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Revisiting the therapeutic landscape of tauopathies: assessing the current pipeline and clinical trials

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Abstract

Microtubule associated protein tau (MAPT) is a naturally occurring protein that plays a significant role in stabilizing microtubules, which are essential for the transport of nutrients and other materials within neurons. In tauopathies, tau protein assembles into mis-folded multimers ranging from soluble oligomers to insoluble aggregates, known as neurofibrillary tangles, neuropil threads and are components of neuritic plaques. These abnormal tau assemblies collectively are thought to disrupt the normal function of neurons and lead to their death. Tauopathies are a leading cause of neurodegeneration, and there are no approved disease modifying therapies targeting the tau pathology for any tauopathy. This review is a two-year update to an initial review of preclinical, clinical, and recently discontinued therapeutic programs in development focused on ameliorating tau pathology. This review outlines the landscape of therapeutic drugs indexed through January 1, 2025. Currently, there are 170 drugs monitored in the pipeline, one less than in the previous period. In the clinic, there are five candidates in phase 3 trials, 15 in phase 2 trials, and 12 in phase 1 trials. In total, there are four less candidates in clinical trials during this review period than the last. New to this review is the inclusion of the clinical development of tau positron emission tomography (PET) ligands which undergo regulatory oversite. In addition to the one FDA-approved tau PET ligand Tauvid™ (flortaucipir), there are six additional tau PET ligands currently in active clinical trials.

Keywords Alzheimer's disease, Drug development, Frontotemporal dementia, Progressive supranuclear palsy, Corticobasal degeneration, MAPT, Tau, Tauopathy, Pick's disease, Argyrophilic grain disease, Primary age-related tauopathy, Positron emission tomography

Introduction

Tauopathies are a diverse group of neurodegenerative disorders characterized by the pathological accumulation of misfolded tau protein in the brain [1]. While Alzheimer's disease (AD) is the most common dementia with prevalent tauopathy thought to be secondary to amyloid-β protein deposition, other distinct disorders are characterized as primary tauopathies. Primary tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD), argyrophilic grain disease (AGD), aging-related tau astrogliopathy (ARTAG), globular glia tauopathy

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(GGT), tangle only dementia (TOD), primary age-related tauopathy (PART), and over 50 mutations to the MAPT gene such as frontotemporal lobar degeneration (FTLD)-tau, and all feature prominent tau pathology and represent significant clinical challenges for both diagnosis and treatment [2–4]. The clinical presentation of tauopathies varies depending on the specific disorder and the brain regions predominantly affected [5]. For instance, AD is primarily characterized by progressive memory impairment [6] while FTLD-tau often presents with behavioral and personality changes, language deficits, or motor dysfunction [7]. PSP typically manifests with vertical gaze palsy, postural instability, and parkinsonism, while CBD is characterized by asymmetric rigidity, apraxia, and cortical sensory loss [5]. Despite these clinical differences, a common thread linking these disorders is the significant role of tau pathology in driving neurodegeneration.

Physiological tau is a soluble natively unfolded protein encoded by the microtubule-associated protein tau (MAPT) gene [8]. The MAPT gene is located on the 17q21 chromosome location and is comprised of 16 exons [9]. Exons 1, 4, 5, 7, 9, 11, 12 and 13 are expressed in all tau isoforms. Alternative splicing of exons 2, 3 and 10 determines which of the six tau protein isoforms are generated: 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R. All isoforms of tau take their name from the presence or absence of four functional domains including an N-terminal region, a proline-rich domain, a microtubule-binding region (MTBR), and a C-terminal region. Alternative splicing of exons 2 and 3 determines whether the N-terminal inserts are present as 0 N (exons 1 and 4), 1 N (exons 1, 2, and 4) and 2 N (exons 1, 2, 3 and 4). The proline-rich domain is present in all isoforms. Alternative splicing of exon 10 leads to the four MTBRs represented by the 3R and 4R designation with domains 1, 3 and 4 included in 3R-isoforms and 1, 2, 3 and 4 included in 4R tau. Tau isoforms are differentially expressed across cell types, cellular compartments, and tissues with the most complete human tau protein (2N4R, full-length tau) containing a sequence of 441 amino acids [10, 11].

Unlike physiological tau which plays a role in synaptic plasticity, cell signaling, stabilizing microtubules crucial for axonal transport and neuronal function, among others, pathological tau undergoes additional post-translational modifications (PTMs) beyond what is physiologically normal, including hyperphosphorylation, truncation, and aggregation into neurofibrillary tangles (NFTs) and neuropil threads [9, 12]. These aggregates cause a loss-of-function for physiological tau thereby disrupting cellular processes, leading to synaptic dysfunction, neuronal loss, and progressive cognitive and motor decline [13, 14]. Moreover, misfolded pathological tau can spread from neuron-to-neuron in a prion-like pattern which may seed aggregation of endogenous tau in neighboring cells [15–17]. Other than phosphorylation, PTMs of tau may include acetylation, deamidation, glycation, glycosylation, methylation, nitration, ubiquitination, and sumoylation which all may contribute to tau-derived neurodegeneration [18, 19]. Complicating the role of pathological tau is the presence of other pathologies which may be a contributor to neurodegeneration. Also, the concept of mixed-pathology has been introduced to capture the spectrum of coincident proteinopathies which may be found in other neurodegeneration disorders like Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) (amyloid-β, α-synuclein and TDP-43) or other comorbidities like cardiovascular disease and diabetes to be considered during the diagnostic practice [20]. This factor complicates the design and implementation of a disease modifying strategy to ameliorate tau pathology, as the extent of interaction between coincident pathologies is understudied and varied patient-to-patient.

Currently, there are no approved disease-modifying therapies that directly target the underlying tau pathology for the tauopathies [21]. Existing treatments for patients diagnosed with a primary tauopathy focus on symptomatic management offering limited and transient relief. That said, the recent approvals of anti-amyloid disease modifying therapies for AD have been shown to slow cognitive decline but do not halt disease progression [22, 23]. Addressing the tau pathology present in these patients has become an emerging focus for the AD and primary tauopathy fields. Therefore, the current lack of comprehensive disease-modifying intervention underscores the urgent need for developing novel therapeutic strategies that target tau pathology [24].

The present review is a follow up to the authors' previous review from two years ago [25]. The purpose of the review is to provide information regarding the present pipeline of anti-tau therapeutics seeking to treat patients suffering from a variety of neurodegenerative disorders involving tau pathology. Like our previous publication, this review includes the different stages of development of the potential therapeutic drugs as well as the mechanisms of action, molecule types, routes of administration, and recent successes and failures within the tauopathy therapeutic area. Where applicable, emerging biomarkers which support the discovery and translation of therapeutics will be covered for completeness. However, novel biological insight on tau pathology and molecular mechanisms underlying tau misfolding and aggregation are beyond the scope of this review.

Methods

The method used in this review is the same as the previous review on this topic [25]. Briefly, curated search results from targeted queries, including keyword searches for microtubule-associated protein tau, MAPT, and tau,

were conducted on GlobalData and SciFinder® databases. To reduce false hits and duplications in the database, individual search queries were also investigated. All filtered results were divided into the clinical development stage appropriate to their individual status. Additional information was retrieved from company websites, Alzforum, PubMed, clinicaltrials.gov, conference proceedings, or direct communication with company or institute investigators leading the programs. The index date for this review is January 1, 2025, and the tables, figures and text apply to the information available on that date. We included trials of drugs in clinical trial phases 1, 2 and 3, as well as drugs in preclinical development and in the discovery phase. Many programs in preclinical and discovery phases, especially in academic research centers, have not been publicly disclosed and therefore, are not included in this review. Tauopathies harbor many types of neuropathology such as inflammation, synaptic dysfunction, oxidative injury, and others that may be indirectly related to tau aggregation but are not themselves an aspect of tau biology. Therefore, clinical trials and drug development programs which target these downstream aspects of tauopathies may have been omitted or are addressed in less detail in this review.

Results

Overview of anti-tau targeting therapeutics in development and their development stages

Our search through January 1, 2025, showed that in total the tau landscape contains 170 therapeutics, which is one less than in the previous review period (Fig. 1). There are no approved drugs that directly target tau. Of all therapeutics, 146 are under active development (all stages except inactive and discontinued) in this period which is 26 more than the last review. This growth comes from having more drugs in the discovery and preclinical phases which comprise 21% and 45% respectively of the current pipeline. There are 32 drugs currently in clinical trials which is four less than in the previous review. Additionally, two drugs are currently filing for IND/CTA status. Twelve drugs are in phase 1, fifteen are in phase 2 and five are in phase 3. This pipeline also identified 19 drugs that are recently inactive, defined as drugs which have not been updated in more than two years if in clinical development, or four years if in preclinical development. Finally, five drugs have recently been discontinued from clinical development.

Across the pipeline, there are 14 drug modalities in development (Fig. 2). Small molecules remain the most abundant modality, comprising 44% of the full landscape. Monoclonal antibodies (mAbs) represent 20% of the compounds in development, with vaccine approaches representing 11%. The other modalities of drugs and their relative abundance in the pipeline (%) include undisclosed approaches (4%), antibodies (4%), fusion proteins (4%), gene therapies (4%), antisense oligonucleotides (ASOs) (3%), small-interfering ribonucleotides (siRNA) (3%), synthetic peptides (3%), aptamer (1%), natural extract (1%), plasma protein fraction (1%), and undisclosed therapeutic protein (1%).

Of the 32 drugs in the clinic, half are administered orally (PO) to the patients (Supplementary Fig. 1). These clinical stage drugs include all small molecules and the one natural extract approach. Twenty-eight percent (28%) of the other drugs are administered intravenously (IV) and correspond to all the mAbs in the clinic. Intrathecally administered drugs account for 9% of drugs in the clinic, corresponding to the ASOs and siRNAs. Subcutaneous

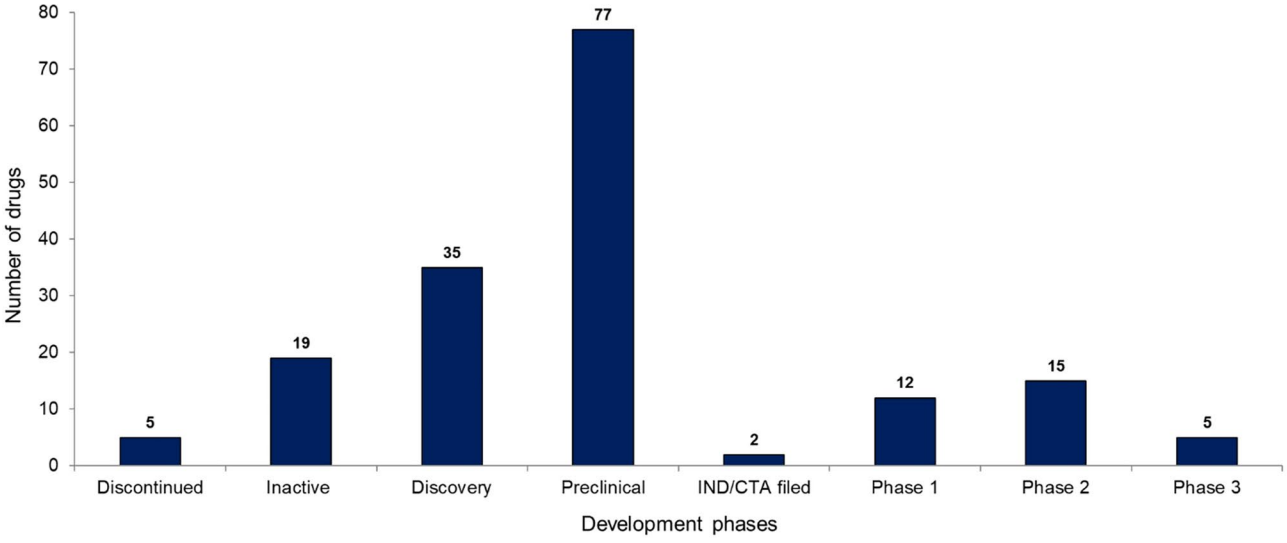

Fig. 1 Tau therapeutic portfolio by current development stage

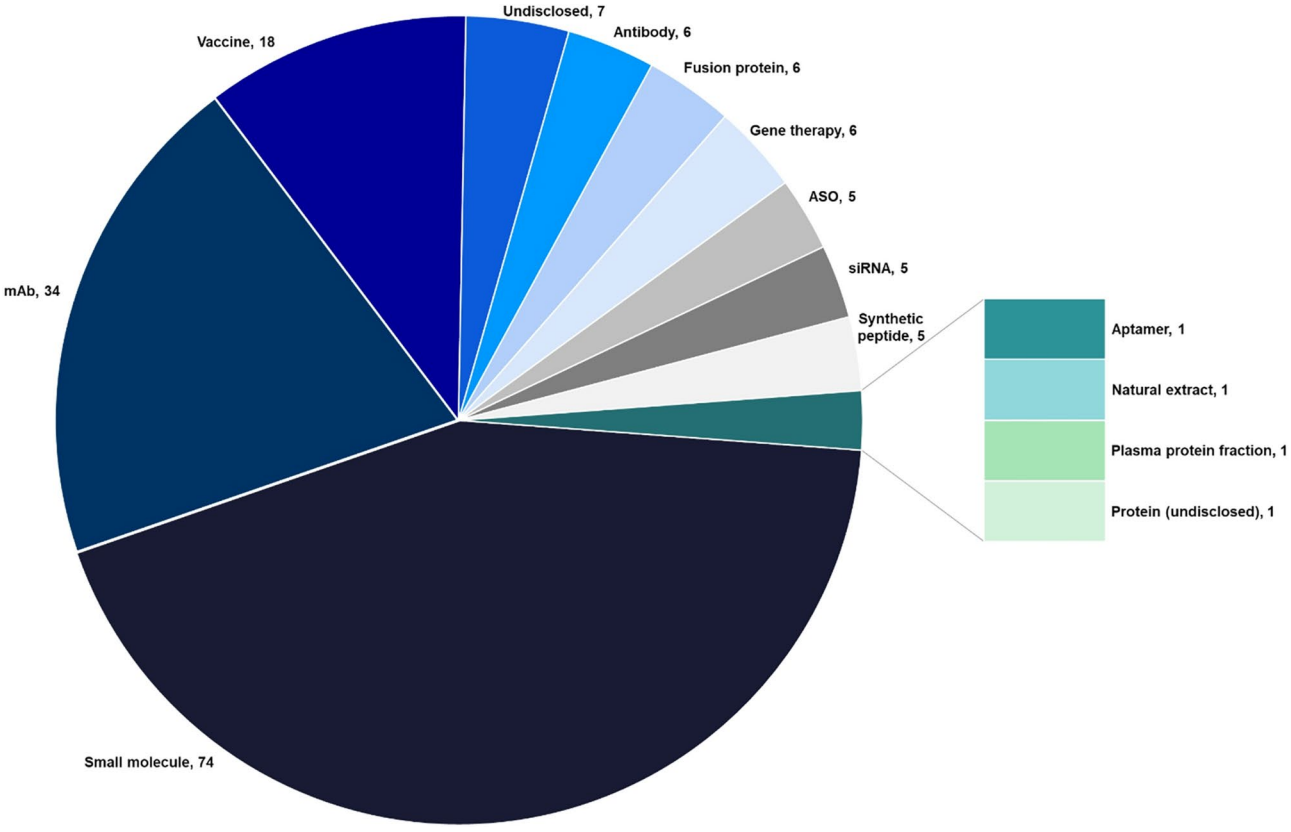

Fig. 2 Tau therapeutic portfolio by molecule type

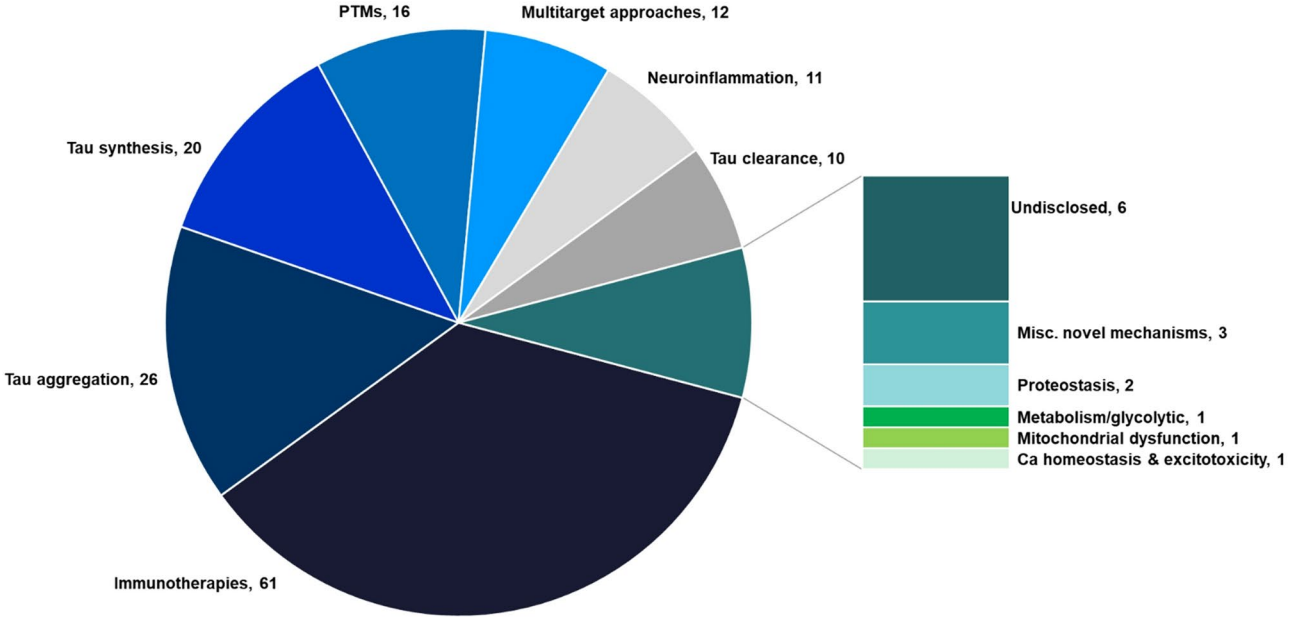

Fig. 3 Mechanisms of action of therapeutic programs targeting tau

(protein drug and a vaccine) and intramuscular (vaccine) administration approaches account for 6% each.

There are 13 categories of mechanisms associated with tau pathology that are being targeted by drugs in the pipeline (Fig. 3). Immunotherapies are the dominant mechanistic approach, accounting for 36% of the drugs. The second largest mechanism is tau aggregation (15%). Drugs targeting tau synthesis and post-translational

modification account for 12% and 9%, respectively. Drugs targeting multiple targets simultaneously account for 7% while neuroinflammatory and tau clearance targeted therapies represent approximately 6% each. There are several drugs in development where the primary mechanism of action is currently undisclosed (4%) while miscellaneous novel mechanisms account for 2%. Of the remaining drugs, less than 1% target each of the following pathways: proteostasis, metabolism/glycolytic pathways, mitochondrial dysfunction and calcium homeostasis and excitotoxicity.

Tau therapeutic pipeline

Phase 3

There are five active phase 3 trials in development comprised of one mAb and four small molecules. All but one of these trials were mentioned in our previous review (Table 1). The new therapeutic program covered in this review is for blarcamesine hydrochloride (ANAVEX 2–73), an orally administered small molecule from Anavex Life Sciences Corporation. ANAVEX 2–73 is believed to work by activating the sigma-1 receptor (SIGMAR1). SIGMAR1 is a protein found in the brain that engages in several cellular processes, including neuroprotection and neuroplasticity [26, 27]. A recent phase 2b/3 clinical trial (ANAVEX2-73-AD-004, NCT03790709) investigated the efficacy and safety of ANAVEX 2–73 in patients with AD. The trial enrolled 508 participants with early AD who were randomized to receive either ANAVEX 2–73 or placebo for 48 weeks [28]. The co-primary cognitive and functional outcomes were assessed as change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13) and Alzheimer's Disease Cooperative Study– Activities of Daily Living (ADCS-ADL) from baseline to 48 weeks. The secondary endpoints included changes in other cognitive and functional measures, as well as safety assessments. The results of the trial indicate that at 48 weeks, ANAVEX 2–73 showed a difference in ADAS-Cog13 and the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) scores compared to placebo. However, the co-primary functional endpoint, ADCS-ADL did not differ between treatment and placebo groups in the double-blind portion of the trial. The most common adverse events during treatment titration were dizziness (placebo 6.0%, blarcamesine 35.8%) and confusional state (placebo 0.6%, blarcamesine 14.3%). The supporting biomarker data was mixed with only plasma

Table 1 Tau therapeutics in phase 3 clinical trials (as of January 1, 2025)

Molecule Type	Company Name	Drug Name	Clinical Trial ID	Indication (trial sites)	Route of Administration	Mechanism of Action
mAb	Eisai Co.	Etalanetug (E2814)	NCT05269394; NCT01760005	AD (AR, AU, BR, CA, CO, FR, DE, IE, IT, JP, MX, NL, PR, ES, UK, US)	IV	A humanized, high affinity, IgG1 antibody recognizing the tau MTBR. E2814 and its murine precursor, 7G6, were revealed by epitope mapping to be bi-epitopic for 4R and mono-epitopic for 3R tau isoforms because they bind to the sequence motif HVPGG.
Small molecule	Anavex Life Sciences Corp.	Blarcamesine hydrochloride (ANAVEX 2–73)	NCT04314934	AD (AU, CA, DE, NL, UK)	Oral	Simultaneous antagonism on presynaptic M2 autoreceptors and on the presynaptic M3 muscarinic heteroreceptors of the glutamatergic neuronal endings in synergy with agonism on the intracellular sigma-1 receptor located on the endoplasmic reticulum contributes to the anti-amnesic activity of the active metabolite. Additionally, SIGMAR1 activation restores cellular homeostasis.
	Annovis Bio	Buntanetap (ANVS-401; Posiphen)	NCT06709014 & NCT05686044 (AD); NCT05357989 (PD)	AD (US); PD (DE, HU, IT, PL, ES, US)	Oral	Inhibits the production of neurotoxic proteins that are derived from the amyloid precursor protein (APP) and tau. It works by inhibiting α-synuclein, tau and APP synthesis.
	BioVie Inc.	Bezisterim (NE-3107, Trolex, HE3286)	NCT04669028	AD (US)	Oral	Inhibits extracellular signal regulated kinase 1 and 2 (ERK 1 & 2), and the activity of other inflammatory mediators like nuclear factor kappa B and tumor necrosis factor.
	TauRx Therapeutics	LMTX (hydromethylthionine mesylate, TRx 237, HMTM)	NCT03446001	AD (BE, CA, FR, IT, PL, ES, UK, US)	Oral	A tau and TDP-43 aggregation inhibitor.

Aβ42/40 ratio increased significantly in blarcamesine-treated patients compared to placebo. Plasma levels of neurofilament light chain (NfL), phosphorylated tau (pTau) 181 and pTau 231 all showed a smaller increase in blarcamesine-treated patients compared to placebo, but did not reach statistical significance. Upon completion, patients were invited to enroll in the open-label extension ATTENTION-AD (NCT04314934) to evaluate the safety and efficacy of daily treatment. A recent press release reported that continuous treatment with ANAVEX 2–73 over three years significantly slowed clinical decline in patients with early AD [29]. A change in dosing regimen during the open-label extension phase reduced the dizziness suffered by patients during the double-blind phase, suggesting that this adverse event can be managed, and the drug maintained a favorable safety profile throughout the extended treatment period. In late 2024, Anavex announced that the European Medicines Agency (EMA) accepted for review the marketing authorization application for ANAVEX 2–73 [30].

Since the last review period, there have been limited updates to TauRx Therapeutics' LMTX (hydromethylthionine mesylate, HMTM). Previously, results on TauRx Therapeutics' 24-month phase 3 Lucidity trial (NCT03446001) revealed a dose-dependent reduction in plasma NfL levels [31]. However, there has been no peer-reviewed publication on these findings since the initial publishing of the trial design [32]. In July 2024, TauRX announced the acceptance of a marketing authorization application for HMTM to the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of mild-to-moderate AD and mild cognitive impairment (MCI) [33]. The expanded access program for the drug remains open for eligible participants (NCT03539380).

BioVie's NE-3107 is a derivative of b-androstenetriol which acts as an oral anti-inflammatory insulin sensitizer by targeting extracellular signal regulated kinase 1 and 2 and nuclear factor kappa beta (NFKB) [34, 35]. Previously in a phase 2 open-label study with MCI to mild AD (NCT05227820), NE-3107 showed improvements to clinician-rated cerebral blood flow and functional brain connectivity [36]. Statistically non-significant changes to biomarkers associated with neuroinflammation were also reported. Towards the end of 2023, NE-3107 completed a phase 3 clinical trial with 439 subjects with mild to moderate probable AD (NCT04669028). Unfortunately, results were inconclusive since an anomalously high number study sites were disqualified for trial protocol violations [37]. A new phase 3 study for mild to moderate AD patients with a once-daily formulation of NE-3107 has been announced but not filed [38]. Additionally, NE-3107 is active in phase 2 trials for PD and traumatic brain injury (NCT06757010, NCT05970575, respectively).

Buntanetap (ANVS-401) from Annovis Bio is an orally administered small molecule that decreases translation of amyloid precursor protein (APP), tau and α-synuclein. The safety, tolerability, pharmacokinetics, and pharmacodynamics of the drug were recently published in a completed phase 1/2 trial as part of the Alzheimer Disease Cooperative Study (NCT02925650) [39]. The drug was safe, and modeling of kinetics showed dose-dependent lowering of APP production. In a phase 3 study (NCT05357989), for patients diagnosed with PD for longer than 3 years, there were declines in aspects of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), as well as total scores and cognition compared with placebo and baseline [40]. A phase 3 study of ANVS-401 in early AD is expected to begin enrollment in 2025 (NCT06709014) [41].

Eisai's Etalanetug (E2814) remains the only biologic in a phase 3 trial. E2814 is a humanized IgG1 antibody targeting the HVPGG epitope in the tau MTBR [42]. By targeting the tau at the second and fourth MTBR, the antibody is selecting for a region of tau at the core of neuropathological filaments to inhibit tau seeding and aggregation. Recent updates from the 2024 Clinical Trials on Alzheimer's Disease (CTAD) conference on the phase 1b/2 study of a small number of patients with dominantly inherited Alzheimer disease (DIAD) taking escalating doses of E2814 showed reductions in both CSF pTau 217 and MTBR-tau243 biomarkers (NCT04971733) [43]. E2814 is also the therapeutic in the tau arm of the Tau NexGen trial of the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), along with the anti-amyloid therapy lecanemab. The study will investigate the benefits of anti-tau therapy while anti-amyloid treatment is given as a baseline (NCT05269394) [44]. The E2814 treatment arm has completed enrollment, and the trial completion date is expected to be in 2028. There is also an actively recruiting phase 2 study with sporadic early AD patients with this drug combination (NCT06602258).

Phase 2

In the current reporting period, there are 15 drugs in phase 2 which is one less from the previous reporting period (Table 2). Small molecule approaches remain the most popular modality, with seven in phase 2. The other eight drugs are composed of: one ASO, four mAbs, one protein and two vaccines.

In the past two years there have been many papers discussing the early clinical findings from Biogen's ASO, BIIB080, developed with IONIS Pharmaceuticals, which is now in phase 2. Data from the phase 1b trial was shown indicating that BIIB080 significantly reduced total tau (t-tau) protein levels, pTau 181 concentration and

Table 2 Tau therapeutics in phase 2 clinical trials (as of January 1, 2025)

Molecule Type	Company Name	Drug Name	Clinical Trial ID	Indication (trial sites)	Route of Administration	Mechanism of Action
ASO	Biogen	BIIB080 ($MAPT_{Rx}$)	NCT05399888	AD (AU, BE, CA, CZ, DK, FI, FR, DE, IT, JP, NL, PL, ES, SE, CH, UK, US)	Intrathecal	ASO that acts by targeting expression of the MAPT gene.
mAb	Bristol-Myers Squibb	BMS-986446 (PRX-005; Anti-MTBR-Tau)	NCT06268886	AD (AU, BE, CA, JP, KR, SG, ES, SE, UK, US)	IV	It is an anti-tau IgG1 humanized antibody. It recognizes an epitope in the R1, R2, and R3 repeats in the MTBR.
	GlaxoSmithKline (partnered with Alector)	AL-101 (GSK-4527226)	NCT06079190	AD (AR, AU, CA, FI, FR, DE, IT, KR, NL, NO, ES, SE, TW, TR, UK, US)	IV	Acts by inhibiting the Sortilin1 (SORT1) receptor to prevent degradation of pro-granulin, increasing its circulating half-life. By restoring progranulin, tau pathologies may be reduced.
	Johnson & Johnson	Posdinemab (JNJ-3657; JNJ-63733657)	NCT04619420	AD (AU, BE, CA, FR, JP, NL, ES, SE, UK, US)	IV	A mAb that targets the proline rich region of tau.
	UCB SA	Bepranemab (UCB-0107, RG 6416)	NCT04867616 (AD); NCT04658199 (PSP, phase 1)	AD (BE, CA, FR, DE, IT, NL, PL, ES, UK, US); PSP (BE, DE, ES, UK)	IV	Recombinant humanized IgG4 that binds to the centralized (AA 235–250) region of tau near the MTBR.
Protein	INmune Bio	Pegipaner-min (XPro™; XPro1595; DN-TNF; INB 03)	NCT05522387; NCT05318976	AD (AU, CA, CZ, FR, DE, PL, ES, UK)	Subcutaneous	Tumor necrosis factor (TNF) R1 antagonist, prevents differentiation and function of myeloid-derived suppressor cells.

Table 2 (continued)

Molecule Type	Company Name	Drug Name	Clinical Trial ID	Indication (trial sites)	Route of Administration	Mechanism of Action
Small molecule	Cervomed (formerly, EIP Pharma)	Neflamapimod (VX 745)	NCT03435861 (AD); NCT05869669 (LBD)	AD (FR), LBD (NL, UK, US)	Oral	Inhibitor of the alpha isoform of the protein enzyme p38 mitogen activated protein kinase (p38 MAPK alpha).
	Ferrer (licensed from Asceneuron)	FNP-223 (ASN90)	NCT06355531	PSP (FR, DE, HU, IT, PL, PT, ES, US)	Oral	Protein O-GlcNAcase inhibitor.
	PharmatrophiX	LM11A-31-BHS	NCT03069014	AD (AT, CZ, DE, ES, SE)	Oral	Blocks the interaction between Aβ peptide and p75NTR, down-regulating the signaling pathways and up-regulating survival signaling.
	T3D Therapeutics	T3D-959	NCT04251182	AD (US)	Oral	Dual agonist of the peroxisome proliferator activated nuclear receptor delta/gamma, aka PPARδ/γ. Implicated in the transcription of genes controlling lipid metabolism and glycolytic pathways.
	Transposon Therapeutics	Censavudine (TPN-101, Festinavir)	NCT04993768 (PSP); NCT04993755 (ALS/FTD)	PSP (US); ALS/FTD (BE, FR, DE, ES, US)	Oral	It is a nucleoside reverse transcriptase inhibitor that blocks HIV-1 reverse transcriptase. The mechanism of action for neurodegeneration is claimed to be through LINE-1 reverse transcriptase, specifically inhibited by TPN-101. LINE-1 elements are a class of retrotransposable elements that are capable of replicating and moving to new locations within the genome. When this process becomes dysregulated, that drives overproduction of LINE-1 DNA, triggering innate immune responses that contribute to neurodegenerative, autoimmune, and aging-related disease pathology.
	Univ. of California, Irvine	Nicotinamide	NCT03061474	AD (US)	Oral	Histone deacetylase inhibitor to reduce tau-induced microtubule depolymerization and tau phosphorylation.
	Vivoryon Therapeutics	Varoglutamstat (PQ912)	NCT04498650, NCT03919162	AD (DK, DE, NL, PL, ES, US)	Oral	Blocks the enzyme glutaminyl cyclase (QPCT), which catalyzes the formation of N3pE amyloid. In addition, QPCTL, an isoform of QPCT, is also required for the stability and full potency of the proinflammatory protein CCL2, reducing neuroinflammation. CCL2 is also a promoter of tau pathology.
Vaccine	GemVax & KAEL Co Ltd	Tertomotide (Riavax, GV1001)	NCT05189210 (AD); NCT06235775 & NCT05819658 (PSP)	AD (NL, PL, ES, US); PSP (KR)	Subcutaneous	It could bind to the gonadotropin-releasing hormone (GnRH) neurons and activate downstream signaling pathways, increasing cAMP levels and affect the degradation of Aβ peptides, reduction of pTau, modulation of neuroinflammation and suppression of neuronal loss.
	Johnson & Johnson (codeveloped with AC Immune)	JNJ-2056 (ACI-35030; JNJ 64042056)	NCT06544616	AD (AU, JP, SE, UK, US)	intramuscular	Liposomal vaccine based on SupraAntigen technology administered through a parenteral route. Targets pTau as an anti-tau active immunotherapy.

the ratio of t-tau to Aβ42 in CSF (NCT03186989) [45]. These reductions were dose-dependent and sustained over time. In a small cohort within the trial population, tau PET using the 18F-MK-6240 tracer measured a reduction of NFTs across all brain regions evaluated [46]. The drug is now in a phase 2 study with full enrollment (NCT05399888). In addition, there is a phase 1 study using coadministration of radiolabeled microdose BIIB080 with BIIB080 in healthy controls to investigate biodistribution, safety and tolerability of the drug anticipated to open in 2025 (NCT06454721).

There are two new mAbs that have been added to the phase 2 landscape. The first is Alector's AL-101 (GSK4527226) developed in collaboration with GlaxoSmithKline. The study is recruiting patients with MCI and AD (NCT06079190). GSK4527226 is designed to elevate the level of progranulin by blocking the sortilin (SORT1) receptor in the brain. Preclinical studies have correlated reduced levels of progranulin to proteinopathies such as those caused by tau pathology [47, 48]. The other new tau antibody in Phase 2 is Bristol-Myers Squibb's BMS-989446 (previously, PRX-005) which is an IgG1 mAb licensed from Prothena. It targets an epitope consistent to both 3R and 4R tau isoforms, and it completed its phase 1 study in 2024 (NCT06084598). In the phase 1 study, BMS-989446 was safe and well tolerated with proportional exposure predictive of pharmacological engagement with MTBR tau [49]. A phase 2 study is actively recruiting patients with early AD (NCT06268886).

Other mAbs in trial include Johnson & Johnson's JNJ-3657 (posdinemab), which released phase 1 data recently [50]. Posdinemab is a humanized IgG1 mAb that binds to the proline-rich domain of tau which is noteworthy for its inclusion of a tau phosphorylated residue at 217 (pTau 217) which is used as a biomarker as discussed below. The drug was well tolerated, showed favorable dose dependent lowering of key biomarkers in AD participants, and proportional pharmacokinetic results. The mAb recently received FDA fast-track designation for treatment of AD and is currently in phase 2b (NCT04619420) [51]. Of note in this trial with posdinemab, plasma pTau 217 was used as a screening biomarker prior to tau PET which reduced the total amount of tau PET scans to support enrollment by nearly a half [52]. As will be discussed later in this review, pTau 217 is being readily adopted as a specific blood biomarker for AD pathology [53]. Bepranemab developed by UCB is in phase 2 for prodromal or mild AD patients (NCT04867616). Bepranemab is a humanized full length IgG4 mAb binding to amino acids 235–250, a central tau epitope [54]. Recently, it was reported that this trial did not result in improved cognition and function, but tau PET showed that tau accumulation was slowed by up to 58% compared to placebo after 80 weeks of treatment [55]. Subgroup analysis split low and high baseline tau tangle levels and ApoE4 mutation carriers and noncarriers. Notably, when ApoE4 carriers with high baseline tau tangles were removed from the analysis, clinical benefit was observed in patients with low baseline tau levels as determined by ADAS-Cog14.

INmune Bio's Pegipanermin (XPro1595) is a protein biologic that targets soluble tumor necrosis factor (TNF) which is linked to inflammation and neurodegeneration in the brain [56, 57]. In 2022, the FDA placed a hold on the phase 2 trial due to a request for additional information around manufacturing [58]. The hold was lifted in 2024, and the trial is now fully enrolled (NCT05318976) [59].

There is one small molecule O-GlcNAcase inhibitor in phase 2 called FNP-223. This was originally Asceneuron's first-generation molecule, formerly known as ASN-90, which was licensed by Ferrer in 2023 [60]. It is actively recruiting patients with PSP in a phase 2 study (NCT06355531).

Neflamapimod (VX745) is an investigational drug being developed by CervoMed (formerly EIP Pharma). It is an inhibitor of p38 MAP kinase alpha. p38 MAP kinase alpha is involved in inflammation and synaptic dysfunction in the brain which may lead to abnormal tau protein [61, 62]. The phase 2 trial for patients suffering from AD was completed in 2021, but no updates have been reported (NCT03435861). Neflamapimod is also being evaluated in a phase 2 trial with patients with dementia with Lewy Bodies (NCT05869669). For that trial, an exclusion criteria of plasma pTau 181 levels above a threshold value will be used since it may indicate tau pathology consistent with AD.

LM11A-31-BHS is a small molecule being developed by PharmatrophiX for the treatment of AD. It is a modified version of an earlier compound called LM11A-31 which activated the p75 neurotrophic receptor (p75NTR) survival pathways and downregulated degenerative signaling allowing for the modulation of signaling pathways related to tau [63]. The phase 2 trial for LM11A-31-BHS was completed in 2020 (NCT03069014). In 2024 it was reported that trial met its primary endpoint of safety and tolerability [64]. No significant effect of treatment was observed on cognitive tests, but slowing of pathologic progression in the CSF biomarkers, structural MRI and FDG PET was reported. Additionally, treated patients showed reduced levels of CSF synaptosomal-associated protein 25 and neurogranin compared to placebo, which are presynaptic and postsynaptic biomarkers of neuronal damage, respectively.

T3D-959 is a small molecule from T3D Therapeutics that activates two nuclear peroxisome proliferator-activated receptors, which are central regulators of glucose and lipid metabolism in the brain. Preclinical studies with T3D-959 showed normalized expression of pTau in in

vivo and ex vivo rat models of sporadic AD [65]. T3D-959 completed a phase 2 trial in 2023 (NCT04251182). The drug was well tolerated with no serious treatment emergent adverse events observed [66]. Treated patients with a high plasma pTau 217/non-pTau ratio showed the best response to the drug based on those subgroups taking 30 mg/day dosing. Primary ADAS-Cog11 and Clinical Global Impression of Change endpoints were not met in the overall population. Amyloid, tau and neurogranin biomarkers were trending positively compared to placebo. A modified intent-to-treat population was queried later because of data-irregularities at several of the clinical sites [67]. This modified intent-to-treat population consisted of 141 of the originally reported 250 subjects in the trial. After 24 weeks of treatment in the 30 mg dose cohort, there was a 73% slowing in cognitive decline compared to placebo as measured by the ADAS-Cog11. Amyloid, tau and neurogranin biomarkers trended positively too. These data from post-hoc analyses will be helpful in designing a subsequent trial to replicate these findings.

Transposon Therapeutics has Censavudine (TPN-101) in two phase 2 trials, one for PSP and one for ALS/FTD associated with hexanucleotide repeat expansion in the C9orf72 gene (NCT04993768 and NCT04993755, respectively). TPN-101 is an inhibitor of LINE-1 reverse transcriptase. For the PSP trial, it was reported that there were reductions in CSF NfL and dose-related reductions in interleukin 6 (IL-6) cytokine levels [68]. For fully treated patients, there also was a stabilization of their clinical symptoms as measured by the PSP Rating Scale (PSPRS) between the 24th and 48th week. Since this report, the FDA has granted TPN-101 Fast Track designation for PSP. Similar biomarker level reductions, reduced rate of decline of respiratory measures, and slowing of progression in the revised ALS Functional Rating Scale were reported in the ALS/FTD-focused trial [69].

The phase 2a trial for patients with early AD with nicotinamide was completed in 2023 and results were recently published (NCT03061474). Overall, nicotinamide treatment was regarded as safe but there were no meaningful impacts on the primary and secondary endpoints relating to CSF biomarkers and cognitive and functional measures [70].

Vivoryon Therapeutics has a first-in-class small molecule inhibitor called Varoglutamstat (PQ912). Varoglutamstat focuses on reducing the formation of pyroglutamate Aβ and reduce neuroinflammation by targeting the enzymes glutaminyl cyclase and iso-glutaminyl cyclase, respectively [71]. Both phase 2a and phase 2b trials for patients with AD (NCT03919162 and NCT04498650, respectively) revealed negative topline data for all primary and key secondary endpoints in 2024 [72, 73].

Tertomotide (GV1001) from GemVax & KAEL Co. is a 16-amino acid peptide that was developed as a cancer vaccine for the treatment of pancreatic cancer, but international trials did not show efficacy [74]. Subsequent preclinical studies in models of neurodegeneration showed antioxidant and anti-inflammatory properties [75, 76]. In earlier phase 2 trials in AD, the treatment was well tolerated and in one the high-dose group showed a slower rate of cognitive decline from baseline in the primary endpoint (NCT03184467) [77]. The drug is now in a larger phase 2 study for AD (NCT05189210). Results from an exploratory phase 2a PSP trial were also recently released (NCT05819658). The phase 2a trial did not meet its primary endpoint of a change in PSPRS compared to placebo, but subgroup data did show a slower decline in PSPRS at one of the dosages administered [78]. A long-term safety and efficacy study for PSP patients in the initial phase 2a study remains active (NCT06235775).

Johnson & Johnson's JNJ-2056 is currently recruiting preclinical AD patients (cognitively normal, tau positive) for a phase 2b clinical trial (NCT06544616). This active immunotherapy aims to stimulate the immune response to phosphorylated tau. In an earlier phase 1/2 study, there were no safety concerns raised and anti-tau IgG and IgM antibodies against phosphorylated tau were detected in all patients (NCT04445831) [79]. The drug has received FDA Fast Track Designation [80].

Phase 1

There are 12 phase one drugs in development targeting tau (Table 3). This is four less programs than the previous reporting period. There are five mAbs and four small molecules in phase 1. There is also one ASO, siRNA and a natural extract in phase 1 at the time of writing.

NIO752 is an ASO developed by Novartis. It is designed to target and reduce levels of tau protein in the brain. NIO752 is currently being evaluated in clinical trials for the treatment of AD and PSP. The initial phase 1 trial targeting PSP was recently completed but no data has been reported (NCT04539041). It consisted of six cohorts, including one placebo and five different dose escalating arms. The five different dosing arms involved four injections of drug over three months, with a nine-month follow up period. Additionally, NIO752 has an active phase 1b trial study PK/PD, safety, and tolerability in patients with early AD who are positive for both CSF amyloid-β and tau with a primary endpoint of a change in CSF tau from baseline (NCT05469360). Additionally, a stable isotope labelling kinetics study was announced and will investigate the rate of tau synthesis in subjects treated with NIO752 announced for AD patients, but it has not begun enrollment yet (NCT06372821).

Eli Lilly has a MAPT-targeting siRNA approach (LY-3954068) which just began recruiting for a phase 1 study

Table 3 Tau therapeutics in phase 1 clinical trials (as of January 1, 2025)

Molecule Type	Company Name	Drug Name	Clinical Trial ID	Indication	Route of Administration	Mechanism of Action
ASO	Novartis	NIO-752	NCT06372821 & NCT05469360 (AD); NCT04539041 (PSP)	AD (FI, FR, ES, SE); PSP (CA, DE UK, US)	Intrathecal	ASO that acts by targeting expression of the MAPT gene.
mAb	ADEL Inc.	ADEL-Y01	NCT06247345	AD (US)	IV	A recombinant IgG1 humanized mAb that recognizes and binds to tau acetylated at lysine-280, thus inhibiting aggregation and propagation of tau seeds and enhancing microglial clearance.
	Aprinoia Therapeutics	APNmAb005	NCT05344989	AD & tauopathies (US)	IV	A tau mAb that targets high molecular weight forms of tau oligomers.
	H. Lundbeck AS	LuAF-87908	NCT04149860	AD (US)	IV	Humanized mouse IgG1 mAb to pTau.
	Merck & Co.	MK-2214	NCT05466422	AD (US)	IV	An anti-tau mAb targeting pSer413.
	Voyager Therapeutics	VY-7523 (VY-TAU01)	NCT06874621	AD (CA, US)	IV	Anti-tau mAb that targets epitopes in the C-terminal domain.
Natural extract	Pharmacobio	DDN-A-0101	NCT06367426	AD (KR)	Oral	Dry extract of Houttuynia cordata administered orally. Anti-inflammation properties are believed to be the main effect which may lower pTau levels.
siRNA	Eli Lilly	LY-3954068 (MAPT siRNA)	NCT06297590	AD (JP, UK, US)	Intrathecal	Acts by inhibiting the expression of MAPT with a siRNA.
Small Molecule	Anavex Life Sciences	ANAVEX 3–71 (AF710B)	NCT04442945	AD & FTD (AU)	Oral	Induces a synchronized sigma-1 receptor activation and M1 muscarinic allosteric/bi-topic modulation via super-sensitization of M1mAChR, through a hypothetical heteromerization with Sig1R. Decreases Aβ, tau-hyperphosphorylation, GSK3beta activation, and prevents apoptosis and mitochondrial dysfunction via increased Bcl2.
	Biogen Inc.	BIIB113	NCT05195008	AD (SE, UK)	Oral	Protein O-GlcNAcase inhibitor.
	Dong-A ST Co.	DA-7503	NCT06391827	AD (KR)	Oral	It binds to pathological and detached forms of tau monomers to inhibit tau oligomer formation and phosphorylation.
	Oligomerix Inc.	OLX-07010	NCT05696483	AD & PSP (US)	Oral	Acts by targeting tau oligomer formation.

with AD patients (NCT06297590). siRNA is a gene silencing therapy which, like ASOs, uses complementary base pairing to match the targeted mRNA sequence and reduce protein synthesis. Whereas ASOs are either single stranded DNA or RNA molecules, siRNA is a double-stranded RNA molecule. Like the MAPT-targeting ASOs, LY-3954068 is administered intrathecally and acts by inhibiting the production of tau.

There are five mAbs in phase 1 trials. Alzheimer's Disease Expert Lab (ADEL), Inc. is recruiting for a phase 1 trial for ADEL-Y01 (NCT06247345). ADEL-Y01 is a humanized mAb targeting tau acetylated at K280 within the MTBR, a modification linked to tau aggregation and pathology in AD and other tauopathies [81]. In preclinical work, ADEL-Y01 inhibited acetylated tau aggregation and propagation, promoted microglial uptake for degradation, and reduced tau pathology and behavioral deficits in mice [82].

APNmAb005 from Aprinoia Therapeutics is a humanized mAb that targets tau oligomers. Preclinical data showed that the murine version bound to a tau epitope associated with synaptic oligomers instead of cytosolic monomeric tau [83]. The same mAb has also been used to identify high molecular weight tau species like oligomeric tau in a new ELISA assay [84]. The phase 1a study completed in 2024 with results not posted yet (NCT05344989) [85].

No results have been published on Lundbeck's phase 1 trial with LuAF-87908 which was completed in 2023 (NCT04149860). This mAb targets phosphorylated tau at the serine 396 site (pSer396) [86]. Preclinical findings demonstrated that the mAb selectively bound to AD,

primary tauopathy and rTg4510 mouse brain extracts and prevented tau seeding in cellular and in vivo assays [87].

MK-2214 by Merck is a mAb actively in a phase 1 trial but is no longer recruiting patients with MCI or mild-to-moderate AD (NCT05466422). The target epitope for the drug has not been disclosed by Merck, but it is believed to be phosphorylated serine 413 (pSer413) [88, 89]. The study has an expected completion date of July 2025.

The final mAb in phase 1 trials is Voyager Therapeutics' VY-7523 (VY-TAU01, NCT06874621). In 2024 it was announced that the first participants were dosed in a Phase 1a trial [90]. In 2025, topline single ascending dose data from healthy patients was reported with dose-proportional pharmacokinetics and no safety/tolerability concerns [91]. Previously presented preclinical data showed that the murine version of VY-TAU01 targeted the C-terminal domain of tau and resulted in greater reductions of tau AT8 signal compared to gosuranemab, zagotenemab and bepranemab [92].

There are four small molecules in phase 1 trials. In addition to its phase 3 candidate blarcamesine, Anavex Life Sciences recently completed a phase 1 study on another candidate called ANAVEX3-71 (AF710B) which has the same mechanism of action. Pharmacokinetic data showed metabolism was linear, dose proportional, and time invariant with no effect from food intake [93]. Also, it was reported that there was no clinical effect on ECG parameters [94]. No follow up phase 2 has been announced, but a phase 2 studying the safety, tolerability, efficacy, pharmacokinetics, and electrophysiology in patients with schizophrenia has been opened and is recruiting (NCT06245213).

Biogen's O-GlcNAcase inhibitor BIIB113 completed its phase 1 trial which included target occupancy analysis using the PET ligand 11 C-BIO-1819578 to monitor binding to O-GlcNAcase in the brain (NCT05195008) [95]. Mild to moderate adverse events, mostly deemed unrelated to the drug, were reported along with high target occupancy verified by PET following single and multiple doses [96]. The data was supportive of launching a phase 2 trial, but no official announcement has been made.

Dong-A ST Co. recently announced a phase 1 trial for DA-7503 to assess safety, tolerability, and pharmacokinetics of the drug (NCT06391827). DA-7503 inhibits tau oligomer formation and phosphorylation. In earlier preclinical data, DA-7503 decreased the pTau and free tubulin levels in an in vitro model of tauopathy using differentiated SH-SY5Y human neuroblastoma cells [97]. Additionally, after two weeks of treatment with DA-7503 there was a resistance to spatial memory deficits and reduced hippocampal pTau levels in a mouse model of tauopathy. The phase 1 trial has not begun enrollment.

OLX-07010 is an oral, small molecule inhibitor of tau self-association preventing oligomer formation developed by Oligomerix which recently launched a phase 1 trial for the drug (NCT05696483). Preclinical studies showed that the drug was not toxic at the doses administered and resulted in minor reductions of self-associated tau species in certain regions of the mouse brain, as well as partially rescued motor impairment determined by rotarod assessments [98–100].

More information has been disclosed from Pharmacobio's DDN-A-0101 phase 1 study for AD in South Korea (NCT06367426). This study is a randomized, double-blind, placebo-controlled trial investigating the safety and tolerability of oral DDN-A-0101 in healthy adults and elderly participants. It will involve both single and multiple ascending doses. DDN-A-0101 is a dry extract of *Houttuynia cordata* Thunb (*H. cordata*) in an oral capsule. *H. cordata* is a rhizomatous, herbaceous, and perennial plant found in Asia, and used in traditional medicine practices [101]. It has a complex chemical composition consisting of alkaloids, essential oils, and flavonoids [102]. One of the flavonoids, quercitrin, is disclosed as a pharmacokinetic marker which will be monitored in the study.

Investigational new drug (IND) or clinical trial application (CTA) filed

There are two drugs listed as in the process of applying and receiving IND or CTA status to start clinical trials (Supplementary Table 1). Annovis Bio's ANVS-405 is targeting the treatment of traumatic brain injury, a secondary tauopathy. This drug is believed to be the intravenous formulation of buntanetap (posiphen) for acute administration [103]. It aims to prevent neuronal death by inhibiting the production of neurotoxic proteins that are derived from the amyloid precursor protein (APP) and tau. The other drug is PRX-123 from Prothena Corp. It is a dual Aβ-tau conjugated linear peptide vaccine being developed for the treatment of AD [104].

Discovery and preclinical development

There are a total of 112 tau therapeutic development programs that have not yet entered clinical stage testing. Of these programs, 77 are in preclinical development phase (Supplementary Table 2). Compared to the last reporting period, it is an increase of 43%. The definition of preclinical is the stage at which a drug is assessed in a model species for in vivo studies with the purpose of understanding the efficacy, toxicity, and pharmacokinetics of the drug. Safety in animals predicting safe use in humans must be shown in this stage before the drug can be progressed to clinical testing in humans. The distribution of drug types and quantity (number) in the preclinical phase of development are as follows: antibody [3], antisense RNAi

oligonucleotide [5], ASO [3], fusion protein [2], gene therapy [5], mAb [15], small molecule [29], synthetic peptide [4], unknown [3] and vaccine [8].

The discovery phase is defined as when the program is in the process of identification and optimization of a molecular type/substance for therapeutic use, with the aim of producing a candidate for preclinical testing. Candidates are primarily identified through the assay of compounds against biological targets. Hits are screened for other characteristics (i.e., bioavailability, toxicity, and potency), and further optimized through appropriate drug design processes. Once a candidate drug is optimized and it prepares to be evaluated in more complex biological systems, it advances to the preclinical stage. There are 35 drug candidates currently in the discovery phase (Supplementary Table 3). The distribution of drug types and quantity (#) in the discovery phase of development are as follows: antibody [2], aptamer [1], fusion protein [4], gene therapy [1], mAb [7], small molecule [13], synthetic peptide [1], unknown [2], vaccine [4].

Recently inactive and discontinued programs

There are 19 programs classified as "inactive" (Supplementary Table 4). This stage is defined as a drug which has not been publicly updated in more than two years if in clinical development, or four years if in preclinical development. Although the information on these drugs might not be extensive due to the lack of public disclosure of information, it is important to consider the volume of research they comprise across a variety of mechanisms. The distribution of drug types and quantity (#) that had been in development but are currently inactive are as follows: mAb [1], plasma protein fraction [1], small molecule [12], unknown [2] and vaccine [3].

Five drug candidates have been discontinued due to lack of efficacy in the clinic (Supplementary Table 5). Genentech terminated the phase 2 trial during the open label extension period for semorinemab, a humanized IgG4 mAb that targets the N-terminal domain of tau (NCT03289143). Analyses of the earlier, blinded, placebo-controlled trial found no evidence that the treatment was clinically effective or that it affected tau PET signal accumulation at any dose. A similar outcome was observed in another phase 2 trial despite a significant effect on cognition measured by the ADAS-Cog11 (NCT03828747) [105]. Pharmacodynamic effects on most plasma and CSF biomarkers in both trials did not show significant differences, so no strong conclusions could be made [106].

There were four small molecules discontinued from the clinic during the reporting period. Cantex Pharmaceuticals terminated three different phase 3 studies for patients with AD treated with Azeliragon, a small molecule antagonist of the receptor for advanced glycation end products (RAGE). The most recent phase 3 trial with Azeliragon was terminated for business purposes (NCT03980730), while two other phase 3 studies were terminated due to a lack of efficacy (NCT02080364 and NCT02916056). The drug still has active trials for other indications. As reported earlier in this review, reMynd's ReS-19T (REM-0046127) targeted calcium dyshomeostasis in AD which is related to both neuronal dysfunction and cell death [107]. Enrollment in the phase 2a trial began in 2022, but it was terminated two years later in 2024 (NCT05478031). A recent presentation revealed that treated participants had improved memory retrieval, brain activity measured by EEG and higher levels of dopamine in CSF [108]. However, unspecified off-target effects (e.g., elevated alanine aminotransferase and aspartate aminotransferase levels) limited the therapeutic window of drug.

Notable discontinuations came from the class of O-GlcNAcase inhibitors. The phase 2 results from Eli Lilly's ceperognastat (LY-3372689) in AD (NCT05063539) were reported. Ceperognastat failed to meet its primary endpoints in a phase 2 trial in early AD. In preclinical studies, ceperognastat demonstrated robust enzyme occupancy (> 80%) at low doses resulting in dose-dependent increases in brain protein O-GlcNAc and tau O-GlcNAc levels consistent with neuroprotection with other OGA inhibitors [109]. Target engagement was confirmed in phase 1 clinical trials with PET studies showing high brain enzyme occupancy levels at well tolerated doses of ceperognastat (NCT03819270, NCT04106206, NCT03944031, and NCT04392271). In the phase 2 trial, ceperognastat failed to slow cognitive decline at either 0.75 or 3 mg doses, with the higher dose showing a greater impairment of the Integrated Alzheimer's disease Rating Scale (iADRS) compared to placebo. Interestingly, brain volume and tau PET signals, as well as plasma pTau 217 and GFAP biomarkers, were reduced at the 3 mg dose of ceperognastat relative to placebo, suggesting the pharmacodynamic effect was achieved but was without clinical benefit [110]. Tau is one of many proteins including synaptic proteins that are post-translationally modified by O-GlcNAcylation. O-GlcNAc inhibition could alter the function of these proteins, and it is possible that this unavoidable "on-target" side effect of ceperognastat contributed to the adverse effects on cognition. Additionally, Asceneuron recently terminated the recently opened phase 2 trial of ASN-51, a second-generation O-GlcNAcase inhibitor, for early AD patients (NCT06677203). Phase 1 studies showed high O-GlcNAcase enzyme occupancy, and the drug was safely tolerated (NCT06390098, NCT05725005 and NCT04759365) [111].

Summary of current tau PET clinical development

The temporal dynamics of tau protein pathology, posited to precede clinical manifestation in both AD and non-AD tauopathies, underscores the critical need for sensitive and specific in vivo imaging biomarkers. While positron emission tomography (PET) tracers targeting tau have demonstrated increasing sensitivity, challenges persist. These include, but are not limited to, the lower burden of tau pathology in primary tauopathies compared to AD, inter-individual variability in pathological load across disease subtypes, complexities associated with tau isoform biology, nuanced binding site interactions, and incompletely characterized distribution patterns [112]. Nevertheless, this ability to directly assess tau burden in living individuals allows for improved diagnostic accuracy, enhanced patient stratification for clinical trials, and the objective monitoring of drug efficacy by tracking changes in tau deposition over time. Moreover, future usage of tau PET ligands may extend beyond early disease detection, potentially enabling refined diagnostic and prognostic stratification based on ligand-specific binding profiles and regional distribution patterns. Regulation of PET ligands differs across the world. In the United States, the FDA primarily oversees the regulation of PET ligands. For clinical use, PET radiopharmaceuticals require FDA approval involving rigorous safety and efficacy evaluations, adherence to current Good Manufacturing Practice (cGMP) regulations, and clinical trials like the development of any other drug [113].

The aim of this section is to briefly cover the current landscape of ongoing active clinical trials related to tau PET tracers [112, 114–116]. Currently, flortaucipir (also known as Tauvid™ and 18F-AV-1451) is the only FDA-approved tau PET tracer that can be used for diagnosis and monitoring in AD [117]. However, the first-generation compound suffers from off-target nonspecific binding and does not appear to have the same tau binding affinity with non-AD tau isoforms [112]. It is also the most used tau PET tracer, currently involved in 66 registered clinical trials (both completed and ongoing), 18 of which are currently recruiting and using flortaucipir to analyze tau deposition. Building on the success of flortaucipir, others have sought to bring forward second-generation compounds with better specificity and optimization. The following second-generation compounds are currently being investigated for use in both AD and non-AD tauopathies (Supplementary Table 6).

The structure for 18F-APN-1607 (also known as florzolotau and 18F-PM-PBB3) was based on the first-generation ligand 11C-PBB3 developed by Aprinoia Therapeutics. It is currently being investigated in a phase 2, multicenter study in the US (NCT04141150) to examine uptake patterns in subjects with AD, mild cognitive impairment due to AD dementia, and healthy controls. Additionally, APN-1607 is being evaluated for utility in non-AD tauopathies including observational studies in Taiwan for PSP (NCT04541836) and observational studies for PSP and FTD in China (NCT05260151). Invicro led a phase 1 trial to evaluate APN-1607 as a tracer for measuring longitudinal changes in tau deposition in PSP patients (NCT05005819) which was completed in the US in mid-2024. Subsequently, the FDA announced a Fast-Track Designation of APN-1607 for the diagnosis of PSP in May 2024 [118].

18F-GTP1 was developed by Genentech as a radioligand for tau pathology specific to AD [119]. It has been or is currently being used in 12 complete or active registered trials. It has been used as the investigational tau PET ligand for several therapeutic trials, including Hoffman-La Roche's terminated phase 3 gantenerumab trials (NCT03444870, NCT03443973) and the active phase 2 bepranemab trial sponsored by UCB Biopharma (NCT04867616). A recent study showed similar patterns of GTP1 tracer uptake compared to MK-6240 and PI-2620 in AD [120]. It is currently in an open label study alongside RO948 and MK-6240 (NCT05464368).

Developed by Hoffman-La Roche, 18F-RO948 (also known as 18 F-RO69558948) is in five active clinical trials focused on AD [121, 122]. Notably, 18F-RO948 is a component of an ongoing phase 1 comparative study which aims to assess its performance against MK-6240 and GTP1 for tauopathy imaging (NCT05464368). An interventional trial is investigating the clinical utility of RO948 compared to amyloid PET in individuals with mild dementia (NCT06618872). Other studies employing RO948 include BioFINDER (NCT05457998), an imaging and plasma biomarker study (NCT06731842), and a multi-site study examining tau pathology and synaptic density (NCT05911178). Preliminary data has also indicated potential utility in specific tauopathies associated with the R406W MAPT mutation [123].

18F-MK-6240 (also known as 18 F-florquinitau) is an investigational tau PET ligand that was originally developed by Merck & Co. and later by Cerveau Technologies, which was acquired by Lantheus in 2023 [121, 122, 124]. MK-6240 binds with high affinity to AD tau [125, 126]. However, this ligand has been observed in recent studies to have less potent binding to non-AD tau isoforms, potentially limiting its utility outside of AD [127, 128]. The tracer is not approved but it is being used to examine tau pathology for investigational purposes in 24 registered studies including a phase 3 trial for the BEACoN Study (Biomarker Exploration in Aging, Cognition and Neurodegeneration) in AD (NCT03860857). The investigators of that study aim to identify the best combination of tests for amyloid, tau, and cognition for predicting longitudinal cognitive decline in AD. A substudy research aim is to analyze tau accumulation using

MK-6240. There are several phase 1 studies ongoing such as a focused ultrasound study for AD (NCT06600880), Roche's head-to-head evaluation with other tau tracers GTP1 and PI-2620 (NCT05464368), and a head-to-head evaluation with the FDA-approved tau tracer flortaucipir (NCT05361382). Ongoing observational studies will use MK-6240 as an investigational biomarker including the BioFINDER study (NCT05457998), and Bio-Hermes-002 (NCT06584357).

18F-PI-2620 was developed by AC Immune in collaboration with Life Molecular Imaging (now a subsidiary of Lantheus) [129]. It has demonstrated high-affinity in vitro binding to tau fibrils derived from AD and non-AD tauopathies [127]. This radioligand is currently under investigation in a total of 18 registered clinical trials, including two ongoing phase 3 studies. In one phase 3 trial, PI-2620 tau PET imaging will be used in patients with atypical AD or FTD to that of healthy controls (NCT05456503). This trial serves as the companion imaging study to the UNICORN (University of Pennsylvania Centralized Observational Research Repository on Neurodegenerative Disease) initiative. The second phase 3 trial, is an open-label, multicenter, non-randomized study sponsored by Life Molecular Imaging, aimed to evaluate the efficacy and safety of PI-2620 through correlation with post-mortem histopathological findings (NCT05641688). Notably, in 2024, PI-2620 received Fast Track Designation from the FDA for AD, PSP, and CBD indications [130]. PI-2620 is also being used to support the Alzheimer's Disease Neuroimaging Initiative (ADNI) program (NCT05617014) and the National Alzheimer's Coordinating Center (NACC) study (NCT04251130). Finally, PI-2620 is being used to track tau accumulation in opioid use disorder (NCT05651516), various neurocognitive disorders (NCT06375213), late-onset psychosis (NCT06336382) and psychosis in AD (NCT05847192).

18F-OXD-2314, developed as a collaboration between University of Pittsburg, University of Toronto and Oxiant Discovery, was based on a previous ligand 18F-CBD2115 which showed strong in vitro tau binding characteristics but had poor brain uptake in preclinical animal models [131]. The follow on ligand, OXD-2314, showed in preclinical work to bind to all isoforms of tau (3R, 4R, and mixed 3R/4R tau fibrils) with high affinity and low off-target binding together with an improved brain uptake in comparison to OXD-2115 [132]. First-in-human trials with a PSP indication have reportedly begun in late 2024 in Canada (Control number 285091) [133].

Discussion

Of the 170 drugs (including those that have been discontinued or are inactive), only 32 are in clinical trials, four less than in the previous review period. Of those therapeutics in trials today, five are in phase 3, 15 are in phase 2, and 12 are in phase 1 (Fig. 1). Despite a reduction in the number of clinical assets, there remains a high amount of preclinical ($n = 77$) and discovery ($n = 35$) programs in active development. Combined, there are 40 more preclinical and discovery programs covered in this update compared to the last period, and their relative percentage of the pipeline has increased from 48% in the prior period to 66% in this current period. While the pathway to launching clinical trials remains complex, the innovative strategies and sustained number of approaches under development offer a tangible sense of optimism.

Overall, there was no change in the distribution of drug modalities between review periods. There remains a heavy weighting to small molecule ($n = 74$), mAb ($n = 34$), and vaccine ($n = 18$) modalities in the pipeline which when combined, account for 74% of the tau pipeline (Fig. 2). There was an increase in RNA-modulating approaches in this period too. Previously, there were four ASOs and three siRNA approaches in development, including two ASOs in phase 2 (BIIB080) and phase 1 (NIO-752). Now, there are both five ASOs and siRNAs in development with the same ASOs in the clinic, and with one siRNA approach initiating a phase 1 trial (LY-3954068). This trend of targeting MAPT RNA is also reflected in five more tau synthesis targeting approaches in development ($n = 20$), a 33% increase from the previous period (Fig. 3). This trend may reflect a shift towards addressing the root cause of tau pathology, rather than just managing downstream effects like PTMs, aggregation or impaired clearance processes.

A takeaway from the decreasing size of the clinical pipeline was the drop out of two O-GlcNAse inhibitors. As seen with the initial negative data from the phase 2 Lilly ceperognastat study, another small molecule inhibitor of O-GlcNAse from Asceneuron withdrew from a recently announced phase 2 study. Combining these withdrawals with the limited updates from Biogen's completed phase 1 BIIB113 study, supporters of this therapeutic approach await Ferrer's results from FNP-223. Note that unlike the other three programs, Ferrer's trial is targeting patients with PSP, not AD. This may spotlight how differing tau isoforms, regional vulnerability, and co-pathology difference between PSP and AD could explain why O-GlcNAse inhibitor therapy might have various levels of effectiveness. Regardless of that trial's outcome, the extensive regulatory role of O-GlcNAcylation in cellular processes requires careful consideration of potential off-target effects [134]. Unintended disruptions to signaling pathways could lead to adverse outcomes. To ensure safety and efficacy, rigorous long-term studies investigating the impact of sustained O-GlcNAcylation modulation on neuroplasticity, cellular resilience, and potential neurotoxicity should be prioritized.

Clinical trials to treat tau pathology for AD will need to consider the inclusion of patients who are currently or have previously undergone anti-amyloid treatments from an FDA approved mAb like donanemab (Kisunla™) and lecanemab (Leqembi™) [135]. The rationale for adding a tau therapeutic to a trial arm for patients who have already received anti-amyloid mAb treatment for AD is based on the understanding that AD is characterized by two primary pathologies: Aβ plaques and NFTs composed of tau protein. While anti-amyloid mAbs aim to reduce amyloid plaques, they may not fully address the neurodegenerative process driven by tau pathology. Research indicates that tau pathology correlates more strongly with cognitive decline in AD than amyloid plaques [136]. In other words, the spatiotemporal progression of tau aggregation in the brain aligns closely with the progression of cognitive impairment. Therefore, targeting tau in addition to amyloid could potentially lead to a more significant impact on slowing or modifying the disease course [137].

For example, the DIAN-TU Tau NexGen study is evaluating the anti-tau mAb (E2814) in individuals with a genetic predisposition to AD (NCT05269394). The first arm of the trial of administering just the anti-tau mAb E2814, another arm of symptomatic participants will receive lecanemab to treat the Aβ plaque formation for six months before randomization to also receive the anti-tau mAb E2814 or a placebo. This sequential treatment approach is based on the understanding that amyloid plaques typically accumulate in the brain before NFTs during AD. This design will allow the researchers to assess if amyloid removal enhances the effectiveness of the anti-tau therapy, and, if amelioration of both major pathologies of AD lead to a greater chance of achieving meaningful clinical benefits for patients. For pre-symptomatic participants in the DIAN-TU Tau NexGen study, the trial design involves a slightly different sequence. These individuals will be randomly assigned to receive E2814 or a placebo for a year before they begin administration of lecanemab. In both trials, the staggered approach allows the clinical teams to evaluate the effects of an anti-tau drug on its own before assessing the combined effects of both the anti-amyloid and anti-tau therapies. This combined approach acknowledges the complex nature of AD and the likelihood that targeting a single pathway might not be sufficient to halt or reverse the disease progression.

One area of continued interest supporting the clinical pipeline is the development and validation of biomarkers to support clinical trial design. Tau biomarkers play an increasingly key role in patient selection for clinical trials of tau-targeting therapies and in monitoring treatment efficacy. Additionally, tau biomarkers can serve as pharmacodynamic markers to assess target engagement and treatment response in clinical trials, providing valuable information on the effectiveness of investigational drugs. The inherent complexity of the tauopathies, coupled with the limitations of current diagnostic techniques, underscores the urgent need for reliable and minimally invasive biomarkers. Liquid biomarkers, accessible through blood or CSF, offer a promising avenue for addressing these challenges. Traditional tau biomarkers in CSF, such as total tau and pTau, have been instrumental in research and clinical practice. For instance, a collection of recent studies has consistently demonstrated the diagnostic accuracy of plasma pTau 217 for AD patients with a strong correlation with Aβ PET, tau PET, and cognition [53, 138–140]. As mentioned previously, pTau 217 is being implemented to support clinical trial selection in both Johnson & Johnson's posdinemab and Eli Lilly's ceperognastat studies. Although the inclusion of an extra test may initially delay the initiation of the trial, it does significantly enhance patient selection by confirming the presence of AD tau pathology, thus ensuring a homogeneous study group. This leads to increased efficiency and reduced costs through pre-screening, minimizing the need for costly procedures like tau PET, and enriching the study population, which in turn reduces the required sample size and accelerates overall recruitment of potential therapeutic responders. Furthermore, pTau 217 prescreening may improve data quality by providing a clear baseline for measuring treatment effects, monitoring response, and enhancing correlation with clinical outcomes. Ethically, it reduces participant burden by utilizing a less invasive blood test and targets therapy to those most likely to benefit.

Research into the genesis of tau pathology is ongoing and may lead to earlier options for treatment. Recently, the characterization of soluble tau assemblies (STAs) in AD has gathered attention [141]. STAs represent early-stage aggregates of tau protein that preceded the formation of NFTs. Researchers have identified that STAs in AD possess a core structure featuring phosphorylation at serine residues 262 and 356 (pTau 262 and pTau 356). To detect these early tau species, a sensitive fluorescence resonance energy transfer (FRET) assay was developed, which demonstrated significantly higher levels of STAs in the CSF of individuals with AD compared to healthy controls and those with other tauopathies. Furthermore, the levels of STAs in CSF have been found to correlate with the presence of tau tangles in the brain, as measured by tau PET imaging, and with the extent of cognitive decline in AD patients. The identification and characterization of STAs and the development of a CSF assay capable of detecting them represent a notable step forward in the ability to identify and potentially target the earliest stages of tau pathology, offering a potential window for earlier therapeutic intervention.

Additionally, extracellular vesicles (EVs) are garnering increasing attention as a promising source of biomarkers for tauopathy diseases. EVs are small membrane-bound vesicles secreted by cells that play a crucial role in intercellular communication by transporting proteins, lipids, and nucleic acids. They are found in various bodily fluids and can carry disease-relevant proteins like tau, potentially reflecting the pathological state of the cells from which they originate. In primary tauopathies, a recent study highlighted the potential of measuring tau and TDP-43 proteins within plasma EVs as a diagnostic biomarker for FTD and ALS [142]. The levels of these proteins in EVs showed strong correlations with clinical and neuropsychological indicators of these diseases, achieving high diagnostic accuracies. Even in other neurological conditions, such as in older individuals with HIV, CSF-derived EVs have shown associations between Aβ42 and the tau/Aβ42 ratio and cognitive impairment, suggesting a broader role for EV-associated tau in neurodegeneration [143]. Encapsulation of tau within EVs may protect it from degradation in peripheral fluids, potentially making the measurement of EV-derived tau a more stable and reliable biomarker for tauopathies compared to free tau.

Finally, tau PET has emerged as a powerful, non-invasive imaging modality that enables the in vivo visualization and quantification of tau pathology within the living brain. This capability is indispensable for various aspects of neurodegenerative disease research and clinical development, including facilitating accurate diagnosis, elucidating the temporal and spatial dynamics of disease progression, and critically, for evaluating the efficacy of novel therapeutic candidates targeting tau. The ability to directly measure tau burden in vivo offers a significant advantage over relying solely on clinical assessments or post-mortem neuropathological examinations. The concept of "fit-for-purpose" ligands suggests that different tau PET ligands might be better suited for specific applications or for visualizing tau pathology, particularly in primary tauopathies. It is notable that while there is currently one approved tau PET ligand, there are six other active tau PET ligands in various stages of clinical development to support the therapeutic development pipeline. Certain ligands may demonstrate a higher affinity for specific tau isoforms (3R or 4R) that are implicated in different tauopathies. Currently, the landscape of tau PET imaging includes one approved ligand, AV-1451 (Tauvid™), and an array of next-generation ligands in various stages of clinical trials, including APN-1607, GTP1, RO948, MK-6240, PI-2620, and OXD-2314. The coexistence of an approved ligand and several investigational ones underscores the ongoing efforts to refine and expand the toolkit for probing tau pathology. The inherent variability among different tauopathies, potentially arising from distinct tau isoforms and their unique aggregation patterns, necessitates a diverse set of diagnostic tools such as these PET ligands. If different ligands exhibit varying affinities for specific tau isoforms or preferential binding to disease specific aggregation structures, the availability of multiple ligands significantly enhances the prospects of pairing the appropriate treatment with the right patient.

In conclusion, the landscape of tau-targeted therapies for tauopathies is undergoing a dynamic evolution, fueled by significant advancements in our understanding of tau pathology and the development of biomarker tools for its detection and monitoring. This review highlights the promising clinical and preclinical pipeline of therapeutic interventions ranging from antibody-mediated clearance and gene silencing to small molecule inhibition. The progress in this field is inextricably linked to parallel innovations in biomarker development, particularly in liquid-based samples and tau PET imaging. These advancements are not only refining diagnostic capabilities across the spectrum of primary and secondary tauopathies but are also playing an increasingly vital role in patient selection for clinical trials, providing critical evidence of target engagement, and serving as surrogate endpoints to assess therapeutic efficacy.

Looking ahead, the continued interactions between tau-targeted therapy development and biomarker innovation is essential for accelerating progress. While significant strides have been made, challenges remain in identifying disease-specific biomarkers for all tauopathies and in translating preclinical successes into clinically meaningful outcomes. Future research should focus on refining existing biomarkers, discovering novel markers for early disease detection, and further validating their utility across different populations. Additionally, given the early positive results of targeted approaches afforded by ASOs like BIIB080, underrepresented therapeutic modalities like ASOs, siRNAs, and selective degraders and novel mechanisms of action are encouraged to be explored for the tauopathies. The combined power of targeted therapeutics and precise biomarkers offers a compelling pathway towards effective disease modification and improved outcomes for individuals affected by this class of devastating neurodegenerative conditions.

Supplementary Information

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Supplementary Material 1

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Author contributions
G.H. is the first author. He primarily focused on data organization, research for the drug and PET programs, creating figures and tables, writing manuscripts, managing references, revising, and facilitating team communication. M.P. and I.G. led the collection and organization of information on the drugs covered in this paper and provided information on the drug candidates. P.M. provided input on drug candidates, relevant biomarker advancements, and contributed to writing. L.H. contributed to the PET section, data analysis, tables and figures generation, reference management, and team communications. All authors have contributed to editing, reviewing, and approving the publication for submission.

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