenia; grade 3 nausea & vomiting (all three 42.8%) |
| Romidepsin and GDP | Phase 1 | 20 (10 with PTCL) | 60% OR in PTCL (all PR), 5.54 months PFS | Grade 3–4 thrombocytopenia (55%), neutropenia, anaemia (both 30%); grade 2–4 infections (75%) |
| Romidepsin and 5-azacytidine | Phase 1 | 31 (11 with PTCL) | 73% OR (55% CR, 18.18% PR) | Grade 3–4 thrombocytopenia (62%), neutropenia (37%), lymphopenia, leukopenia, lung infection (all three 25%) |
| Romidepsin and doxorubicin | Phase 1 | 23 (12 with PTCL) | 27% OR (all CR), 3.5 months TTR, 4.2 months DOR, 2.1 months PFS | Persistent grade 4 neutropenia (8%), grade 3 thrombocytopenia (33%), grade 3 anaemia (17%) |

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CT, clinical trial; ICE, ifosfamide, carboplatin and etoposide; GDP, gemcitabine, dexamethasone and cisplatin; TCL, T-cell lymphoma
overall response rate was found to be 29%, of which complete response was shown in 14%, partial response in 15%, and stable disease was observed in 13% of patients. The median time to response was 1.4 months and the median duration of the response was almost 10 months. The most responsive PTCL subtype was found to beAITL as well (50% overall and 40% for complete responses). The median progression-free survival was 2 months, while the overall survival was 21 months. The treatment-related AEs predominantly included haematologic reactions, such as thrombocytopenia (51%; 16% grade 3), leukopenia (40%; 12% grade 3) and neutropenia (22%; 8% grade 3). Other common toxicities included QTc interval prolongation (13%; all grade 1–2), fatigue (10%; all grade 1–2), anorexia (8%; 2% grade 3), diarrhoea, nausea (both 8%; all grade 1–2), increased alanine aminotransferase levels (7%; 1% grade 3), increased γ-glutamyltransferase levels, pulmonary infection (both 6%; 1% grade 3), increased aspartate aminotransferase levels and vomiting (both 5%; 1% grade 3).

A larger real-world study (n = 383) evaluated the drug in two main groups: tucidinostat as a monotherapy (n = 256) and tucidinostat in combination with other agents (n = 127). In the tucidinostat monotherapy group, the overall response was 39.06% with 28.52% reaching partial responses and 64.45% disease control rate. In the combined regimens, the response was 51.18% with 39.37% showing partial response and 74.02% disease control rate. In this population, the common AEs in tucidinostat monotherapy included thrombocytopenia (25%), neutropenia (19.1%), fatigue (18.4%), nausea and vomiting (14.1%) and anaemia (11.3%). Tucidinostat in combination with a chemotherapeutic regimen included thrombocytopenia (28.4%), neutropenia (25.2%), fatigue (24.4%), anaemia (17.3%), nausea and vomiting (12.7%), and increased alanine (9.5%) and aspartate (6.3%) aminotransferase levels.

Overall, the approved PTCL HDAC inhibitors have shown near-similar efficacy and safety profiles. The FDA-approved agents belinostat and romidepsin are recognized as suitable in clinical practice, with the overall evidence on romidepsin currently the most extensive. Tucidinostat, being an orally active agent, is an important addition to HDAC inhibitors for treatment of PTCL, although it is important to evaluate the drug in a wider population to establish its full potential. The evidence on combinatory regimens in PTCL have so far been limited to only romidepsin, which has shown improved responsiveness in most regimes; however, the AE profiles in the regimens were generally associated with higher rates of grade 3–4 reactions, suggesting the need for further optimization.

4.3 | HDAC inhibitors in multiple myeloma

MM is a rare disease and the second most-common haematologic malignancy of terminally differentiated B plasma cells. The disease is characterized by a high rate of relapse and drug resistance, highlighting the need for more optimized treatment strategies. Panobinostat in a combination therapy is the only HDAC inhibitor that has been approved by the FDA for treatment of MM. Panobinostat is identified in 31 clinical studies in ClinicalTrials.gov and we review the two primary studies that contributed to its approval.

The approval of panobinostat as part of combinatorial bortezomib plus dexamethasone regimen in MM was based on the results of a randomized, double-blind, placebo-controlled, multicentre phase 3 study (n = 768; n_placebo = 381, n_panobinostat = 387) in patients with relapsed MM who had received one to three prior therapeutic options. Overall, the study showed panobinostat to be an efficacious addition to the bortezomib and dexamethasone regimen, resulting in longer progression-free survival (median value 12 months vs. 8 months in the control group) and a better overall response (61% vs. 55%), characterized by longer duration (13 months vs. 11 months), shorter time to response (1.5 months vs. 2 months) and a higher percentage of patients reaching complete responses (28% vs. 16%). Partial responses represented the bulk, consistent with other known HDAC inhibitors; however, their percentage in the treatment group was lower (33% vs. 39%). Stable disease was observed in 17% of patients vs. 19% in the control group. The actual approval was nevertheless based on the results of a smaller study group (n = 147) that underwent at least two prior regimes including bortezomib and dexamethasone. Here, the median progression-free survival was observed to be 10.6 months (vs. 5.8 months in the control group), the overall responsiveness was 59% (vs. 39%), characterized by 12-month duration (vs. 7 months) and the time to reach it as 1.5 months. Consistent with the previous population, the proportion of complete responses was higher as well (22% vs. 8%). The common AEs overall included thrombocytopenia (98% vs. 84% in the placebo group), lymphopenia (83% vs. 74%), leukopenia (81% vs. 48%) and neutropenia (75% vs. 36%), along with diarrhoea (68% vs. 42%), asthenic conditions (57% vs. 41%) and nausea (36% vs. 21%). Peripheral neuropathy, while also noted to be a common AE (61%) in the panobinostat group, was slightly more common in the placebo group (67%). In the pre-treated subset, the AE profile was found to nearly similar; however, the proportion of patients experiencing diarrhoea was higher (76% vs. 47%). The possible impact of genetic polymorphisms on the safety and efficacy profiles of panobinostat is limited to single-agent use, in which a study showed no differences in the pharmacokinetics of patients heterozygous or homozygous for CYP3A5* alleles.

We have additionally identified several investigational panobinostat-containing therapeutic options in MM, primarily modifications to the established panobinostat and bortezomib plus dexamethasone regimen. Two multi-combination studies include panobinostat in four-drug regimens, including bortezomib, dexamethasone and thalidomide, or lenalidomide. Other regimens investigated previously included combinations with melphalan, prednisone and thalidomide, melphalan alone and carfilzomib. Two investigational regimes in active phase 2 trials include panobinostat in combination with carfilzomib plus dexamethasone (NCT03256045), and in combination with gemcitabine hydrochloride, busulfan and melphalan (NCT02506959). Table 5 summarizes the available clinical evidence.
To summarize, panobinostat is recognized as a potential therapeutic option in MM. Unlike the T-cell lymphomas, panobinostat has only shown favourable profiles as a part of combinatory regimens; as a single agent, panobinostat was reported to produce only one partial and one minimal responses overall ($n = 38$). The current investigational combinatory regimens are showing a positive impact on patient responsiveness, survival and severity of AEs, suggesting they are interesting alternatives to the established regimen.

### 5 | INVESTIGATIONAL INDICATIONS IN APPROVED HDAC INHIBITORS

#### 5.1 | Novel neoplastic indications in approved HDAC inhibitors

All of the approved HDAC inhibitors are currently in clinical trials investigating treatments for additional types of neoplastic conditions, both as a monotherapy and as part of combinatory regimens. A broad range of advanced solid neoplasms, notably brain and pulmonary cancers, and haematological malignancies, such as acute myeloid leukaemia and B-cell lymphoma, have been initiated within the past 5 years. In total, nearly 60 active clinical studies are identified with vorinostat and include three active phase 3 trials for neoplastic indications with combination therapies for high-grade glioma (NCT01236560), multiple myeloma (NCT01554852), and acute lymphoblastic leukaemia and lymphoma (NCT03117751). Active trials with belinostat include eight cancer studies such as ovarian carcinoma, adenosarcoma and chondrosarcoma. Tucidinostat is identified in more than 50 active trials in ClinicalTrials.gov for treatment of a range of haematological malignancies as well as solid neoplasms such as advanced breast cancer, melanoma, pulmonary neoplasms, renal cell carcinoma and soft tissue sarcoma. In advanced breast cancer (hormone receptor-positive, HER2-negative metastatic), tucidinostat was studied in combination with exemestane (NCT02482753; $n = 365$; $n_{tucidinostat} = 244$, $n_{placebo} = 121$), showing an 18% overall response (all partial; vs. 9% in the placebo group). Disease stabilization was observed in 56% (vs. 54%), while 20% have worsened (vs. 36%). The progression-free survival was 7.4 months (vs. 3.8 months). Panobinostat is involved in more than 20 clinical trials with one phase 3 trial for acute myeloid leukaemia and myelodysplastic syndromes.

#### 5.2 | Non-neoplastic indications in approved HDAC inhibitors

Vorinostat, romidepsin, tucidinostat and panobinostat are currently in active phase 1 and 2 clinical trials as monotherapies and in...
combination regimens for treatment of a variety of non-oncology indications as well. Vorinostat has recently been evaluated in Niemann-Pick type C disease for safety and its effect on two biomarker serum values, which were shown to generally decrease (NCT02124083). Furthermore, valproic acid has also been investigated in preclinical studies for Niemann-Pick type C1 disease and it was recently posited that, in combination with chloroquine, valproic acid could provide a potential mechanism that could have therapeutic benefit in patients with specific mutations.138

Vorinostat is currently in trials for Alzheimer’s disease (NCT03056495) as well as epilepsy (NCT03894826) and Crohn’s disease (NCT03167437). In preclinical studies, it is being investigated in frontotemporal dementia due to progranulin deficiency where it has reported limited overall benefit.139

Romidepsin, along with panobinostat, vorinostat and tucidinostat, are currently in phase 1 and 2 trials for treatment of patients with HIV infection. The agents are believed to activate the latent (i.e., transcriptionally inactive) HIV-1 virus, making it more susceptible to antiretroviral therapy. It had also been found that HDAC inhibitors decrease HIV release from macrophages in a dose-dependent manner and inhibit HIV dissemination through HDAC-mediated autophagy.140 Panobinostat, studied in male patients taking antiretroviral therapy with virological suppression for at least 2 years, has shown acceptable tolerability and mean 2.4-fold increase in cell-associated unspliced HIV RNA 2 hours after initiating therapy. HIV DNA was found to be decreased with eventual return to the baseline values, while the mean infectious units per million was found to be largely unchanged.141 Romidepsin, studied in combination with Vacc-4x, a synthetic p24 gag peptide vaccine, and recombinant human granulocyte macrophage colony-stimulating factor (rhuGM-CSF), also showed a decrease in HIV-1 DNA and an increase in cell-associated unspliced HIV-1 RNA values.142,143 A similar pattern of the T-cell-associated HIV RNA increase was observed in vorinostat after serial exposures to the drug in 72 hour intervals; however, no latent infection frequency decrease within the resting T-cells was observed.144 Tucidinostat is currently being investigated in a phase 1 study on the effect of the agent when combined with chimeric antigen receptor (CAR)-T or T cell receptor (TCR)-T-cell therapy on HIV-1 latent reservoir (NCT03980691).

6 | INVESTIGATIONAL HDAC INHIBITORS IN CLINICAL DEVELOPMENT

We identified 21 HDAC inhibitors that have reached clinical development; 11 agents belong to the hydroxamate class (Table 6) and 11 are non-hydroxamate agents, including two carboxylic acids discussed in the following section (Table 7). Consistent with the overall direction of research in this field, almost all of these agents are undergoing evaluation in a range of haematologic and solid neoplasms and show varying efficacy and safety profiles.

Among the particularly interesting directions is the development of isozyme-selective inhibitors. Recently published results on the novel agent ricolinostat, an orally active HDAC6-selective inhibitor that belongs to the hydroxamate class, showed a satisfactory efficacy profile in relapsed/refractory MM when in combination with a proteasome inhibitor lenalidomide and dexamethasone.145 This phase 1b trial reported a 55% overall responsiveness \( n = 38 \), while in a phase 1/2 trial investigating the drug in combination with another proteasome inhibitor, bortezomib and dexamethasone achieved 37% response \( n = 57 \).146 Modulating HDAC6 is an attractive approach in MM; it regulates acetylation of α tubulin and the aggresome

| Drug name | Enzyme specificity | Indications investigated | Highest CT phase |
|-----------|--------------------|--------------------------|-----------------|
| Abexinostat | HDAC 1, 2, 3, 6, 10 | DLBCL, MCL, AML, ALL, FL, RCC, MDS, sarcoma, skin cancers, NSCLC | Phase 3 |
| Fimepinostat (CUDC-907) | HDAC 1, 2, 3, 10 | Lymphomas, brain tumours | Phase 1/2 |
| Quisinostat (JNJ26481585) | HDAC 1, 6, 9 | Ovarian cancer, CTCL, NSCLC | Phase 2 |
| Ricolinostat (ACY-1215) | HDAC 6 | MM, DNP, lymphomas, BC, gynaecological cancers, CLL | Phase 2 |
| Trichostatin A | HDAC 7, 8 | Haematological cancers | Phase 1 |
| Nanatinostat (VRx-3996) | HDAC 9 | EBv-associated malignancies | Phase 1/2 |
| CG200745 | HDAC 9, 11 | MDS, pancreatic cancer | Phase 1/2 |
| Pracinostat | Pan-HDAC | MDS, AML, MF, PC, sarcoma | Phase 3 |
| Resminostat | Pan-HDAC | CTCL, HCC, HL, CRC, pancreatic cancer, NSCLC | Phase 2 |
| CUDC-101 | Pan-HDAC | Advanced solid tumours | Phase 1 (discontinued) |
| MPT0E28 | Pan-HDAC | Advanced solid tumours | Phase 1 |

AML, acute myeloid leukaemia; BC, breast cancer; CLL, chronic myeloid leukaemia; CRC, colorectal carcinoma/cancer; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; FL, follicular lymphoma; HCC, hepatocellular carcinoma; HL, Hodgkin’s lymphoma; HNSCC, head and neck squamous cell carcinoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; NSCLC, non-small cell lung cancer; PC, prostate cancer; RCC, renal cell carcinoma
TABLE 7  Investigational non-hydroxamate HDAC inhibitors in clinical trials. This table presents a summary of the completed and/or currently ongoing clinical trials involving investigational non-hydroxamate HDAC inhibitors.155

| Drug name          | Chemical class | Enzyme specificity | Indications investigated                  | Highest CT phase |
|--------------------|----------------|--------------------|-------------------------------------------|------------------|
| Tacedinaline (CI-994) | Benzamide      | HDAC 1             | Solid and haematological cancers          | Phase 3 (discontinued) |
| Entinostat         | Benzamide      | Class 1 HDACs      | PC, BC, BIC, AML, CRC, LL, RCC, melanoma, NSCLC, gynaecological cancers, CNS tumours, MDS, pancreatic cancer, NE tumours | Phase 2          |
| Domatinostat       | Benzamide      | Class 1 HDACs      | CTCL                                      | Phase 2          |
| RG2833             | Benzamide      | HDAC 3             | Friedreich’s ataxia                       | Phase 1          |
| Givinostat         | Benzamide      | Pan-HDAC           | MDs, PV, JIA                              | Phase 2          |
| KA2507             | Cyclic peptide | HDAC 6             | Melanoma                                  | Phase 1          |
| Mocetinostat       | Benzamide      | Pan-HDAC           | UC, NSLC, HL, DLBCL, FL, leiomyosarcoma, melanoma | Phase 2          |
| OBP-801            | Cyclic peptide | Pan-HDAC           | LC, lymphoma, RC, glaucoma                | Phase 1a         |
| AR-42              | Benzamide      | Pan-HDAC           | RCC, sarcoma, meningioma, VS, AML         | Phase 1          |
| Pivanex (AN-9)     | Carboxylic acid | HDAC 1             | NSCLC, melanoma, LL                      | Phase 2          |
| AMX0035            | Carboxylic acid | Pan-HDAC           | Amyotrophic lateral sclerosis, Alzheimer’s disease | Phase 2/3        |

BIC, bladder cancer; CNS, central nervous system; CRC, colorectal cancer; DMD, Duchenne muscular dystrophy; JIA, juvenile rheumatoid arthritis; LC, lung cancer; LL, lymphoblastic leukaemia; MDs, muscular dystrophies; NE, neuroendocrine; PV, polycythemia vera; RC, renal cancer; UC, urothelial carcinoma; VS, vestibular schwannoma.

degradation pathway, removing misfolded and polyubiquitinated proteins,147 thereby overcoming a mechanism of resistance to proteasome inhibitors.

Nanatinostat, selective to HDAC9, has shown interesting results in a phase 1b trial for treatment of Epstein–Barr virus (EBV)-associated lymphomas when in combination with a ganciclovir prodrug valganciclovir, where the overall response was reported to be 53%, of which 29% had complete responses.148 Here, HDAC inhibitors appear to act by sensitizing the EBV(+) lymphoma cells to nucleoside antiviral agents, such as ganciclovir.149

An interesting investigational direction in HDAC inhibitor research is combining the drugs with immunotherapeutic agents, such as cancer vaccines, adoptive cell therapeutics or immune checkpoint inhibitors.150 Several combinations have entered trials targeting tumours and mostly include immune checkpoint inhibitors: panobinostat with ipilimumab for treatment of melanoma (phase 1; NCT02032810), entinostat with nivolumab for non-small cell lung cancer (phase 2; NCT01928576), vorinostat with pembrolizumab for breast cancer (phase 2; NCT02395627) and head and neck/salivary gland cancers (phase 1/2; NCT02538510), and entinostat with pembrolizumab for uveal melanoma (phase 2; NCT02697630). Entinostat has also been evaluated for renal cell carcinoma in combination with high dose interleukin-2 (n = 47).151 showing 37% objective response rate, a progression-free survival of 13.8 months, and an overall survival of 65.3 months.

Non-hydroxamate HDAC inhibitors address a diverse range of non-neoplastic indications, particularly the benzamide class of agents, where studies for muscular dystrophies, juvenile idiopathic arthritis (JIA), and Friedreich’s ataxia have been identified. Notably, results from a phase 2 study involving givinostat, a benzamide that targets HDACs 1–10, showed positive histological changes as well as some functional improvements in paediatric patients with Duchenne muscular dystrophy.152 It is now in two clinical trials for Duchenne muscular dystrophy (phase 3: NCT0285179 and phase 2/3: NCT03373968) and also a phase 2 trial for Becker muscular dystrophy (NCT03238235). Givinostat was also shown to be safe and efficacious in patients with JIA based on a phase 2 trial153; however, a subsequent phase 2 study for polyarticular course JIA was terminated due to lack of enrolment.

RG2833, a benzamide that specifically targets HDAC3, has been studied in a phase 1 clinical trial for treatment of Friedreich’s ataxia. Preclinical studies showed that pemelc o-benzamide compounds like RG2833 are capable of correcting the frataxin (FXN) deficiency associated with Friedreich’s ataxia through FXN gene silencing.154–156 Results from a phase 1b trial showed positive effects on HDAC inhibition (up to 50% inhibition) and on FXN mRNA levels (an average 1.5- to 1.6-fold induction within 24 hours post-dosing).157 RG2833 is currently undergoing chemical modifications to improve its stability and pharmacokinetic properties.158

DAC-0060 and FRM-0334, the uncategorized HDAC inhibitors, have both reached clinical phases of development, although they are characterized by limited data. DAC-0060, a small-molecule pan-HDAC inhibitor for topical use, has been under investigation for basal cell carcinoma in combination with the retinoid tazarotene (Zorac® 0.1% gel) in an ongoing phase 2b trial since 2013 with results not yet released (EudraCT No. 2013–003336-72). It appears to be discontinued due to the lack of development reports. FRM-0334 (formerly EVP-0334) is a Class 1 and 2-selective orally active HDAC inhibitor with cognitive function-enhancing activity that has been studied in preclinical trials (results reported in Refs 159,160). In a phase 1 clinical study in Europe, it was found to be well tolerated at all doses; however, a randomized placebo-controlled multicentre phase 2 trial (NCT02149160) appears to be discontinued due to the closure of the sponsoring company.161
CARBOXYLIC ACIDS AS HDAC INHIBITORS

Carboxylic acids, such as valproic acid and phenylbutyrate derivatives, have also been explored pre-clinically and clinically for their potential HDAC-inhibiting activity.

Valproic acid is a well-established drug in several types of seizures (Depakene®, Stavzor®). Its exact mechanism of action in epilepsy is largely unknown; however, it is assumed that the antiepileptic effect is more due to its GABA-ergic effect, due to valproic acid's weak inhibitory activity against HDAC enzymes. Interest in recent evidence suggests that epigenetic aberrations do play a role in epileptogenesis and that HDAC inhibition may indeed be an attractive mechanism to target for treatment and prevention of epilepsy. In a preclinical study involving sodium butyrate, another short-chain fatty acid with HDAC inhibiting activity, daily administration was found to prevent the development of temporal lobe epilepsy in the experimental models. While acute HDAC inhibition showed little-to-no effect on seizure control, chronic inhibition resulted in long-lasting anti-epileptogenic and epileptogenesis-delaying effects.

Valproic acid is also being actively investigated in phase 2 clinical trials for treatment of neoplastic indications as well. Among the most recent studies are valproic acid in combination with a complex regimen consisting of rituximab plus CHOP for treatment of diffuse large B-cell lymphoma, in combination with hydralazine for CTCL, and also in combination with cisplatin and cetuximab for advanced radioiodine-resistant thyroid cancers and squamous cell carcinoma of head and neck. Valproic acid seems to be effective in the majority of these indications, and only advanced radioiodine-resistant thyroid cancer has shown lack of efficacy when treated with valproic acid; however, it is not fully clear whether this is due to valproic acid's HDAC inhibitory activity.

Phenylbutyrate (PBA), as sodium (Buphenyl®, Ammonaps®) and glycerol (Ravicti®) salts, is approved by the FDA and EMA in urea cycle disorders. Similar to valproic acid, however, PBA is characterized by multiple mechanisms of action, and acts as ammonia scavenger for the approved indication. Several pre-clinical studies, nevertheless, point to its possible roles as an HDAC inhibitor, exemplified by cancer, diabetes and some neurological disorders. In cancer, PBA inhibits the growth and proliferation of LN-229 glioblastoma cell lines. In neurology, PBA ameliorates cognitive deficit associated with AD. In diabetes, PBA was found to exert a protective effect on the β-cells and to improve insulin resistance.

Clinically, PBA have been explored in phase 1 and 2 clinical trials for treatment of cancer, a range of neurodegenerative diseases, including AD, amyotrophic lateral sclerosis, and Parkinson’s disease. In cancer, recurrent malignant glioma is presently the only indication where PBA have shown a clinical response (5% overall response rate; n = 20). In neurologic disorders, sodium PBA has been studied in combination with tauroursodeoxycholic acid (AMX0035), showing promising results for treatment of amyotrophic lateral sclerosis from a phase 2/3 safety and efficacy study (NCT03127514). Results showed a statistically significant slowing of decline on the ALSFRS-R over placebo (P < .05). Currently, nearly 90% of the participants from this study are receiving the drug in a phase 2 open-label extension trial (NCT03488524). AMX0035 is also in an active phase 2 trial for Alzheimer’s disease (NCT03533257) that completed enrolment in June 2020 with results expected to be released in the first quarter of 2021.

Pivanex (pivaloyloxymethyl butyrate; AN-9) is another example of a carboxylic acid explored as an HDAC inhibitor. In vitro and in vivo studies have shown activity in leukaemic cells, melanoma, ovarian, breast, lung and colorectal tumours and glioma. ClinicalTrials.gov records have shown studies of pivanex as a single agent in malignant melanoma (phase 1/2; NCT00087477) and chronic lymphocytic leukaemia (phase 2; NCT00083473). Additionally, pivanex has been evaluated as a single agent in advanced solid tumours (phase 1, n = 28), showing a single partial response in previously untreated metastatic non-small cell lung cancer (NSCLC); a subsequent phase 2 study in patients with advanced NSCLC (n = 47) has shown partial response as the best result as well (n = 3). Pivanex has also been evaluated in combination with docetaxel (phase 2; NCT00073385). The dose escalation study (n = 12) has initially shown a positive efficacy profile (three responding patients, of whom one reached complete resolution) and an acceptable tolerability; however, a subsequent phase 2b study was terminated for safety concerns.

DISCUSSION

Our analysis shows that while neoplastic indications continue to dominate within the current clinical research on investigational HDAC inhibitors, studies for non-neoplastic indications are achieving success in clinical trials, for example with AMX0035 for treatment of ALS. Several interesting advances have been made, in particular regarding HIV infections where treatment is currently being evaluated in four of the already approved HDAC inhibitors. The present evidence, however, is modest, partly due to small sample sizes and thus highlighting the need for further studies. Several agents including vorinostat and the novel drug RG2833 have also shown results in addressing neurodegenerative diseases such as Alzheimer's disease, frontotemporal dementia and Friedreich's ataxia, while another novel agent AMX0035 has high expectations. HDAC inhibitors, both repurposed and novel agents, also seem to progress clinically in treating inflammatory diseases, including Crohn's disease and JIA, as well as muscular dystrophies.

It is intriguing that when comparing the two major classes of HDAC inhibitors, the evidence based on the established HDAC inhibitors does not seem to indicate a significant superiority of hydroxamates compared to non-hydroxamates in the clinical setting, despite earlier evidence reporting higher overall HDAC inhibiting activity for the former. In fact, the currently approved non-hydroxamic acids, such as romidepsin and tucidinostat, provide fairly superior and longer-lasting overall response rates in the respective approved indications, compared to hydroxamates (Table 1).
reason for this could be the pharmacokinetic differences between the
drugs.\textsuperscript{177} The orally available vorinostat has a short half-life (2 hours)
and its time to reach peak plasma concentration is 5.5 hours, while
tucidinostat has a much longer half-life value (17–18 hours) with the
time to reach peak plasma concentration ranging from 1–2 hours. In
parenteral agents (i.e., romidepsin and belinostat), the half-life period
in the hydroxamate agent is also slightly lower (1.1 to 2.9 hours in
belinostat, as compared to 3 hours in romidepsin).

Two major ongoing issues that surround the use of and research
into HDAC inhibitors are treatment resistance and lack of progress
in targeting solid tumours. Several mechanisms had been described
to date, such as P-gp-mediated drug efflux mechanisms in
romidepsin or overexpression of the BCL-2 family proteins and
JAK–STAT pathways in vorinostat.\textsuperscript{9,178} The identification of predictive
markers, such as the recently described LAIR-2 in pre-treatment
CTCL,\textsuperscript{179} could be a valuable strategy to improve the therapeutic
decision-making at an early stage. Another interesting approach
could be further development of dual inhibitors, such as dual JAK–
HDAC inhibitors\textsuperscript{180} or combinatory regimens, such as panobinostat
and JAK-2 inhibitor TG101209.\textsuperscript{178} Regarding solid tumours, an
important milestone is the 2019 approval of tucidinostat in combina-
tion with exemestane in hormone receptor-positive, HER2-negative
metastatic breast cancer patients; the importance of knowing how
HDAC inhibition impacts tumour biology\textsuperscript{181} presents an important
lesson to learn for future efforts to explore HDAC inhibitors in solid
tumours.

There also is an apparent need for more extensive, larger-scale
clinical studies to establish the full potential of this therapeutic class
for treatment of neoplasms, as well as other indications. Among the
important issues to address are the lack of comprehensive data
regarding the quality-of-life changes associated with the use of HDAC
inhibitors and also the lack of clinical data from larger scale trials with
an active comparator. In CTCL and related diseases, specific quality-
of-life issues such as excessive itching are often the most notable for
patients, while factors such as impact of toxicity on the overall
condition as well as onerous financial aspects of treatment are likely
to negatively affect treatment adherence. Another important issue is
the apparent dependence of both the toxicity and effectiveness of
HDAC inhibitors on genetic polymorphisms and the use of HDAC
inhibitors in combinatory regimens.

The overall future prediction for development of new HDACs
looks promising despite the fact that there have not been many new
drug approvals in recent years. The number of clinical trials of
new agents may suggest that new approvals are likely to grow. The
global market of HDAC inhibitors has reached more than US$97
million in 2018 and has been predicted to grow by 32% annually.\textsuperscript{182}
The compounds’ annual growth rate during the 2019–2023 period
has also been predicted to be about 7% and the 2026 market value is
expected to be more than US$160 million.\textsuperscript{183} Neoplasms comprise
the largest share of indications (53%) while neurological conditions
are the second highest category.\textsuperscript{183} This analysis suggests that the
indication field is broadening through a high number of clinical trials,
while we also notice that there are several fields of preclinical
development such as neurodegeneration, muscular dystrophies and
arthritis that are also being investigated.

\section{CONCLUSION}

Here we provide a comprehensive overview of HDAC drug develop-
ment with a focus on novel substances and clinical trials. There is a
clear trend towards diversification and several new opportunities for
drug development are emerging. It is notable that the HDAC inhibitors
of non-hydroxamic nature overall exhibit better performance in clinici-
trial trials. There is also an increased focus on drug resistance, toxicity
and approaches to deal with the relatively modest activity of some
HDACs, thus prompting an interest in combinatory regimens. It is
likely that the structural features of non-hydroxamate HDAC inhibi-
tors will require continuous focus in order to enhance their activity.
The promising activity of HDAC inhibitors in non-neoplastic condi-
tions such as HIV infection, dementia and muscular dystrophies has
increased the scope of the research activity, both in clinical trials and
preclinical development. Additional non-neoplastic indications are
likely to move from preclinical stage to clinical trials within the near
future. We predict that the evaluation of combinatory regimens, in
particular for the approved agents, will continue to grow in order to
assess the possibilities of maximizing their clinical effectiveness and
safety.

\section*{NOMENCLATURE OF TARGETS AND LIGANDS}

Key protein targets and ligands in this article are hyperlinked to
corresponding entries in http://www.guidetopharmacology.org, and
are permanently archived in the Concise Guide to Pharmacology
2019/20.\textsuperscript{184}

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\section*{COMPETING INTERESTS}

The authors declare that there are no conflicts of interest.

\section*{CONTRIBUTORS}

A.D.B. collected data, performed analysis, wrote the manuscript and
designed the study. M.M.A. collected data, contributed in editing.
J.J. performed data collection and editing. V.N.C. provided tuition and
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editing. H.B.S. conceived the study, provided tuition and participated
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