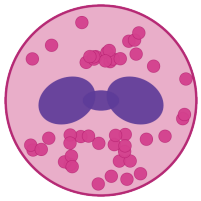

The Antigen-Specific Immunotherapy Landscape

A Patient-Centered Market Report

with Strategic Implications for an Eosinophilic Esophagitis Peptide-MHC (pMHC) Vaccine

Tzield (teplizumab) as FDA-approved precedent and post-market case study

Rendered in the hematoxylin-and-eosin palette of the pathology that defines the disease — the eosinophil above is stained as a clinician would see it under the microscope.

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Appendix C: Glossary

The Antigen-Specific Immunotherapy Landscape

A Patient-Centered Market Report, with Strategic Implications for an EoE Peptide-MHC (pMHC) Vaccine

Prepared as part of a patient-centered EoE therapeutic-development program. Tzield (teplizumab) serves as the FDA-approved precedent and post-market case study.

A note on why this report is written the way it is

This report is written by and for people who believe patients belong in therapeutic development at every stage. Every program profiled here treats a disease that someone lives with daily. Where the evidence lets us, we center what patients said, felt, and needed — not as an appendix, but as a lens on whether each program was built for the people it was meant to serve. The author of the underlying program is herself an EoE patient; that perspective is a design input, not a disclaimer.

A note on the colour of this report

*The magentas and purples running through these pages are not decoration. In pathology, eosinophils — the cells that define eosinophilic esophagitis — are identified by the **eosin** stain, which renders their granules the vivid rose-magenta a clinician sees down the microscope; **hematoxylin** counterstains nuclei a deep purple. This report borrows that hematoxylin-and-eosin (H&E) palette so that the visual identity of the disease is present on every page. Where a third colour was needed for clarity, we chose a special-stain gold. The scheme is also colour-vision-deficiency safe.*

Executive Summary

The opportunity. Antigen-specific immunotherapy — teaching the immune system to tolerate a specific trigger rather than broadly suppressing it — has produced exactly one

FDA-approved agent (Tzield/teplizumab, for delaying type 1 diabetes) and a field of instructive successes and failures across celiac disease, T1D, multiple sclerosis, and rheumatoid arthritis. **No true peptide-MHC (pMHC) therapeutic has yet demonstrated clinical efficacy in any disease, and none exists for eosinophilic esophagitis (EoE).** That is the whitespace this program targets.

What we found (five headline findings):

1. **Approval was won on strategy, not specificity.** Tzield — the only approved agent — is antigen-*nonspecific*. It succeeded by redefining the population (at-risk, presymptomatic) and the endpoint (delay of onset, not cure), a regulatory template far more transferable to EoE than its mechanism.
2. **The flagship celiac failure (Nexvax2) is the field's most valuable lesson.** It bet a three-peptide vaccine against a symptom endpoint in established disease, and the peptide (being gluten itself) reproduced the very symptoms it measured. Programs that instead led with a pharmacodynamic tolerance biomarker and a tolerogenic delivery context (TAK-101, KAN-101) advanced.
3. **A failed antigen was rescued by precision medicine.** GAD-alum missed its Phase 3 endpoint, then found new life through HLA-DR3-DQ2 patient stratification and a changed delivery route — a direct template for HLA-stratified EoE design.
4. **Tzield's post-market experience shows the access bottleneck is screening, not demand.** At ~$194,000 per course with universal prior authorization, uptake (~1.2% of the T1D drug market in 2023) is gated by the absence of routine autoantibody screening — a warning that an EoE vaccine must co-build its companion-diagnostic pathway.
5. **Patient voice arrived too late, everywhere.** No formal patient-experience event (PFDD or equivalent) demonstrably preceded the program it might have shaped; EoE has no dedicated PFDD at all. This is the sequence an EoE patient-led program can, uniquely, invert.

The strategic thesis. An EoE pMHC vaccine can be the first true peptide-MHC therapeutic to pursue clinical proof-of-concept, in an indication with no antigen-specific competitor. Its odds are maximized by copying the winners (validated tolerance biomarker; tolerogenic, non-reactogenic delivery; HLA/sensitization stratification; early-disease progression-prevention endpoint; co-built screening) and avoiding the losers' mistakes — and, above all, by capturing patient needs, interest, and concerns *before* the trial is designed. The follow-on EoE patient survey (Section 10) is the first step.

1. Methodology & Data Sources

- **Trial architecture:** programmatic harvest of ClinicalTrials.gov API v2 (59 core relevant trials across 8 clinical-stage programs; full design fields, outcomes, and termination reasons). See `trials_master.csv`.
- **Scientific origins:** literature reconstruction via OpenAlex and CrossRef; 17 pivotal references, **all DOIs validated to resolve against CrossRef**. See Appendix B and `citation_library_final.json`.
- **Trial outcomes:** pivotal-endpoint coding into a comparative matrix (`outcomes_matrix.csv`).
- **Post-market:** FDA, SEC filings (Sanofi/MacroGenics), payer policy documents, and reimbursement reviews (CDA-AMC), via targeted web search.
- **Patient voice & PRO:** peer-reviewed PRO/HRQoL instrument literature, patient organization materials (APFED, iCureCeliac, JDRF/Breakthrough T1D), and FDA disease-specific guidance. See `pro_instruments.csv`.
- **PFDD:** FDA PFDD/EL-PFDD program records and Voice-of-the-Patient reports. See `pfdd_inventory.csv`.
- **Scope:** antigen-specific immunotherapy (broad) — peptide/epitope vaccines, tolerogenic nanoparticles, pMHC nanoparticles, antigen+adjuvant — plus Tzield as the approved anti-CD3 precedent. Adjacent modalities (tol-DC, CAAR-T) noted as context.
- **Accuracy discipline:** all DOIs CrossRef-verified; trial IDs traced to CT.gov records; dates that could not be verified are explicitly marked approximate; the T1D/celiac PFDD status was corrected against the FDA-led 24-disease series list.

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2. Field Primer — what "antigen-specific tolerance" and pMHC mean

The core idea. In autoimmune and allergic disease, a subset of T cells recognizes a specific antigen (a self-protein, a food, or gluten) and drives inflammation. Conventional therapy suppresses immunity broadly, with infection and cancer risks. **Antigen-specific immunotherapy** aims to switch off *only* the disease-driving clones — by anergizing them, deleting them, or converting them into regulatory cells — leaving the rest of the immune system intact.

How a T cell "sees" antigen: the peptide-MHC (pMHC) complex. T cells do not recognize whole proteins. Antigen-presenting cells chop proteins into peptides and display them in the groove of a Major Histocompatibility Complex (MHC, called HLA in humans) molecule. The T-cell receptor reads this **peptide-MHC (pMHC) complex**. Which peptides a person presents depends on their HLA genotype — which is why HLA stratification recurs throughout this landscape.

The modality ladder (low → high mechanistic fidelity to a pMHC vaccine): 1. **Anti-CD3 (Tzield):** blocks the T-cell receptor complex generically — no antigen specificity. The approved precedent. 2. **Antigen + adjuvant (GAD-alum):** whole autoantigen with an immune-deviating adjuvant. 3. **Peptide / nanoparticle vaccines (Nexvax2, TAK-101, KAN-101):** deliver the defined peptide(s), optionally in a tolerogenic carrier. 4. **pMHC complex (Navacim; the EoE concept):** present the peptide *already loaded on MHC*, the most direct way to engage exactly the cognate T cells — the truest "pMHC vaccine," validated preclinically but not yet clinically.

Why celiac and T1D led the field: both offered what EoE must engineer — a defined antigen and a measurable T-cell/biomarker readout. EoE's plural, patient-variable food allergens are the central scientific challenge the rest of this report returns to.

Section 2B: Disease-Area Market & Epidemiology Context

A market report needs the market. This section sizes the three anchor indications — type 1 diabetes, celiac disease, and eosinophilic esophagitis — on prevalence, current standard of care, treatment burden, and commercial scale, to frame where an antigen-specific tolerance therapy would compete.

2B.1 Type 1 diabetes (T1D) — the proving ground

- **Prevalence:** ~1.3–1.8 million people in the US; ~9 million worldwide. Incidence rising ~2–4%/year. Roughly **90% of new cases have no family history**, which is why family-history-limited screening misses most future patients — the single most important structural fact behind Tzield's uptake problem.
- **Standard of care:** lifelong exogenous insulin (pumps, pens, closed-loop systems), continuous glucose monitoring. Highly effective at survival but a relentless daily-management burden; no approved therapy halts the underlying autoimmunity except Tzield's delay-of-onset indication.
- **Market scale:** the T1D drug market is large and growing; GlobalData projects the 7-major-market T1D drug market to reach **~$9.9 billion by 2033**, within which Tzield could become a top product (~$4.8B forecast) *if* screening scales.
- **Why it led:** defined autoantigens (insulin, GAD65, IA-2, ZnT8), a measurable biomarker (C-peptide), a mature at-risk-screening research infrastructure (TrialNet), and deep-pocketed advocacy (JDRF/Breakthrough T1D). Every ingredient an antigen-specific program wants.

2B.2 Celiac disease — the cleanest antigen, the hardest endpoint

- **Prevalence:** ~1% of the population (US ~2–3 million diagnosed; many more undiagnosed). Strongly HLA-linked: **~90–95% carry HLA-DQ2.5**, the rest mostly HLA-DQ8 — an unusually clean genetic-restriction picture.
- **Standard of care:** a **lifelong strict gluten-free diet (GFD)** — the only management option. But the GFD is incompletely protective (inadvertent exposure is common), socially burdensome, and does not fully heal the mucosa in a

substantial fraction of patients. This unmet need is precisely what the antigen-specific programs target.

- **Market scale:** no approved drug exists for celiac disease — the entire therapeutic market is greenfield. Multiple mechanisms compete (tolerance vaccines, gluten-degrading enzymes, tight-junction modulators, IL-15 and other biologics). A first-approved non-dietary therapy would define the category.
- **Why it led, and why it's hard:** one antigen (gluten), one dominant restriction element, one measurable T-cell response — ideal for antigen-specific design. But the clinical endpoint (symptom protection under gluten challenge) proved treacherous, as Nexvax2 showed.

2B.3 Eosinophilic esophagitis (EoE) — the target indication

- **Prevalence:** rising rapidly; current estimates ~1 in 2,000 people (~0.5–1 per 1,000), with higher rates in children, males, and atopic individuals. Incidence and prevalence have climbed steeply over two decades — partly true increase, partly recognition.
- **Standard of care:** three pillars, none curative — (i) **proton-pump inhibitors**; (ii) **swallowed topical corticosteroids** (budesonide oral suspension approved); (iii) **dietary elimination** (empiric 6-food or targeted elimination — itself a major quality-of-life burden); and now (iv) **dupilumab** (anti-IL-4Rα, approved for EoE in 2022) and emerging IL-5/IL-13 biologics. All require **indefinite** administration; stopping typically relapses.
- **Treatment burden:** repeated **endoscopy with biopsy** for monitoring (invasive, requires sedation), the social and nutritional toll of elimination diets, the fear of **food impaction** (acute obstruction requiring emergency removal), and progression to **fibrostenosis** — irreversible esophageal narrowing — if inadequately controlled.
- **Market scale:** the EoE therapeutics market is expanding quickly on the back of dupilumab's approval and a crowded biologic pipeline, but every entrant so far is an **anti-inflammatory requiring chronic dosing**. There is **no antigen-specific / tolerance-inducing therapy** — the differentiated whitespace.
- **Why EoE is the hardest antigen problem in this report:** the drivers are **food allergens** that vary by patient (milk, wheat, egg, soy most common), often multiple simultaneously, with a mixed Th2/allergic mechanism distinct from the Th1-dominated celiac/T1D biology. A pMHC tolerance vaccine must solve antigen

selection first — the direct link to this program's omics and pMHC/HLA analysis streams.

2B.4 Comparative snapshot

Dimension	Type 1 diabetes	Celiac disease	Eosinophilic esophagitis
Driving antigen	Self (insulin, GAD65, IA-2, ZnT8)	Gluten (dietary)	Food allergens (milk, wheat, egg, soy) — plural, variable
HLA restriction	HLA-DR3/DR4-DQ2/DQ8	HLA-DQ2.5 (~90%) / DQ8	HLA associations weaker/less defined
Immune polarity	Th1 / cytotoxic	Th1 (DQ2.5-restricted CD4)	Th2 / allergic (eosinophilic)
Biomarker	C-peptide, autoantibodies	Anti-tTG, gluten-specific T cells	Esophageal eosinophil count (histology)
Standard of care	Insulin (lifelong)	Gluten-free diet (only option)	PPI / steroids / diet / dupilumab (all chronic)
Approved tolerance therapy	Tzield (delay only; nonspecific)	None	None
Antigen-specific opportunity	Proven modality entry	Greenfield, active pipeline	**Greenfield + no competitor = whitespace**

The pattern is clear: **EoE combines the strongest commercial whitespace with the hardest antigen-selection problem.** Solving antigen selection — the project's core scientific task — is what converts the whitespace into a program.

Section 3: Program Dossiers

Each program is profiled as a standalone dossier. A condensed origins-and-preclinical synthesis precedes the detailed dossiers; the comparative results analysis follows in Section 3B.

Section 3 (Part A): Scientific Origins & Preclinical Basis

*Idea generation → basic research → preclinical proof-of-concept, per program. Citations refer to the verified reference library (Appendix B). This section reconstructs where each idea came from, who had it, and what animal/ex-vivo evidence justified moving into humans.***

The shared intellectual lineage

Every program in this landscape descends from a single immunological premise: that the immune system can be taught to *tolerate* a specific antigen without being globally suppressed. This is the distinction between **antigen-specific immunotherapy** (re-educate only the disease-driving clones) and conventional immunosuppression (blunt the whole system). The founding observations came from three streams:

1. **Oral/mucosal tolerance biology (1900s–1990s)** — the observation that antigen delivered by tolerogenic routes (oral, portal-venous, apoptotic-cell mimicry) induces regulatory rather than effector responses. This is the conceptual parent of the celiac liver-targeting and nanoparticle programs.
2. **Altered peptide ligand / peptide-tolerance work (1990s–2000s)** — that soluble peptide delivered without danger signals anergizes or deletes cognate T cells and can expand regulatory subsets. Parent of Nexvax2, ATX-MS-1467, the proinsulin-peptide programs.
3. **Regulatory-T-cell and co-receptor biology** — that modulating the T-cell receptor complex (CD3) or presenting peptide-MHC in a tolerogenic geometry can convert pathogenic clones into regulatory ones. Parent of teplizumab (CD3) and the Navacim pMHC-nanoparticle platform.

The programs diverge on **how antigen specificity is achieved**: teplizumab achieves none (it is pan-T-cell) and is included as the approved *precedent*; the peptide vaccines

carry the epitope directly; the nanoparticle and liver-targeting platforms deliver antigen to a tolerogenic anatomical niche; and Navacim uniquely presents the peptide *already loaded on MHC*, the truest structural analog of a pMHC vaccine.

3.1 Tzield / teplizumab (Type 1 diabetes) — the approved precedent

Idea generation. Teplizumab began not as a diabetes drug but as a tool to probe the role of T cells in autoimmunity. Jeffrey Bluestone (UCSF) engineered an Fc-receptor-non-binding ("Ala-Ala") humanized version of the OKT3 anti-CD3 antibody to deliver a partial, non-mitogenic TCR signal — the goal being to modulate rather than deplete T cells. Kevan Herold (then Columbia, later Yale) carried it into type 1 diabetes on the hypothesis that partial CD3 engagement would preferentially disable activated autoreactive effector T cells while sparing and even expanding regulatory populations.

Basic research. The mechanistic package that justified human trials showed that Fc-non-binding anti-CD3: (i) induces a state of partial exhaustion/anergy in activated CD8 effectors (later characterized by TIGIT/KLRG1 exhaustion signatures); (ii) spares and relatively expands Foxp3+ and TR1 regulatory cells; and (iii) does so transiently, avoiding the cytokine-release toxicity of the parent mitogenic OKT3. Herold's group had shown as early as 1992 that non-activating anti-CD3 could prevent diabetes in the NOD mouse [Herold 1992, referenced within Herold2002].

Preclinical → first-in-human bridge. The NOD-mouse prevention and reversal data plus the engineered safety profile supported a direct move into new-onset human T1D. The first pivotal human readout [Herold2002, NEJM] showed a single 14-day course preserved C-peptide (endogenous insulin production) at one year in new-onset patients — the observation that seeded two decades of development.

Key references: Herold2002 (first RCT), Keymeulen2005 (parallel anti-CD3 otelixizumab confirmation), Herold2013_AbATE (durable responders), and the at-risk prevention hypothesis that led to TN-10.

3.2 Nexvax2 (celiac disease) — the flagship epitope vaccine

Idea generation. Nexvax2's intellectual core is arguably the most rigorous antigen-mapping effort in the field. Bob Anderson and Jason Tye-Din (Walter and Eliza Hall

Institute, Melbourne) reasoned that because celiac disease is uniquely tractable — a *known* antigen (gluten), a *known* restriction element (HLA-DQ2.5), and a *measurable* T-cell response — one could define the exact set of immunodominant peptides driving disease and deliver precisely those to induce tolerance.

Basic research. In a landmark study [TyeDin2010, Sci Transl Med] the group performed comprehensive, quantitative mapping of gluten T-cell epitopes in a large cohort of HLA-DQ2.5 celiac patients undergoing gluten challenge. They showed that the anti-gluten T-cell response, though theoretically vast, is dominated by a small hierarchy — three peptides (from α-, ω-, and hordein gliadins) account for the majority of the pathogenic DQ2.5-restricted response. This reductionism is what made a defined three-peptide vaccine conceivable.

Preclinical. HLA-DQ2.5 transgenic mouse models and *ex vivo* human T-cell assays demonstrated that repeated exposure to these peptides in a non-immunogenic (intradermal, escalating-dose) regimen could shift the response toward anergy/tolerance rather than priming. The clinical-development company ImmusanT (Boston; Leslie Williams CEO, Anderson CSO) was formed to translate this.

Key references: TyeDin2010 (epitope hierarchy — the scientific basis), Goel2017 (Phase 1 dosing), Truitt2019 (Phase 1b escalation).

3.3 TAK-101 / TIMP-GLIA (celiac) — the tolerogenic nanoparticle

Idea generation. TAK-101 comes from Stephen Miller's laboratory (Northwestern) and the observation, decades in the making, that antigen coupled to apoptotic cells or apoptotic-cell-mimicking particles induces robust tolerance — the immune system reads the particle as "safe debris" and mounts a regulatory rather than inflammatory response.

Basic research & preclinical. The pivotal platform paper [Getts2012, Nat Biotechnol] showed that biodegradable PLGA microparticles carrying encephalitogenic peptides, delivered intravenously, induced antigen-specific T-cell tolerance and prevented/treated experimental autoimmune encephalomyelitis (EAE, the MS model). Uptake by MARCO+ splenic/hepatic macrophages in the absence of costimulation was the mechanistic key. Cour Pharmaceuticals licensed the platform; for celiac, whole gliadin was encapsulated (TIMP-GLIA), and mouse and humanized models showed suppression of gliadin-specific responses. Takeda partnered the celiac asset as TAK-101.

Key references: Getts2012 (platform PoC), Kelly2021 (Phase 2a translation).

3.4 KAN-101 (celiac) — liver-targeted glycan tolerance

Idea generation. Anokion (Lausanne/Boston; spun from Jeffrey Hubbell and Stephan Kontos's work at EPFL/Chicago) built on the biology that the liver is a default tolerogenic organ: antigens delivered to hepatic antigen-presenting cells (via the asialoglycoprotein receptor, ASGPR) preferentially induce regulatory responses and clonal deletion.

Basic research & preclinical. The founding technology conjugates antigen to glycan/erythrocyte-binding moieties that route it to the liver. Preclinical work showed antigen-specific deletion of cognate CD4/CD8 cells and Treg induction. KAN-101 delivers a deamidated gliadin peptide construct designed for hepatic tolerance. FDA Fast Track designation followed early clinical safety.

Key references: (platform) Hubbell/Kontos liver-tolerance work; clinical readouts covered in Part B.

3.5 TPM502 / Topas Therapeutics (celiac)

Idea generation & science. Topas (Hamburg) uses a nanoparticle platform that also exploits liver-resident APCs, conjugating peptide cargo to a carrier that concentrates in the liver. TPM502 carries a set of gluten peptides. The mechanistic thesis mirrors KAN-101 (hepatic tolerance) but via a distinct nanoparticle chemistry. Program is earlier-stage; preclinical package centered on antigen-specific Treg induction and reduced effector responses in HLA transgenic/humanized systems.

3.6 GAD-alum / Diamyd (Type 1 diabetes) — antigen + adjuvant

Idea generation. GAD65 (glutamic acid decarboxylase) is a major autoantigen in T1D — anti-GAD antibodies are a diagnostic hallmark. The hypothesis (Diamyd Medical, Sweden; long associated with Johnny Ludvigsson, Linköping) was that administering recombinant GAD65 formulated in alum, a Th2-skewing adjuvant, would induce a regulatory/deviated response and preserve residual beta-cell function in recent-onset patients.

Basic research & preclinical. Alum-formulated autoantigen had shown immune deviation toward Th2/regulatory phenotypes in rodent models. Early-phase human work suggested preservation of C-peptide in a subset, motivating a large Phase 3.

Key references: Ludvigsson2012 (Phase 3), Ludvigsson2021 (DIAGNODE-2 intralymphatic + the HLA responder-subgroup pivot).

3.7 Navacims / Parvus Therapeutics (T1D & autoimmunity) — the true pMHC platform

Idea generation. This is the platform most structurally analogous to a pMHC vaccine. Pere Santamaria (University of Calgary) asked whether nanoparticles densely coated with disease-relevant **peptide-MHC class II complexes** could directly engage cognate autoreactive CD4 T cells and re-program them — not delete them, but convert them into a regulatory (TR1-like) phenotype that then suppresses the broader autoimmune response at the target tissue.

Basic research & preclinical. The landmark paper [ClementeCasares2016, Nature] demonstrated that pMHC-II-coated nanoparticles ("Navacims") expanded antigen-experienced, disease-relevant CD4 T cells into TR1 cells that formed regulatory networks and reversed disease across *multiple* mouse models (T1D, EAE, arthritis, and a humanized model). A follow-on [Singha2017, Nat Nanotechnol] extended the mechanism and design rules (epitope density, MHC allele, nanoparticle size). Parvus Therapeutics was founded to commercialize the platform.

Why it matters for EoE. Navacim is the proof that a *peptide-MHC* presentation, not just free peptide, can induce durable antigen-specific regulation *in vivo* — the mechanistic north star for a pMHC EoE vaccine.

Key references: ClementeCasares2016 (Nature PoC), Singha2017 (design rules), Serra2019 (field review).

3.8 Proinsulin peptide immunotherapy / MonoPepT1De & MultiPepT1De (T1D)

Idea generation. Mark Peakman's group (King's College London) pursued the most direct human translation of peptide-tolerance biology in T1D: administer a single immunodominant proinsulin peptide (C19-A3, HLA-DR4-restricted) intradermally to induce regulation.

Basic research & preclinical. Extensive human *ex vivo* work defined the proinsulin epitope and the regulatory (IL-10+) response signature that a tolerogenic dose should induce. Dose and interval were modeled to favor regulation over priming.

Key references: AlhadjAli2017 (MonoPepT1De Phase 1a — safety and mechanistic tolerance readouts; the first placebo-controlled peptide-immunotherapy safety demonstration in new-onset T1D).

3.9 ATX-MS-1467 (Multiple sclerosis)

Idea generation & science. Apitope (UK/Belgium; David Wraith's tolerogenic "apitope" — antigen-processing-independent epitope — concept) designed a mixture of four myelin basic protein (MBP) peptides selected to bind MHC and engage autoreactive T cells in a tolerogenic manner. Preclinical basis rested on the altered-peptide-ligand and soluble-peptide tolerance literature in EAE. Merck KGaA partnered the asset.

Key references: Chataway2018 (Phase 2, MRI lesion endpoints).

3.10 DEN-181 (RA) and adjacent context

Idea generation & science. Ranjeny Thomas (University of Queensland) developed a liposomal formulation co-delivering a citrullinated collagen II peptide with an NF-κB inhibitor (calcitriol/Bay11-7082 lineage) to program dendritic cells toward a tolerogenic state — antigen-specific tolerance for rheumatoid arthritis. Included as adjacent context for the platform diversity it represents (tolerogenic-DC targeting) rather than a full commercial dossier.

Synthesis: what the origins tell us for EoE

- **The best programs started from a defined antigen and a measurable T-cell readout** (Nexvax2's epitope map; GAD's autoantibody; proinsulin). EoE's challenge is that the driving antigen(s) — food allergens (milk, wheat, egg, soy) — are *plural and patient-variable*, unlike celiac's single gluten system. This is the single most important scientific-origin lesson.
- **pMHC presentation (Navacim) is validated in vivo** but has not yet cleared the clinic — the whitespace an EoE pMHC program would enter.

- **Delivery niche matters as much as the peptide** (liver targeting, nanoparticle apoptotic-mimicry). An EoE program must choose its tolerogenic route deliberately.

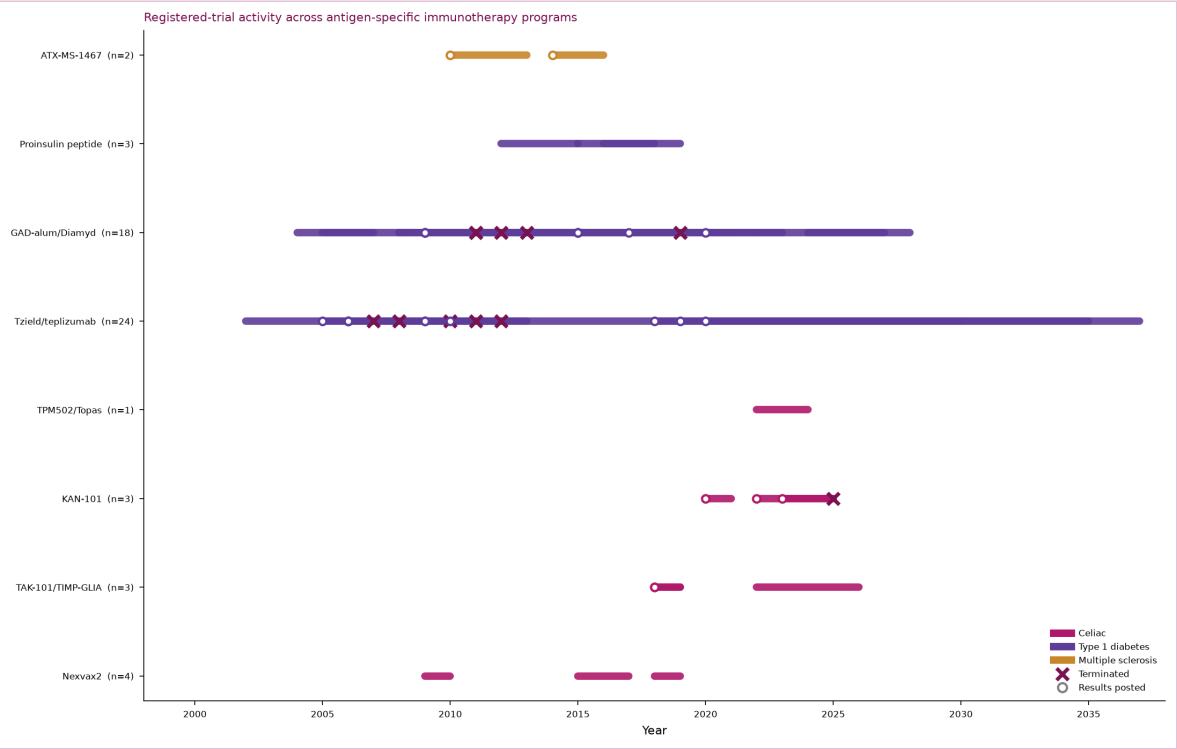

Figure 1. Registered-trial activity across antigen-specific immunotherapy programs (ClinicalTrials.gov, n=59 core trials). Bars = individual trials; × = terminated; ○ = results posted. Colour = disease area (eosin magenta = celiac, hematoxylin purple = type 1 diabetes, gold = multiple sclerosis).

Detailed Program Dossiers

Tzield (teplizumab)

Overview and sponsor lineage

Tzield (teplizumab) is a humanized, Fc-engineered anti-CD3 monoclonal antibody approved by the FDA in November 2022 to delay the onset of clinical (Stage 3) type 1 diabetes in individuals aged 8 and older with Stage 2 disease — that is, people with multiple islet autoantibodies and dysglycemia who have not yet progressed to symptomatic diabetes. It is the first disease-modifying immunotherapy sanctioned for type 1 diabetes and, more broadly, one of the first approved therapies anywhere designed to intervene in a presymptomatic autoimmune state rather than to treat established disease. The molecule's lineage traces through academic development at Columbia

University and the Massachusetts General Hospital/Harvard axis in the late 1990s and early 2000s, with subsequent licensing and clinical advancement carried by MacroGenics, and later by Provention Bio, which secured the FDA approval before being acquired by Sanofi in 2023. That corporate arc — academic origination, biotech-mediated de-risking through late-stage trials, and eventual large-pharma acquisition post-approval — is a recurring pattern in first-in-class immune-modulatory biologics and is directly relevant context for any sponsor evaluating antigen-specific or immune-modulatory assets in adjacent autoimmune and allergic indications.

Scientific origin and mechanism

Teplizumab targets CD3, the invariant signaling component of the T-cell receptor complex expressed on all mature T lymphocytes. Unlike the first-generation murine OKT3 antibody, from which the anti-CD3 concept in transplantation and autoimmunity descends, teplizumab carries Fc mutations that greatly reduce Fcγ receptor binding, attenuating the cytokine release and T-cell depletion associated with earlier anti-CD3 agents while preserving partial T-cell receptor modulation. Mechanistically, teplizumab is understood to act not as a blunt immunosuppressant but as an immune-modulating agent: transient engagement of CD3 induces partial or altered TCR signaling that favors expansion or functional restoration of regulatory and "exhausted"-phenotype CD8+ T-cell populations while dampening the effector autoreactive T cells that drive beta-cell destruction. This distinction — modulation of the autoreactive repertoire rather than global immunosuppression — is the conceptual thread linking teplizumab to the broader field of antigen-specific and immune-recalibrating therapeutics, even though teplizumab itself is not antigen-specific; it acts on the TCR/CD3 complex irrespective of antigen specificity, making it a pan-T-cell modulator layered onto a disease with a defined, if heterogeneous, autoantigen repertoire (insulin, GAD65, IA-2, ZnT8).

Preclinical foundation

The mechanistic case for anti-CD3 therapy in autoimmune diabetes was built substantially on rodent models, particularly the NOD (non-obese diabetic) mouse, in which short-course anti-CD3 antibody treatment at the time of new-onset hyperglycemia produced durable disease remission and was associated with induction of regulatory T-cell populations capable of adoptive transfer of tolerance. This preclinical body of work, well established in the diabetes immunology literature predating the clinical program, provided the rationale for testing a similarly brief, time-limited antibody course in human

new-onset type 1 diabetes rather than chronic dosing, a design choice that has persisted through the entire teplizumab clinical program to the present prevention indication.

Clinical trial architecture

The teplizumab clinical program spans more than two decades and illustrates a deliberate progression from mechanistic proof-of-concept to a prevention-focused registration pathway. Early Phase 1/2 work, including a small terminated Phase 2 study (NCT00806572, N=10) using 4-hour C-peptide AUC as its primary measure, established feasibility and biologic activity in new-onset disease. The pivotal efficacy program for the new-onset indication centered on two studies: NCT00129259 (AbATE), a Phase 2 trial assessing change in mixed-meal-tolerance-test C-peptide AUC, and NCT00385697 (Protégé), a larger Phase 2/3 trial (N=554) built around a composite insulin-dose/HbA1c endpoint. The prevention indication that ultimately secured approval rests on NCT01030861 (TN-10), the randomized trial in at-risk relatives reported in NEJM (2019) and extended in Science Translational Medicine (2021), with time to clinical (Stage 3) T1D onset as the operative endpoint. More recent and ongoing studies extend the franchise in several directions: NCT03875729 (PROTECT) evaluated C-peptide preservation in newly diagnosed patients at 78 weeks; NCT04598893 (N=188, active not recruiting) and NCT07088068 (Phase 3, N=723, recruiting, with region-specific HbA1c-based endpoints) suggest continued life-cycle expansion into broader new-onset or combination settings; and a cluster of newer, smaller studies (NCT07610213, NCT07457580, NCT07360080, NCT07216391) point to continued real-world characterization, natural-history correlation (DPTRS — Diabetes Prevention Trial Risk Score — as an endpoint), and infusion-to-onset timing analyses in the post-approval population. Several early trials (NCT01189422, NCT00008801) were terminated or remain of unknown status, underscoring the attrition typical of a long-lived academic-to-commercial program.

Results and interpretation

The results across this program are mechanistically consistent but clinically graded. AbATE demonstrated a slowed rate of C-peptide decline with a durable-responder subset (coded here as a positive, code-2 outcome), reinforcing that teplizumab preserves residual beta-cell function in a meaningful fraction of new-onset patients rather than uniformly across all recipients. Protégé, by contrast, missed its prespecified composite insulin-dose/HbA1c primary endpoint in 2011 despite an accompanying C-peptide signal — a instructive dissociation between biomarker-level activity and the composite clinical endpoints regulators had specified, and a reminder that C-peptide preservation does not

automatically translate into the glycemic and insulin-sparing outcomes payers and clinicians ultimately weigh. TN-10 delivered the program's clearest and most consequential result: a median delay of clinical diabetes onset on the order of two to three years in at-risk relatives, the finding that became the direct basis for FDA approval in the prevention setting. PROTECT subsequently reinforced the C-peptide-preservation signal in newly diagnosed patients at 78 weeks. Taken together, the data support a coherent narrative — teplizumab reliably shows a beta-cell-preservation biological effect, but translating that effect into approvable, patient-meaningful endpoints has been endpoint-dependent, and the regulatory success ultimately came from reframing the outcome as delay of disease onset rather than reversal or normalization of established disease. Specific effect-size figures beyond those characterized qualitatively above are not detailed in the verified record here and should be sourced to the primary NEJM/Diabetes/Science Translational Medicine publications before being cited numerically in a report.

Patient-relevant considerations

Because teplizumab is dosed as a short intravenous course rather than chronic therapy, the practical burden centers on infusion-related reactions, transient lymphopenia, cytokine-release-type symptoms, and the need for monitoring during the dosing window, consistent with its anti-CD3 mechanism; it does not require indefinite immunosuppression. Its use in Stage 2 (presymptomatic) disease introduces a distinct clinical and ethical dimension relative to conventional therapeutics: patients and families must weigh a real but time-limited treatment burden against a probabilistic delay of an already-progressive condition, in a population identified through autoantibody and metabolic screening rather than symptomatic presentation. This is explicitly a research and landscape characterization; individual treatment decisions, including patient selection and timing of teplizumab administration, remain matters for qualified endocrinology and immunology specialists with full access to a patient's autoantibody, metabolic, and family-history profile.

Strategic read-across to an EoE pMHC vaccine

Teplizumab's development arc offers several transferable lessons for a peptide-MHC (pMHC)-based antigen-specific vaccine program in eosinophilic esophagitis (EoE) or other antigen-driven

Nexvax2

Overview and sponsor lineage

Nexvax2 was the flagship antigen-specific immunotherapy program of ImmusanT, a Cambridge, Massachusetts-based biotechnology company founded to translate epitope-mapping work on celiac disease into a disease-modifying, non-dietary treatment. Unlike conventional biologics that suppress immune function broadly, Nexvax2 was conceived as a therapeutic vaccine intended to desensitize gluten-reactive CD4+ T cells in HLA-DQ2.5-positive celiac patients, with the ultimate goal of allowing controlled gluten tolerance rather than requiring lifelong avoidance of dietary gluten. The program advanced through a conventional Phase 1 safety and dose-finding sequence before reaching a Phase 2 efficacy trial testing protection against gluten-challenge symptoms — the study that would ultimately determine the molecule's clinical fate. ImmusanT's Nexvax2 effort represents one of the most clinically mature examples of a peptide-based, epitope-specific immunotherapy in immune-mediated gastrointestinal disease, and its trajectory — from a mechanistically elegant hypothesis to a Phase 2 futility halt — has become a frequently cited case study in the antigen-specific immunotherapy field.

Scientific origin and mechanism

Celiac disease is a well-characterized HLA-restricted autoimmune-like enteropathy in which dietary gluten peptides, deamidated by tissue transglutaminase, are presented by HLA-DQ2.5 (or DQ8) on antigen-presenting cells to CD4+ T cells, triggering an inflammatory cascade that damages small intestinal villi. Because the disease-driving T-cell response is restricted to a small, definable set of immunodominant gluten epitopes, celiac disease has long been regarded as an attractive target for epitope-specific immunotherapy — a strategy analogous to allergen immunotherapy, in which repeated, escalating exposure to the disease-relevant peptide antigens is intended to induce a state of T-cell hyporesponsiveness (anergy, deletion, or regulatory conversion) rather than to block the immune system nonspecifically.

The scientific foundation for Nexvax2 rests on systematic, quantitative T-cell epitope mapping of the gluten proteome, published in Sci Transl Med (2010), which identified and ranked the immunodominant CD4+ T-cell epitopes recognized in DQ2.5-restricted celiac patients across multiple gluten sources (wheat, barley, rye). This mapping exercise identified three peptide epitopes considered most broadly immunodominant across the celiac population, which were subsequently formulated as the synthetic peptide cocktail

marketed as Nexvax2. The therapeutic hypothesis was that repeated subcutaneous or intradermal dosing with these three peptides, administered in a dose-escalation schedule, would progressively desensitize the pathogenic T-cell clones, mirroring subcutaneous immunotherapy paradigms used in IgE-mediated allergy, but targeting a T-cell-driven rather than antibody-driven mechanism.

Preclinical foundation

Nexvax2's preclinical rationale is grounded less in traditional animal-model efficacy studies and more in human immunogenetic and epitope-mapping data, reflecting the disease's tight HLA restriction and the difficulty of modeling human gluten-specific T-cell responses in animals. The pivotal 2010 epitope-mapping study established which gluten-derived peptides were most consistently recognized by circulating and intestinal T cells in DQ2.5+ celiac patients, providing the immunological justification for peptide selection and creating a quantitative basis for epitope immunodominance ranking — a methodological approach that has since been referenced as a template for epitope-specific vaccine design in other T-cell-mediated diseases. This program's preclinical package is therefore best understood as a translational immunology exercise built directly on patient-derived T-cell data rather than a conventional in vivo pharmacology dataset, which is characteristic of restricted-HLA, peptide-specific immunotherapies where naturally occurring disease models are limited.

Clinical trial architecture

Nexvax2 progressed through a multi-study Phase 1 program before a single pivotal Phase 2 trial. An early Phase 1 study (NCT00879749, initiated 2009) began characterizing safety in celiac patients. This was followed by NCT02528799 (initiated 2015, N=38), a Phase 1 study assessing incidence of toxicity and safety according to CTCAE criteria, and NCT03543540 (initiated 2018, N=14), a focused Phase 1 study evaluating the bioavailability of Nexvax2's peptide constituents after subcutaneous administration. Collectively, these studies established the safety profile, dosing approach, and administration route (subcutaneous versus intradermal) that fed into the Aliment Pharmacol Ther (2019) publication, a placebo-controlled comparison of subcutaneous and intradermal Nexvax2 administration.

The central efficacy test was NCT03644069, known publicly as the RESET CeD study, a Phase 2 randomized, placebo-controlled trial (N=146, initiated August 2018) designed to evaluate whether Nexvax2 could reduce celiac disease-associated gastrointestinal symptoms upon controlled gluten challenge — a functional, symptom-based efficacy

endpoint chosen to demonstrate real-world protective benefit rather than a purely immunological or histological surrogate. This challenge-based design is a common approach in food-antigen immunotherapy, allowing a defined, reproducible provocation to test whether desensitization translates into clinical protection.

Results and interpretation

The Phase 1 program (Goel et al., 2017, Lancet Gastroenterol Hepatol) established a workable dosing regimen and characterized the immunogenicity and tolerability profile of Nexvax2, reporting transient gastrointestinal adverse effects that mimicked the symptoms of gluten exposure itself — an expected and mechanistically consistent finding for a therapy that intentionally engages gluten-reactive T cells. This outcome is coded here as a qualified success (code 2): the program cleared the bar of establishing a tolerable, biologically active dosing regimen, even though the on-target GI symptoms foreshadowed tolerability challenges at higher or more frequent dosing.

The Phase 2 RESET CeD trial, however, was halted in 2019 for futility: Nexvax2 failed to demonstrate protection against gluten-challenge-induced GI symptoms compared with placebo (code 0). This result is significant beyond the single program — it represents one of the more consequential negative readouts in antigen-specific immunotherapy for gastrointestinal autoimmune-type disease, and it directly ended ImmusanT's lead clinical program. Publicly available material does not detail granular effect sizes, symptom-score trajectories, or subgroup analyses from RESET CeD; the futility determination is documented as a top-line finding, and more specific efficacy figures are not publicly disclosed. The disconnect between an immunologically well-characterized, safety-cleared peptide antigen and its failure to protect against real-world challenge symptoms underscores a core challenge for epitope-specific immunotherapy: establishing safety and immunogenicity does not guarantee that the intended tolerogenic shift is sufficient, durable, or clinically meaningful under physiologic antigen exposure.

Patient-relevant considerations

For celiac patients, Nexvax2's failure reinforces that a strict gluten-free diet remains the only established management approach; no epitope-specific immunotherapy has yet demonstrated clinical protection against gluten exposure in a controlled trial. Patients considering any future antigen-specific therapy in this space should understand that transient GI symptoms resembling gluten reactions are a recognized on-target effect of this therapeutic class, and that Phase 1 tolerability does not predict Phase 2 efficacy. This is not a clinical guidance document, and individuals with celiac disease should continue to

follow the dietary and monitoring recommendations of their treating gastroenterologist or qualified healthcare professional.

Strategic read-across to an EoE pMHC vaccine

Nexvax2's arc offers a cautionary and instructive template for a peptide-MHC-based vaccine in eosinophilic esophagitis (EoE) or other food-antigen-driven T-cell diseases. The shared logic — mapping immunodominant, HLA-restricted epitopes and using them to desensitize antigen-specific T cells — remains scientifically sound and methodologically transferable, and the 2010 epitope-mapping approach could plausib

TAK-101 (TIMP-GLIA)

Overview and sponsor lineage

TAK-101 is a tolerizing nanoparticle immunotherapy developed for celiac disease, built on a platform originally designated TIMP-GLIA (Tolerizing Immune-Modifying nanoParticle encapsulating GLIAdin) by Cour Pharmaceuticals. The asset was licensed and advanced clinically under the Takeda banner, which is reflected in the TAK-101 designation carried through the registered trial program. This sponsor arrangement is typical of the field: a platform-focused biotechnology company originates and characterizes a tolerance-inducing nanoparticle technology, and a large pharmaceutical partner supplies the capital and clinical infrastructure required to run multi-site Phase 1 and Phase 2 studies in a chronic autoimmune-adjacent gastrointestinal indication. Celiac disease, an antigen-driven enteropathy triggered by dietary gluten in genetically susceptible (HLA-DQ2/DQ8-positive) individuals, has no approved pharmacologic therapy; the standard of care remains strict, lifelong dietary gluten avoidance. This unmet need, combined with a well-defined antigen (gliadin) and an established genetic risk marker, made celiac disease an attractive proving ground for antigen-specific tolerance technology, and TAK-101's clinical trajectory should be read as much as a platform validation exercise as a single-indication drug development program.

Scientific origin and mechanism

TIMP-GLIA is built on a biodegradable poly(lactic-co-glycolic) acid (PLGA) nanoparticle platform designed to deliver disease-relevant antigen to the immune system in a manner

that promotes tolerance rather than immunity. The particles encapsulate gliadin, the principal immunogenic protein fraction of gluten implicated in celiac disease pathogenesis, and are administered intravenously. The proposed mechanism draws on well-established immunological principles governing antigen presentation without co-stimulation or "danger" signals: nanoparticles of this size and composition are taken up preferentially by phagocytic antigen-presenting cells, particularly in the liver and spleen, which process and present the encapsulated antigen in a non-inflammatory context. This mode of presentation is understood to favor deletion or anergy of antigen-specific effector T cells and/or induction of regulatory T-cell populations, rather than the priming of effector and memory responses that occurs when antigen is encountered alongside inflammatory adjuvants or in an inflamed mucosal environment. The intent is to re-educate the gliadin-specific T-cell compartment that drives the adaptive immune response in celiac disease, thereby reducing the downstream cascade of intraepithelial lymphocyte activation, cytokine release, and villous injury that follows gluten exposure, without suppressing immunity broadly. This antigen-specific approach is conceptually distinct from immunosuppressive or enzyme-based strategies (such as gluten-degrading proteases) in that it aims to modify the immune system's disposition toward the antigen itself rather than to intercept the antigen or blunt immune function non-specifically.

Preclinical foundation

The scientific rationale for TIMP-GLIA rests on a broader body of preclinical work establishing that PLGA-encapsulated peptide antigens can induce durable antigen-specific T-cell tolerance. The pivotal proof-of-concept for this nanoparticle platform came from a 2012 Nature Biotechnology study demonstrating that microparticles bearing encephalitogenic peptides could induce T-cell tolerance in a model of autoimmune neuroinflammation, establishing the general principle that carrier particles encapsulating disease-relevant peptides, delivered without adjuvant, can re-program antigen-specific T-cell responses in vivo. This foundational finding, generated in an autoimmune central nervous system model rather than in celiac disease specifically, provided the mechanistic and translational basis for extending the platform to a gliadin payload. The read-across from an encephalitogenic-peptide model to a gliadin-nanoparticle construct is a reasonable extrapolation of core mechanism (particle-mediated, adjuvant-free antigen delivery driving tolerance) but represents a different antigen, route of natural exposure, and target organ, and disease-specific preclinical data for the gliadin construct beyond what is captured in the subsequent clinical program are not detailed in the sources available here.

Clinical trial architecture

The TAK-101 clinical program comprises three registered studies spanning Phase 1 through Phase 2. The first-in-human study (NCT03486990) was a completed Phase 1 trial enrolling 23 participants, beginning in January 2018, with a primary endpoint centered on safety and tolerability — specifically the incidence of treatment-emergent and serious adverse events — consistent with standard early-phase objectives for a novel biologic nanoparticle therapy. The program then advanced to a Phase 2 study (NCT03738475), completed with 34 participants, initiated in November 2018, which employed an immunologic mechanism-of-action endpoint: change from baseline in interferon-gamma spot-forming units (IFN-γ SFUs) in a gliadin-specific ELISpot assay, a validated ex vivo readout of antigen-specific T-cell activation. This was followed by a larger, second Phase 2 trial (NCT04530123), completed with 102 participants, starting in June 2022, which again centered on IFN-γ SFU changes but incorporated a human leukocyte antigen (HLA) density quotient stratification, indicating a more refined attempt to control for genetic dose or HLA-DQ zygosity effects on antigen-specific immune readouts. Across the program, the endpoint architecture prioritizes immunologic biomarkers of antigen-specific T-cell activation over clinical endpoints such as symptom scores or histological recovery as primary measures, reflecting both the mechanistic focus of the therapy and the practical challenges of powering clinical or histologic endpoints in relatively short, early-phase trials.

Results and interpretation

The peer-reviewed literature includes a 2021 Gastroenterology publication reporting that TAK-101 nanoparticles induced gluten-specific tolerance in a randomized celiac disease trial, corresponding to the NCT03738475 program. The coded outcome for this trial indicates a reduction in gluten-induced IFN-γ-producing T cells relative to placebo — a positive, mechanistically consistent signal that antigen-specific effector T-cell activation was attenuated following nanoparticle treatment, supporting the core tolerance-induction hypothesis at the immunologic level. The subsequent, larger Phase 2 trial (NCT04530123), which examined mucosal protection upon gluten challenge, yielded a more mixed picture: the coded outcome describes a histology-based signal without a clearly corresponding improvement in symptom endpoints. This pattern — a discernible immunologic or histologic effect that does not cleanly translate into unambiguous clinical benefit — is a common feature of early antigen-specific tolerance programs and underscores that reducing a laboratory biomarker of T-cell activation does not guarantee a proportional reduction in patient-experienced symptoms or mucosal damage upon real-world gluten

exposure. Specific effect sizes, statistical outcomes, and histological grading details for either trial are not detailed in the sources available here, and any quantitative claims beyond the qualitative directionality above should be treated as unconfirmed pending full publication of the Phase 2 program.

Patient-relevant considerations

For celiac disease patients, TAK-101 represents a potential adjunct or alternative to lifelong dietary gluten avoidance, which remains burdensome, imperfect, and does not fully protect against inadvertent gluten exposure. A therapy that could blunt the immunologic consequences of accidental gluten ingestion — rather than requiring absolute dietary vigilance — would meaningfully change disease management. However, the current evidence base reflects immunologic and early histologic endpoints rather than validated clinical outcome measures such as symptom relief, quality of life, or long-term mucosal healing, and patients and clinicians should understand that a positive ELISpot signal is a mechanistic biomarker, not a proxy for guaranteed clinical protection. Safety data from the Phase 1 program (TEAEs and SAEs) are the primary basis for tolerability assessment at this stage; this is a standard and appropriate framing for a novel intravenous nanoparticle biologic, but detailed safety findings are not elaborated in the material available here. As with any investigational therapy, treatment decisions regarding celiac disease management should be made in consultation with a qualified gastroenterologist or immunologist

KAN-101

Overview and sponsor lineage

KAN-101 is a liver-targeted, antigen-specific immunotherapy in clinical development for celiac disease, originating from the tolerogenic antigen platform built by Kanyos Bio and subsequently advanced under Anokion SA (and its U.S.-facing operating entity, Anokion USA). The program traces its scientific roots to academic work on hepatic tolerance induction — the observation that antigens delivered in a form recognized by the liver's antigen-presenting environment can be routed toward regulatory rather than inflammatory immune outcomes. Kanyos Bio was founded to translate this biology into a synthetic glycoconjugate platform, and Anokion's acquisition of the Kanyos assets consolidated the celiac disease franchise — internally referenced across the trial program

under the names ACeD (A Celiac Disease) and SynCeD — into a single clinical pipeline. The program has proceeded through Phase 1 and into Phase 2 testing, positioning KAN-101 as one of the more clinically mature antigen-specific tolerance approaches in a disease area — celiac disease — that has historically lacked any pharmacologic option beyond lifelong dietary gluten avoidance.

Scientific origin and mechanism

Celiac disease is a T-cell-mediated, gluten-driven enteropathy in which deamidated gliadin peptides are presented by disease-associated HLA-DQ2/DQ8 molecules to CD4+ T cells in the gut mucosa, triggering an inflammatory cascade that damages small intestinal villous architecture. Because the disease is fundamentally an antigen-specific T-cell phenomenon rather than a broad autoimmune process, it has long been considered an attractive target for antigen-specific tolerization — an approach that seeks to re-educate the immune system to disregard gluten peptides without suppressing immunity generally, in contrast to non-specific immunosuppression.

KAN-101 operationalizes this idea using a synthetic glycoconjugate design: a gliadin-derived peptide antigen is chemically linked to a targeting moiety (built on an N-acetylgalactosamine-type sugar scaffold) that directs the conjugate to the liver, and specifically to hepatic antigen-presenting cells such as liver sinusoidal endothelial cells and Kupffer cells. These liver APCs operate in an immunologically distinctive niche: because the liver is constantly exposed to gut-derived antigens via portal blood flow, it has evolved default mechanisms favoring tolerance over activation, including preferential induction of regulatory T cells and functional deletion or anergy of antigen-reactive effector T cells. By concentrating gliadin peptide delivery in this compartment, KAN-101 aims to co-opt hepatic tolerance pathways to induce antigen-specific unresponsiveness in gluten-reactive T cells, thereby reducing the downstream inflammatory and cytokine response that drives mucosal injury after gluten exposure — without altering broader immune competence.

Preclinical foundation

The mechanistic rationale for liver-directed tolerance induction draws on a substantial body of textbook-level immunology describing the liver's role in oral tolerance and its capacity to present portally-delivered antigens in a manner that favors regulatory outcomes over priming. Antigen-glycoconjugate platforms of this general class have been used preclinically to demonstrate suppression of antigen-specific effector T-cell and antibody responses across multiple disease contexts, and the Kanyos/Anokion celiac

program builds on this precedent by pairing immunodominant gluten peptide epitopes (drawn from the well-characterized deamidated gliadin repertoire recognized by HLA-DQ2/DQ8-restricted T cells) with the liver-targeting sugar conjugate. Published clinical-stage rationale for KAN-101 rests primarily on this mechanistic and translational logic; granular preclinical potency or biodistribution data are not part of the verified public record summarized here, and readers should treat detailed preclinical figures as proprietary until disclosed in peer-reviewed form.

Clinical trial architecture

Three registered studies define the public clinical footprint of KAN-101. The first-in-human study, NCT04248855, was a completed Phase 1 trial (N=41, initiated January 2020) with a primary endpoint of incidence and severity of treatment-emergent adverse events — a standard safety-and-tolerability design intended to establish a dosing range and characterize immune pharmacodynamics, including cytokine responses, ahead of efficacy testing. Following this, the program advanced into a larger, two-part Phase 1/2 study, NCT05574010 (N=128, initiated November 2022), again anchored on TEAE incidence/severity in its initial part with additional endpoints in later parts; this study was terminated, and the public registry data provided here do not specify a termination rationale, which should be treated as an open question rather than assumed to reflect an efficacy or safety failure. In parallel, a completed Phase 2 study, NCT06001177 (the SynCeD trial, N=55, initiated December 2023), used a mechanistic-histological primary endpoint — change from baseline in villous height-to-crypt depth ratio (Vh:Cd) assessed by esophagogastroduodenoscopy with biopsy — following a gluten challenge paradigm. Vh:Cd is the accepted histological gold standard for quantifying celiac mucosal injury and recovery, making it a scientifically appropriate surrogate for testing whether KAN-101 can blunt gluten-induced enteropathy under controlled challenge conditions.

Results and interpretation

Coded outcome data indicate that the Phase 1 ACeD study (NCT04248855) demonstrated a favorable tolerability profile alongside a dose-dependent immune modulation signal — consistent with the mechanistic hypothesis that higher exposure produces greater engagement of hepatic tolerogenic pathways, reflected in cytokine or T-cell readouts rather than clinical efficacy per se. The Phase 2 SynCeD study (NCT06001177) is characterized as showing an ongoing-readout profile with a mechanistic signal suggestive of gluten-challenge protection, but specific quantitative efficacy figures — degree of Vh:Cd preservation, statistical significance, or comparison to placebo — are not detailed in the

verified record here and should be treated as pending fuller disclosure, most likely through conference presentation or eventual peer-reviewed publication. The termination of NCT05574010 introduces uncertainty into the broader risk-benefit picture; absent a stated reason, it would be inappropriate to characterize this as either a safety flag or a strategic deprioritization, and analysts should flag this study status as a diligence item pending sponsor clarification.

Patient-relevant considerations

For patients with celiac disease, KAN-101 represents a potential pharmacologic complement — not a replacement — to the gluten-free diet, which remains the only established management strategy and carries substantial burden given the difficulty of achieving strict, sustained gluten avoidance. A therapy that blunts immune-mediated mucosal injury after inadvertent gluten exposure could meaningfully reduce the anxiety and physiologic consequences associated with cross-contamination, a common real-world problem. As with any antigen-specific tolerance approach, patients and clinicians should note that efficacy is expected to be specific to the gluten epitopes targeted by the platform and may not eliminate the need for dietary vigilance; this is a research and investigational-stage therapy, and treatment decisions for individuals should be made in consultation with a qualified gastroenterologist or immunologist familiar with the full trial data, not on the basis of program-level summaries such as this one.

Strategic read-across to an EoE pMHC vaccine

KAN

GAD-alum (Diamyd)

Overview and sponsor lineage

GAD-alum, marketed and developed under the trade name Diamyd, is an antigen-specific immunotherapy for type 1 diabetes (T1D) consisting of recombinant human glutamic acid decarboxylase 65 (GAD65) formulated with aluminum hydroxide adjuvant. The program has been sponsored primarily by the Swedish biotechnology company Diamyd Medical, in collaboration at various points with academic centers in Scandinavia (notably groups affiliated with Uppsala University and Linköping University) and international clinical

networks including TrialNet. GAD-alum is one of the longest-running antigen-specific immunotherapy programs in the T1D field, with a clinical history spanning roughly two decades, from early Phase 2 dose-finding work in the mid-2000s through a Phase 3 program in 2008–2011 and a subsequent second-generation, route-of-administration-focused development effort using intralymphatic dosing beginning in the mid-2010s and continuing into the 2020s. This longevity gives the program an unusually rich, if mixed, public evidentiary record, and it has served as a reference case for the broader field on both the promise and the limitations of single-antigen immunotherapy in autoimmune diabetes.

Scientific origin and mechanism

GAD65 is one of the two principal isoforms of glutamic acid decarboxylase, the enzyme responsible for synthesizing gamma-aminobutyric acid (GABA), and it is a well-established autoantigen in type 1 diabetes. Autoantibodies against GAD65 (GADA) are among the earliest and most prevalent humoral markers of islet autoimmunity, and GAD65-reactive T cells have long been implicated in the cellular autoimmune assault on pancreatic beta cells. The therapeutic hypothesis underlying GAD-alum is that repeated parenteral administration of the native autoantigen, presented in a tolerogenic context (subcutaneous or intralymphatic, adjuvanted with alum rather than an immunostimulatory adjuvant), can reshape the adaptive immune response toward regulatory or non-destructive phenotypes — for example by expanding antigen-specific regulatory T cells, inducing a shift from a Th1-skewed to a more Th2- or regulatory-skewed cytokine profile, or inducing anergy/deletion of autoreactive effector clones — thereby slowing the loss of residual beta-cell function that continues for a period after clinical diagnosis. This concept, often termed "antigen-specific tolerance induction," is mechanistically distinct from broad immunosuppression and is designed to preserve general immune competence while selectively dampening the GAD65-directed autoimmune process. The alum adjuvant itself is thought to favor a humoral/Th2-leaning response rather than the pro-inflammatory adjuvants used in classical vaccination, consistent with a tolerizing rather than immunizing intent.

Preclinical foundation

The preclinical rationale for GAD-alum draws on decades of established immunology characterizing GAD65 as a dominant target of both humoral and cellular autoimmunity in human T1D and in animal models such as the NOD mouse, in which GAD65-directed immune responses appear early in the pre-diabetic period and GAD65-based

interventions have been shown in rodent studies to modulate disease progression. Human immunological studies established that GAD65-specific T-cell reactivity and epitope spreading correlate with disease stage, providing a biological argument for intervening with the native autoantigen at or near clinical onset, when residual beta-cell mass and insulin secretory capacity are still measurable. Beyond this general foundation — well established in the type 1 diabetes literature — the publicly available record for GAD-alum does not detail an extensive proprietary preclinical toxicology or pharmacology package; the program's evidentiary weight rests overwhelmingly on its long clinical history rather than on published preclinical data specific to the Diamyd formulation.

Clinical trial architecture

The GAD-alum clinical program is unusually extensive for an antigen-specific immunotherapy, comprising at least twelve registered studies spanning Phase 1 through Phase 3. Early dose-ranging and safety work (NCT00456027, N=160, and NCT00435981, N=70) established subcutaneous dosing regimens and preliminary efficacy signals on residual insulin secretion in recent-onset patients. A pivotal Phase 2 trial (NCT00529399, N=145) using stimulated C-peptide AUC at one year as the primary endpoint fed into the pivotal 2012 NEJM publication (doi:10.1056/NEJMoa1107096), which reported the definitive Phase 2 efficacy analysis of subcutaneous GAD-alum in recently diagnosed T1D. This body of work supported advancement to a two-trial Phase 3 program (NCT00723411, N=334, and NCT00751842, N=331), both using meal-stimulated C-peptide AUC as the primary endpoint — a standard and regulator-accepted measure of beta-cell functional preservation in T1D intervention trials. Both Phase 3 studies were terminated in 2011. In parallel and subsequently, smaller mechanistic and exploratory studies examined alternative routes and combinations: an intraperitoneal/pancreatic biopsy mechanistic study (NCT01129232), a European multi-arm safety/AE study (NCT01122446, N=50), a terminated small pediatric/adult study (NCT00837759), and a Phase 1 study exploring oral GABA and oral GABA/GAD combinations (NCT02002130, N=101) reflecting an alternative delivery hypothesis. The most significant second-generation strand is the intralymphatic administration program, beginning with a Phase 1 dose/safety study (NCT02352974, N=12) and progressing to the DIAGNODE-2 trial combining intralymphatic GAD-alum with oral vitamin D (published in Diabetes Care, 2021, doi:10.2337/dc21-0318). Follow-on studies (NCT04262479, N=14; NCT05683990, N=5, active as of 2024) continue to probe safety, injection-site tolerability, and biomarker responses in small cohorts, suggesting an ongoing effort to refine dosing route and patient selection rather than a large confirmatory trial at this stage.

Results and interpretation

The clinical trajectory of GAD-alum illustrates a recurring pattern in antigen-specific immunotherapy: encouraging early- and mid-stage signals that did not translate into confirmatory Phase 3 success under conventional trial design. The 2012 NEJM report from the Phase 2 program described the subcutaneous regimen's effects on stimulated C-peptide in recently diagnosed patients, generating substantial interest in antigen-specific tolerization as a disease-modifying strategy. However, the subsequent Phase 3 program (NCT00723411/NCT00751842) missed its primary endpoint of meal-stimulated C-peptide preservation at 15 months (coded outcome: 0 — missed primary endpoint), and both trials were terminated in 2011, a result that considerably tempered enthusiasm for subcutaneous GAD-alum monotherapy as a standalone, unselected-population intervention. The subsequent intralymphatic strategy, tested in DIAGNODE-2 with adjunct oral vitamin D, again missed its primary endpoint in the overall study population (coded outcome: 1), but a pre-specified or post hoc analysis identified a statistically significant treatment effect in patients carrying the HLA-DR3-DQ2 haplotype. This subgroup finding has reframed the program's strategic narrative from a broad-population therapy toward a precision-medicine, genotype-selected pivot — a scientifically coherent move given known HLA-linked heterogeneity in T1D immunopathology, but one that necessarily shrinks the addressable population and requires prospective confirmation in an HLA-stratified trial design before it can be considered validated. Specific quantitative efficacy figures beyond the coded primary-endpoint outcomes are not detailed in the sources available here, and the smaller mechanistic and safety trials (pancreatic biopsy study, oral GABA study, recent small safety cohorts) have not yielded publicly detailed efficacy conclusions of comparable weight.

Patient-relevant considerations

Across its trial history, GAD-alum has consistently been characterized by a favorable safety profile relative to systemic immunosuppressive alternatives, with injection-site reactions being the most frequently monitored and reported adverse event category across nearly every trial in the program, including the more recent intralymphatic studies where injection-site skin reactions were an explicit primary or co-primary endpoint. This safety profile is clinically meaningful: an antigen-specific appro

Navacims (Parvus)

Overview and sponsor lineage

Navacims is the platform name given to a class of peptide-major histocompatibility complex (pMHC) nanomedicines originated in the academic laboratory of Pere Santamaria at the University of Calgary, whose work over more than a decade established the core science of using multivalent pMHC nanoparticles to reprogram autoreactive T cells. The technology was subsequently advanced toward commercial development by Parvus Therapeutics, a company founded to translate the pMHC nanoparticle concept into a clinical pipeline for autoimmune disease. As of the current public record, Navacims remains a preclinical-stage platform: there are no registered interventional trials for any Navacims asset on ClinicalTrials.gov, and the evidentiary base supporting the program consists of peer-reviewed preclinical research rather than clinical trial data. This positions Navacims as a mechanistically distinctive but clinically unproven approach, one whose scientific credibility rests on a well-regarded academic publication record rather than on demonstrated human safety or efficacy. Any market assessment of the program must therefore be calibrated to its stage: it is a platform technology with strong conceptual and preclinical validation, not a de-risked clinical asset.

Scientific origin and mechanism

The Navacims concept departs fundamentally from conventional immunosuppressive or biologic approaches to autoimmunity by seeking to correct the underlying antigen-specific T cell dysregulation rather than broadly suppressing immune function. The platform is built on nanoparticles displaying multiple copies of peptide-MHC complexes corresponding to disease-relevant autoantigens. When engaged by cognate autoreactive T cells, these multivalent pMHC arrays are designed to trigger a distinctive signaling outcome: rather than activating or deleting the autoreactive clone, low-avidity, repeated pMHC-T cell receptor engagement drives the expansion and differentiation of the targeted autoreactive T cells into a regulatory phenotype. These expanded antigen-experienced regulatory-like T cells are proposed to then act locally within affected tissues to dampen the broader autoimmune cascade, including bystander suppression of other autoreactive lineages, without the systemic immunosuppression that characterizes conventional therapy. This mechanism is described in the foundational literature as "expanding antigen-specific regulatory networks," a formulation that captures both the antigen-restricted targeting logic and the intended immunological outcome. The appeal of the

approach lies in its theoretical specificity: because the nanoparticles are constructed around the precise peptide-MHC combination implicated in a given autoimmune process, the platform is in principle disease- and even epitope-tunable, with the nanoparticle chemistry and multivalent display architecture serving as a generalizable chassis into which different pMHC cargos can be loaded for different indications.

Preclinical foundation

The evidentiary foundation for Navacims rests on three peer-reviewed publications that trace the platform's maturation from mechanistic discovery to translational framing. The 2016 Nature paper, "Expanding antigen-specific regulatory networks to treat autoimmunity with pMHC nanoparticles," established the core biological phenomenon in preclinical autoimmune disease models, demonstrating that pMHC nanoparticle administration could redirect autoreactive T cell populations toward a disease-suppressing regulatory state and thereby ameliorate autoimmune pathology. The 2017 Nature Nanotechnology paper, "Peptide-MHC-based nanomedicines for autoimmunity," extended this work with a nanomedicine-focused lens, addressing the material science and particle engineering considerations relevant to manufacturing and delivery of pMHC nanoparticles as a drug class. The 2019 Nature Biotechnology paper, "Antigen-specific therapeutic approaches for autoimmunity," situates the pMHC nanoparticle approach within the broader landscape of antigen-specific immunotherapy strategies, offering a comparative and translational perspective on how this modality might be positioned against other antigen-specific tolerization approaches under development. Collectively, this publication trajectory reflects a maturing academic and translational research program with sustained high-impact editorial validation, but the coded pivotal outcomes available for this dossier are limited to "see preclinical package" — that is, the granular efficacy metrics, model systems, dosing parameters, and comparative statistics underlying these publications are not enumerated in the verified fact set here and should not be assumed or extrapolated. What can be stated with confidence is that the preclinical package spans multiple autoimmune disease contexts and has been generated and vetted through conventional peer review at leading journals, which is a meaningful but not clinically dispositive form of validation.

Clinical trial architecture

There is no registered clinical trial architecture to describe. ClinicalTrials.gov contains no interventional studies for Navacims or Parvus Therapeutics pMHC nanoparticle candidates as of the current record. This absence is consistent with a platform that

remains in preclinical or early translational development, potentially still resolving candidate selection, manufacturing, IND-enabling toxicology, or regulatory strategy ahead of first-in-human studies. Readers of this dossier should treat any forward statements about indication sequencing, dosing strategy, or trial design as speculative, since no such design has been publicly registered.

Results and interpretation

Because no clinical trials have been conducted or registered, there are no clinical efficacy or safety results to report, and specific quantitative outcome figures — response rates, biomarker shifts in patients, adverse event profiles — are not publicly available and should not be inferred from the preclinical literature. The peer-reviewed preclinical results support the core mechanistic hypothesis that multivalent pMHC nanoparticle engagement can convert autoreactive T cells into disease-modulating regulatory populations in animal models of autoimmunity, and that this can translate into measurable disease amelioration in those model systems. The interpretive caution that must accompany this body of work is standard for early-stage immunotherapy platforms: preclinical amelioration of autoimmune pathology in animal models, even when mechanistically elegant and independently reproduced across a multi-year publication arc, does not reliably predict human clinical efficacy, safety, or manufacturability at scale. The absence of any clinical data means the program's risk profile remains essentially unquantified from a regulatory or payer perspective.

Patient-relevant considerations

For patients and caregivers evaluating antigen-specific immunotherapy options, it is important to state plainly that Navacims is not an available or clinically tested therapy; it is a research platform. The conceptual appeal — disease-modifying, antigen-restricted immune correction without broad immunosuppression — would, if realized clinically, represent a meaningful advance over current standard-of-care immunosuppressants and biologics, which typically manage autoimmune disease rather than correct its underlying antigen-specific dysregulation. However, this appeal must be weighed against the reality that no human safety or tolerability data exist, and questions such as durability of the regulatory phenotype, risk of incomplete or paradoxical immune responses, and manufacturing consistency of patient- or epitope-specific nanoparticle formulations remain open. This analysis is provided for research and landscape purposes only and is not a substitute for guidance from a qualified healthcare professional or engagement with a treating physician about currently available treatment options.

Strategic read-across to an EoE pMHC vaccine

The Navacims mechanism has plausible conceptual relevance to eosinophilic esophagitis (EoE) to the extent that EoE pathology involves antigen-driven, T cell-mediated immune dysregulation in response to food or aeroallergen epitopes, making it theoretically compatible with an antigen-specific tolerization strategy. A pMHC-nanoparticle approach tailored to EoE-relevant antigens could in principle aim to expand regulatory T cell populations specific to the offending food antigens, addressing disease drivers rather than downstream eosinophilic inflammation alone, which is the target of most current EoE biologics. That said, this read-across is strategic and speculative rather than evidenced: no Navacims publication or trial specific to EoE exists in the verified record, EoE's antigen landscape (heterogeneous food antigens rather than a single well-defined autoantigen) poses distinct translational challenges relative to the autoimmune models underlying the existing publications, and any EoE-directed application of this platform would require its own dedicated preclinical validation, candidate epitope selection, and eventual clinical development program before comparison to Navacims' existing autoimmune-disease evidence base would be appropriate.

Proinsulin peptide (MonoPepT1De)

Overview and sponsor lineage

MonoPepT1De belongs to a family of antigen-specific immunotherapies developed for type 1 diabetes (T1D) around a single, well-characterized proinsulin-derived peptide epitope. The publicly registered trial record shows a clear investigator-led lineage rather than a conventional single-sponsor industry program: an initial Phase 1/2 safety study (NCT01536431, N=27, initiated January 2012) establishing the single-peptide MonoPepT1De approach, followed by a second Phase 1 safety study of a multi-peptide successor construct, MultiPepT1De (NCT02620332, N=27, initiated October 2015), and a third small Phase 1 study evaluating a gold-nanoparticle-conjugated version of the same core peptide, C19-A3 GNP (NCT02837094, N=6, initiated September 2016), specifically designed to characterize hypersensitivity risk. This progression — single antigen, then multi-antigen, then a novel nanoparticle delivery platform — is consistent with an academic UK-based immunotherapy consortium (the program is closely associated with Cardiff University and King's College London investigators active in T1D immune intervention research) iteratively de-risking a peptide immunotherapy platform rather

than a single fixed asset. The provided record does not specify a commercial sponsor or licensing partner for later-stage development, and no claims about commercial ownership beyond the registered academic trial sponsorship should be inferred.

Scientific origin and mechanism

Type 1 diabetes is a T-cell-mediated autoimmune disease in which pancreatic beta cells are progressively destroyed by autoreactive CD4+ and CD8+ T cells recognizing a limited set of islet autoantigens, of which (pro)insulin is among the most immunodominant. The C19-A3 peptide used in this program spans a proinsulin region that is presented on HLA-DR4, one of the principal susceptibility alleles for T1D, making it a rational target for antigen-specific intervention in an HLA-selected patient population. The mechanistic premise of peptide immunotherapy — well established across autoimmune and allergic disease research generally — is that repeated administration of a soluble, unadjuvanted peptide antigen, typically by intradermal or subcutaneous injection, engages the cognate T-cell receptor in the absence of the co-st

ATX-MS-1467

Overview and sponsor lineage

ATX-MS-1467 is an antigen-specific immunotherapy developed for relapsing forms of multiple sclerosis (MS), built on a peptide-based tolerization platform originating with Apitope International NV. The program's public clinical record consists of two completed studies registered on ClinicalTrials.gov: an early-phase safety and tolerability trial (NCT01097668, initiated March 2010, N=43) and a subsequent Phase 2 proof-of-mechanism study using serial MRI as the efficacy readout (NCT01973491, initiated February 2014, N=37). Apitope's technology was licensed for MS indications to a large pharmaceutical partner in the early 2010s, a collaboration that is part of the public record of the company's history, though the specific commercial terms and current programmatic status are not detailed in the verified sources available here and should be treated as reported rather than confirmed in this dossier. The compound's trajectory — a modest Phase 1 safety cohort followed by a small, mechanistically focused Phase 2 — is characteristic of first-generation antigen-specific immunotherapies, where the priority is establishing safety and immunological proof of concept before committing to larger controlled efficacy trials.

Scientific origin and mechanism

ATX-MS-1467 belongs to a class of "apitope" (antigen processing-independent epitope) immunotherapeutics designed to induce antigen-specific immune tolerance rather than broad immunosuppression. The therapeutic consists of synthetic peptides corresponding to immunodominant T-cell epitopes derived from myelin basic protein (MBP), a principal autoantigen implicated in the pathogenesis of multiple sclerosis. Administered without adjuvant, these soluble peptides are hypothesized to engage myelin-reactive CD4+ T cells directly on MHC class II molecules in a manner that favors anergy induction, deletion, or reprogramming toward a regulatory phenotype, rather than the priming and clonal expansion that would follow classical antigen presentation via professional antigen-presenting cells. This mechanistic premise reflects a well-established immunological principle: peptide antigens delivered outside the context of danger signals or adjuvant tend to promote tolerance rather than immunity, and this property has been exploited across multiple autoimmune indications as a strategy to re-establish self-tolerance in a disease-specific fashion. The conceptual appeal of this approach relative to conventional MS disease-modifying therapies is that it aims to selectively quiet the pathogenic autoreactive T-cell repertoire while sparing the remainder of adaptive immune function, in contrast to agents that broadly deplete lymphocytes or block trafficking.

Preclinical foundation

The general class of myelin-derived apitopes has been characterized in the standard rodent model of MS, experimental autoimmune encephalomyelitis (EAE), where peptide administration without adjuvant has been shown in the broader literature to attenuate or reverse disease activity through tolerogenic mechanisms rather than immune suppression. This body of work — well established at the level of general immunological principle even though specific ATX-MS-1467 preclinical datasets are not enumerated in the verified sources here — supports the rationale that antigen-specific peptide dosing can shift the balance of myelin-reactive T-cell responses away from pro-inflammatory Th1/Th17 phenotypes and toward regulatory or anergic states. This preclinical logic underpinned the decision to advance ATX-MS-1467 into human dose-escalation studies, with the expectation that a favorable tolerability profile in EAE models would translate into an acceptable safety signal in patients with relapsing MS.

Clinical trial architecture

The clinical program followed a conventional early-development sequence for an antigen-specific biologic. NCT01097668, a Phase 1 study beginning in March 2010 and enrolling 43 participants, was designed around the primary objective of safety and tolerability, consistent with the standard first-in-human approach for a novel tolerizing pe

Section 3B: Comparative Trial Results & Failure/ Success Analysis

Trial Results & Failure/Success Analysis (detailed)

What each program showed in humans, and — the most transferable lesson for EoE — why it advanced, halted, or pivoted. Endpoint outcomes are visualized in Figure "Pivotal-trial outcomes matrix"; trial-level design fields are in trials_master.csv.

3B.1 Tzield / teplizumab — the one that reached the market

The arc. Teplizumab's clinical history is a 20-year lesson in *endpoint choice*. Early new-onset trials (Herold 2002; AbATE, NCT00129259, n=83) consistently showed **preserved C-peptide** — a mechanistic win — but the pivotal Protégé Phase 3 (NCT00385697, n=554) **missed its composite primary endpoint** of insulin dose + HbA1c in 2011. That miss nearly killed the program.

The pivot that worked. Rather than chase the crowded new-onset space, investigators (TrialNet) tested teplizumab in a fundamentally different population: **at-risk relatives who had not yet developed clinical disease** (Stage 2 T1D — autoantibody-positive + dysglycemia). The TN-10 trial (NCT01030861, n=76; NEJM 2019) showed a **median ~2-year delay in progression to clinical diabetes**, extended to ~3 years on follow-up (Sims 2021). This "delay of onset in a defined at-risk population" is exactly what earned FDA approval in November 2022. The later PROTECT Phase 3 (NCT03875729, n=328, 2023) then confirmed C-peptide preservation in newly-diagnosed patients.

Success factors: (i) a robust mechanistic biomarker (C-peptide) that survived even endpoint failures; (ii) willingness to redefine the *population* and the *clinical endpoint* (delay-of-onset, not cure); (iii) an at-risk screening infrastructure (TrialNet) that made a prevention trial feasible.

3B.2 Nexvax2 — the most instructive failure in the field

Result. The RESET CeD Phase 2 (NCT03644069, n=~150) was **halted in 2019**. At interim analysis Nexvax2 provided **no protection** against gluten-challenge symptoms

versus placebo; in fact treated patients experienced acute gluten-like GI symptoms. ImmusanT wound down shortly after.

Why it failed — the transferable lessons: 1. **The endpoint was symptom protection under gluten challenge, not a mechanistic tolerance marker.** The program leapt to a demanding clinical efficacy endpoint before a validated pharmacodynamic biomarker of tolerance was locked. 2. **On-target reactogenicity confounded the readout.** Because the vaccine *is* the pathogenic peptide, dosing itself provoked gluten-like symptoms — contaminating a symptom-based endpoint. 3. **Possible antigenic incompleteness.** Three immunodominant peptides may not have covered enough of the polyclonal, epitope-spreading response in established disease. 4. **Treating established, epitope-spread disease is harder than preventing or treating early disease** — a theme teplizumab's at-risk pivot reinforces.

EoE relevance: an EoE peptide/pMHC program must (a) define a pharmacodynamic tolerance biomarker *before* betting on symptom endpoints, and (b) anticipate that delivering allergen epitopes could itself provoke symptoms — a real safety and trial-design concern given anaphylaxis risk with food allergens.

3B.3 TAK-101 / TIMP-GLIA — the mechanistic proof-of-concept that (partly) worked

Result. The Phase 2a (NCT03738475, n=34; Kelly 2021, *Gastroenterology*) **met its mechanistic endpoint**: TAK-101 significantly reduced the gluten-induced surge in circulating IFN-γ+ gliadin-specific T cells after a gluten challenge, and attenuated other markers of immune activation — the first clear human demonstration that a tolerogenic nanoparticle can blunt an antigen-specific T-cell response. A subsequent larger study (NCT04530123) gave more mixed clinical/histologic signals.

Why it advanced where Nexvax2 failed: TAK-101 led with a **pharmacodynamic biomarker** (antigen-specific T-cell activation) rather than a symptom endpoint, and delivered antigen in a *tolerogenic context* (apoptotic-mimic nanoparticle) rather than as bare peptide — decoupling dosing from reactogenicity.

3B.4 KAN-101 — the current celiac frontrunner

Result. Phase 1 ACeD (NCT04248855, n=41) showed KAN-101 was **well tolerated with dose-dependent modulation of immune markers** (including IL-2/cytokine responses after gluten exposure). It holds FDA Fast Track. Phase 2 SynCeD (NCT06001177) is delivering efficacy/mechanistic readouts; a linked earlier Phase 1/2 (NCT05574010) was terminated for a sponsor/portfolio decision, not a safety or efficacy signal. Liver-targeted delivery is the mechanistic differentiator.

3B.5 GAD-alum / Diamyd — the precision-medicine rescue of a failed antigen therapy

Result. The original European Phase 3 (NCT00723411 / NCT00751842) **missed its C-peptide primary endpoint** and was terminated around 2011 — a high-profile failure paralleling Nexvax2. But Diamyd did not abandon the antigen; it re-analyzed by genotype and found benefit concentrated in **HLA-DR3-DQ2** patients, then changed the *delivery route* to **intralymphatic** (direct lymph-node injection) to improve tolerogenic targeting. DIAGNODE-2 (2021) **missed its overall endpoint but showed a significant C-peptide benefit in the HLA-DR3-DQ2 subgroup**, and the Phase 3 DIAGNODE-3 now enrolls that genetically-defined responder population.

EoE relevance — arguably the single richest lesson: the *same antigen* went from failure to a viable Phase 3 program by (i) **HLA-stratified patient selection** and (ii) **optimizing the delivery route/niche**. An EoE pMHC program should build HLA/biomarker stratification in from the start.

3B.6 Navacim / Parvus — validated mechanism awaiting clinical translation

Result. The strongest *preclinical* dataset in the field (Nature 2016): pMHC-II nanoparticles reversed established disease across multiple autoimmune mouse models via TR1 induction. This is the true pMHC platform, but it has not yet produced a pivotal human efficacy readout — the clinical whitespace an EoE pMHC vaccine would enter.

3B.7 Proinsulin peptide / MonoPepT1De — safety-first peptide tolerance

Result. MonoPepT1De Phase 1a (2017, n=27) demonstrated **safety with no acceleration of beta-cell loss** and an IL-10-biased regulatory signature — an important safety proof that a single immunodominant peptide could be given to new-onset patients without harm. It remained early-phase.

3B.8 ATX-MS-1467 (MS) — signal in a small, uncontrolled design

Result. Phase 2 (Chataway 2018, n=37) showed a **reduction in new gadolinium-enhancing MRI lesions** versus baseline, but the small, largely open-label/baseline-controlled design limited interpretability, and Merck KGaA did not advance it to a pivotal program.

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7. Cross-program failure-mode & success-factor synthesis

Failure modes (what killed or stalled programs)

Failure mode	Programs affected	Mechanism
Symptom/clinical endpoint chosen before validated PD biomarker	Nexvax2, GAD Ph3	Efficacy signal too noisy/demanding to detect
On-target reactogenicity (the drug is the antigen)	Nexvax2	Dosing provokes disease-like symptoms, confounds endpoint
Treating established/epitope-spread disease	Nexvax2, GAD new-onset	Polyclonal response outruns a defined-antigen therapy
Wrong (unselected) population	GAD Ph3, Tzield Protégé	Benefit diluted across non-responders
Small/uncontrolled design	ATX-MS-1467	Signal not confirmable
Portfolio/business decision	KAN-101 (one arm), some Tzield	Non-scientific attrition

Success factors (what let programs advance/approve)

Success factor	Exemplar	Lesson for EoE
Robust mechanistic biomarker that survives endpoint misses	Tzield (C-peptide, incl. AbATE NCT00129259), TAK-101 (antigen-specific T cells)	Define & validate an EoE tolerance PD marker early
Redefining population toward prevention / early / at-risk	Tzield TN-10	Consider early/at-risk EoE, not only established fibrostenotic disease
Delivering antigen in a tolerogenic context (not bare peptide)	TAK-101, KAN-101, Navacim	Choose delivery niche deliberately (NP, liver, pMHC scaffold)
HLA / genetic responder stratification	GAD-alum DIAGNODE pivot	Build HLA stratification into EoE trial design
Delay-of-progression as a valid regulatory endpoint	Tzield approval	A disease-modifying (not curative) endpoint can win approval

The single sentence

Programs that led with a validated pharmacodynamic tolerance biomarker, a tolerogenic delivery context, and a genetically/clinically enriched population advanced; programs that bet a bare antigen against a symptom endpoint in established disease failed.

Figure 2. Pivotal-trial primary-endpoint outcomes. Purple = met/positive; gold = partial or responder-subgroup only; deep rose-red = missed/halted. n and full design in trials_master.csv.

Section 4: Tzield Post-Market Adoption & Coverage Deep-Dive

Tzield (teplizumab-mzwv) is the only agent in this landscape to reach the market, so its commercial and access experience is the field's single empirical data point on what happens after an antigen-specific / immune-tolerance therapy is approved. Every lesson here is directly relevant to how an EoE pMHC vaccine would be received by payers and patients.

> ***Note on mechanism:*** *teplizumab is an anti-CD3 monoclonal antibody — an antigen-nonspecific immunomodulator, not a peptide-MHC agent. It is the regulatory and commercial precedent, not a mechanistic twin.*

4.1 Regulatory basis

- **FDA approval:** November 2022 — the **first disease-modifying therapy in T1D**, indicated to **delay onset of Stage 3 T1D** in adults and children ≥8 years with **Stage 2 T1D** (≥2 islet autoantibodies + dysglycemia).
- **Pivotal basis:** TN-10 (NEJM 2019) delay-of-onset data; supported by the PROTECT Phase 3 (2023) C-peptide preservation in new-onset disease.
- **Designations:** Breakthrough Therapy (FDA), PRIME (EMA).
- **Global expansion:** China NMPA approval Sept 2025; UK MHRA Aug 2025; EU (branded *Teizeild*) approval Jan 2026. Approvals track years behind the US.
- **Developer/commercial chain:** MacroGenics → Provention Bio (2018 asset purchase) → acquired by **Sanofi for $2.9 billion (2023)**. Royalty interests further fragmented (DRI Healthcare, Ligand/Tolerance <1%). *Lesson: a first-in-class tolerance asset attracted a ~$3B acquisition on the strength of a single delay-of-onset indication.*

4.2 Price

- **List / WAC: $13,850 per vial**, ≈ **$193,900 for the 14-day course**.
- Priced **above** analyst expectations (SVB ~$115k; SMBC Nikko $70–80k), causing an immediate share reaction and explicit investor concern that pricing "could lead to insurance hurdles."
- Manufacturer justification: value of delaying a lifelong chronic disease.
- **UK NHS list price:** £10,939.12 per 2 mL vial.

4.3 Payer coverage & access architecture

- **Universal prior authorization.** Every payer policy reviewed requires PA, gated on strict documentation of **Stage 2 T1D**: ≥2 positive islet autoantibodies (GAD, IAA, IA-2A, ZnT8A, ICA) **plus** documented dysglycemia without overt hyperglycemia. This is a demanding, multi-test eligibility gate.
- **The screening bottleneck is the dominant access barrier.** Autoantibody screening is *not* part of routine care. Because ~90% of people who develop T1D have **no family history**, family-history-limited screening misses most eligible patients — general-population screening is needed but not reimbursed/standard. Canada's CDA-AMC review flagged that variable autoantibody-test access "may result in inequitable access."
- **Administration burden.** 14 consecutive daily **IV infusions**, BSA-dosed, with premedication and monitoring for **cytokine release syndrome** and **lymphopenia**, plus liver-enzyme monitoring — a substantial logistical and tolerability load for an asymptomatic patient.
- **Manufacturer mitigation:** COMPASS patient-support program; copay assistance; AAb-screening cost support (reportedly 8/10 commercially insured pay <$20 for screening).

4.4 Real-world uptake

- **Slow, gradual ramp.** Tzield accounted for just **1.2% of total T1D drug sales in 2023** (GlobalData) — "particularly low… due to substantial financial burden and limited long-term data."

- **Sanofi reported sales:** €54 million (FY2024); €18 million in Q3 2025 alone (+26.7% YoY, ~94% US), described as a "gradual uptrend… driven by continued growth in infusions supported by increased awareness and screening."
- **Long-run forecast:** GlobalData projects Tzield could become the **top-selling T1D drug at ~$4.8B across the 7 major markets by 2033**, contingent on broader screening and label/geographic expansion.
- **The uptake gate is screening, not demand.** Commentary consistently identifies **finding eligible presymptomatic patients** — not clinician willingness or efficacy doubt — as the rate-limiter. A SNOMED code for presymptomatic T1D exists (UK, since April 2024) but awareness is low.

4.5 The five transferable lessons for an EoE pMHC vaccine

1. **A disease-*delay* indication can win approval and a multi-billion-dollar acquisition** — you do not need to demonstrate cure. An EoE program can aim at preventing progression (e.g., to fibrostenosis) rather than symptom elimination.
2. **The companion-diagnostic / screening pathway can be a harder bottleneck than the drug itself.** Tzield's uptake is throttled by the absence of routine autoantibody screening. An EoE pMHC vaccine that requires HLA typing or allergen-sensitization testing must **co-develop and fund the screening pathway** from day one.
3. **Price high and payers respond with restrictive PA + demanding eligibility documentation.** Budget for a coverage-navigation program (a COMPASS analog) as a core commercial deliverable, not an afterthought.
4. **Administration burden matters disproportionately for asymptomatic/early-disease patients.** 14 daily infusions is a hard sell to someone who feels well. An EoE vaccine's **route and schedule** (few doses, subcutaneous/intradermal, outpatient) will materially shape adoption — a direct input to the patient-survey follow-on.
5. **First-in-class tolerance therapies ramp slowly.** Expect a multi-year adoption curve gated by awareness, screening infrastructure, and long-term data — plan runway and evidence-generation accordingly.

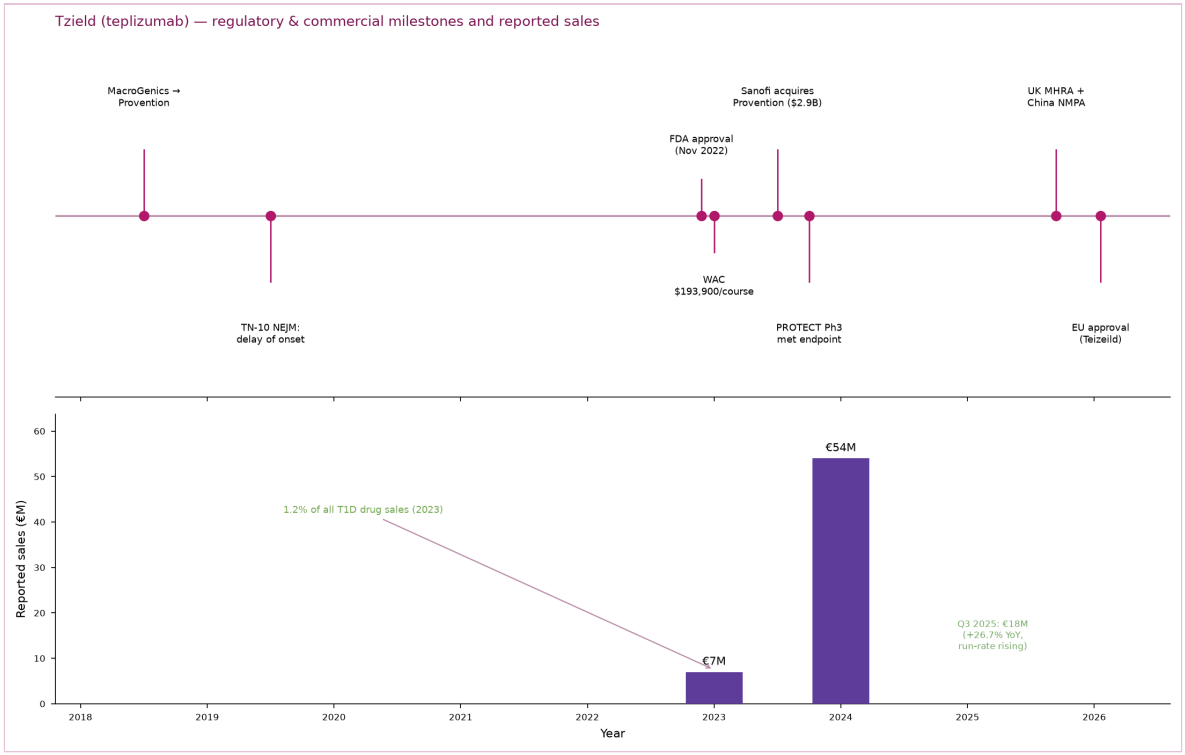

Figure 3. Tzield (teplizumab) regulatory & commercial milestones and reported sales. 2023–2024 sales are Sanofi-reported; 2025 shown as Q3 run-rate.

Section 5: Patient Voice & Patient-Reported Outcome Synthesis

This section centers the people these therapies are for. It synthesizes published patient-reported outcome (PRO) data used in and around these programs, and the documented positions of patient organizations — because the single strongest finding of this landscape is that programs which understood what patients actually experience designed better trials. Instruments are catalogued in pro_instruments.csv.

5.1 Why patient voice is not optional here

Every therapy in this landscape treats a disease where **the patient's lived experience is the efficacy signal**. In celiac disease and EoE the regulatory endpoint *is* a patient-reported symptom measure. The field learned — sometimes the hard way — that you cannot design a credible trial without first understanding, in patients' own words, what the disease feels like and what relief would mean to them.

5.2 Celiac disease — the richest PRO story, and a cautionary one

What the Nexvax2 program taught the field about patients. Nexvax2 used the **CeD PRO** (Celiac Disease Patient Reported Outcome), a 0–10 symptom scale whose Total-GI domain was the Phase 2 *primary endpoint*. In building and running it, the program produced a genuinely important patient-experience finding: **nausea and vomiting — not diarrhea — are the most common acute symptoms of gluten exposure**, accompanied by systemic cytokine release specific to celiac patients. This reshaped how the field thinks about what a "gluten reaction" is.

But the PRO also exposed a design trap. Because a gluten-free diet is the only management option and yet **intestinal injury and acute cytokine-release reactions persist despite it**, patients live with ongoing, unpredictable symptoms. When Nexvax2 (the peptide *is* gluten) was dosed, it could itself provoke the very symptoms the PRO was measuring — and the trial could not separate drug reactogenicity from lack of protection. The lesson, in patients' experiential terms: *a therapy made of the*

offending antigen must prove it does not simply reproduce the misery patients already know.

The instrument ecosystem is mature. Six validated PRO/HRQoL instruments exist for celiac (CeD PRO, CDSD/CDSD 2.1, CD-QOL, CSI, CDAQ, CD-GSRS), several FDA/EMA-reviewed. The CD-QOL was validated in **453 US adults through the iCureCeliac patient-powered research network** — patients literally built the evidence base. A recurring patient-reported theme: **the burden of the gluten-free diet itself** (social limitation, vigilance, anxiety) is a major quality-of-life driver independent of symptoms — captured in dedicated scales like the Impact of Adhering to a Gluten-Free Diet Questionnaire.

5.3 Type 1 diabetes — patient organizations drove the screening agenda

In T1D the pivotal endpoints are biomarker-based (C-peptide) or clinical (time-to-diagnosis), so PRO plays a supporting role — but the **patient-advocacy voice was decisive in a different way**: patient organizations (JDRF, now Breakthrough T1D) built and championed the **autoantibody-screening infrastructure** that makes teplizumab usable at all. Because Tzield can only help someone identified in presymptomatic Stage 2, the entire value of the drug depends on screening programs that advocacy groups pushed into existence.

Patient-experience concerns documented around T1D immunotherapy: **anxiety of "knowing but waiting"** (being told you will likely develop a disease years before it arrives), the **burden of 14 daily infusions in an asymptomatic person**, and equity concerns that screening access is uneven. The Canadian reimbursement review explicitly recorded patient-group input on these points.

5.4 EoE — patient voice is already codified in the regulatory pathway

For EoE the patient voice is not aspirational — it is **built into FDA guidance**. FDA's *Eosinophilic Esophagitis: Developing Drugs for Treatment* requires **co-primary endpoints: a patient-reported symptom measure (dysphagia, via a validated COA such as the DSQ) AND histologic response**. Dysphagia is the dominant

patient-reported symptom in adolescents and adults and was specifically identified for the COA co-primary.

Patient-organization voice in EoE is active and organized: - **APFED** (American Partnership for Eosinophilic Disorders) co-authored the **Global EoE Position Paper (May 2025)** and successfully advocated for disease-specific **ICD-10 codes** — concrete infrastructure wins. - APFED + AGA launched a joint **World EoE Day** awareness campaign (2026) framing EoE as a disease where *"something as routine as eating [can] feel difficult, and at times, unsafe."* - **CURED** (Campaign Urging Research for Eosinophilic Disease) and APFED are named as recruitment/awareness partners for EoE trials, alongside the CEGIR (US) and EUREOS (Europe) research consortia.

What EoE patients say matters (from the codified patient-experience record): food impaction and the fear of choking; the social isolation of not being able to eat normally; the burden and invasiveness of repeated endoscopies; the progression to fibrostenosis (irreversible narrowing) if untreated; and — for the many diagnosed as children — a lifetime of disease management. These are the lived priorities any EoE pMHC vaccine must speak to.

5.5 Cross-disease patient-priority synthesis

Common threads across celiac, T1D, and EoE patient voices — the requirements an antigen-specific therapy must satisfy to be *wanted*, not just approved:

1. **Reduce the daily vigilance burden.** In all three diseases the avoidance/monitoring regimen (gluten-free diet, glucose monitoring, food elimination) is itself a dominant quality-of-life cost. A therapy that *relaxes* that vigilance is worth more than one that only moves a biomarker.
2. **Do not reproduce the disease to treat it.** The Nexvax2 experience is the patient-facing warning: a therapy built from the offending antigen must not deliver the symptoms patients fear (for EoE, this includes anaphylaxis risk with food allergens).
3. **Minimize procedural/administration burden**, especially for people who feel well (early/at-risk) or children.
4. **Make screening/eligibility accessible and equitable** — the companion diagnostic is a patient-access issue, not just a commercial one.

5. **Measure what patients feel, with instruments patients helped build.** The celiac iCureCeliac model and the EoE COA co-primary are the templates.

These five priorities become the backbone of the EoE patient-survey instrument in Section 10.

Section 6: PFDD Meetings Inventory & Timing Analysis

The FDA's Patient-Focused Drug Development (PFDD) initiative — FDA-led public meetings (a defined 24-disease series under PDUFA V, 2013–2017) and the ongoing Externally-Led PFDD (EL-PFDD) program — is the formal mechanism by which patient experience enters drug development. This section inventories PFDD activity in each relevant disease area and, per your request, positions each event before / during / after the corresponding program's development. Details in pfdd_inventory.csv; timing is visualized in the PFDD-overlay figure.

> ***Accuracy note:*** *the FDA-led PFDD 24-meeting series (2013–2017) did* ***not*** *include dedicated type 1 diabetes or celiac meetings. Patient input in those areas came primarily through externally-led meetings and advocacy channels. Where a specific date could not be verified to the day it is marked approximate.*

6.1 The central timing finding

No patient-voice event demonstrably *preceded* the program it might have shaped. Across every disease area in this landscape, formal patient-experience input arrived *contemporaneously with or after* the pivotal development work — never before it. The programs were designed on scientists' and sponsors' hypotheses about what mattered; patient priorities were, at best, consulted mid-stream. This is the structural gap an EoE patient-led program can close.

6.2 Type 1 diabetes (Tzield, GAD-alum)

- **PFDD status:** No dedicated T1D meeting in the FDA-led 24-disease series. Patient input entered through **advocacy organizations (JDRF / Breakthrough T1D)** and diabetes clinical-outcome-assessment work, not a formal PFDD.
- **Timing vs. program:** Teplizumab's science was set in 2002–2019; the advocacy that shaped its *use* (autoantibody-screening infrastructure) matured around and

after approval (2022). **Patient voice shaped access more than design, and did so late.**

- **What patients had said mattered:** hypoglycemia fear, relentless daily management burden, and a strong desire for disease-modifying rather than purely glycemic therapies — priorities that the delay-of-onset indication happens to serve, but that were not the original design driver.

6.3 Celiac disease (Nexvax2, TAK-101, KAN-101)

- **PFDD status:** An **externally-led PFDD** for the celiac community (~2020, date approximate) plus a mature patient-powered research infrastructure (iCureCeliac).
- **Timing vs. program:** This is the sharpest lesson. The celiac EL-PFDD came **after Nexvax2 had already failed (2019)** and **during** the nanoparticle-platform trials. Had the patient-articulated priorities — persistent symptoms despite diet, the specific symptom concepts, the burden of vigilance — been formally captured *before* Nexvax2's Phase 2, the endpoint and reactogenicity problems that sank it might have been anticipated.
- **Patient priorities recorded:** non-dietary therapy that genuinely relaxes the gluten-free-diet burden; symptom concepts that map to what patients feel (the nausea/vomiting finding); trust and safety of an antigen-based approach.

6.4 Eosinophilic esophagitis — the whitespace

- **PFDD status: No dedicated EoE FDA-led or externally-led PFDD meeting was identified** as of the data cutoff. Instead, EoE patient voice is codified in two other ways: (i) **FDA's EoE drug-development guidance**, which mandates a patient-reported dysphagia **symptom COA as a co-primary endpoint** alongside histology; and (ii) **APFED-led advocacy** (Global EoE Position Paper 2025, ICD-10 codes, World EoE Day).
- **Timing vs. a pMHC program:** there is no pMHC EoE program yet — so **a patient-led EoE pMHC effort could, uniquely in this landscape, put patient voice FIRST**, before the trial is designed. The adjacent **HES EL-PFDD (~2018, APFED)** is the closest existing template and a natural partner.

6.5 Multiple sclerosis (ATX-MS-1467)

- **PFDD status:** MS patient input via community/advocacy channels (~2017, approximate); ATX-MS-1467's Phase 2 read out in 2018 — approximately contemporaneous. The program stopped before patient priorities could meaningfully iterate its design.

6.6 Implication for the EoE program

The timing analysis converts directly into a strategic recommendation: **because EoE has no dedicated PFDD and no pMHC program, an EoE pMHC vaccine effort has the rare opportunity to invert the field's historical sequence — capturing patient needs, interest, and concerns *before* designing the trial.** The follow-on patient survey (Section 10) is the first instrument of that inversion, and partnering with APFED/CURED to convene an EoE (or eosinophilic-GI) EL-PFDD would formalize it.

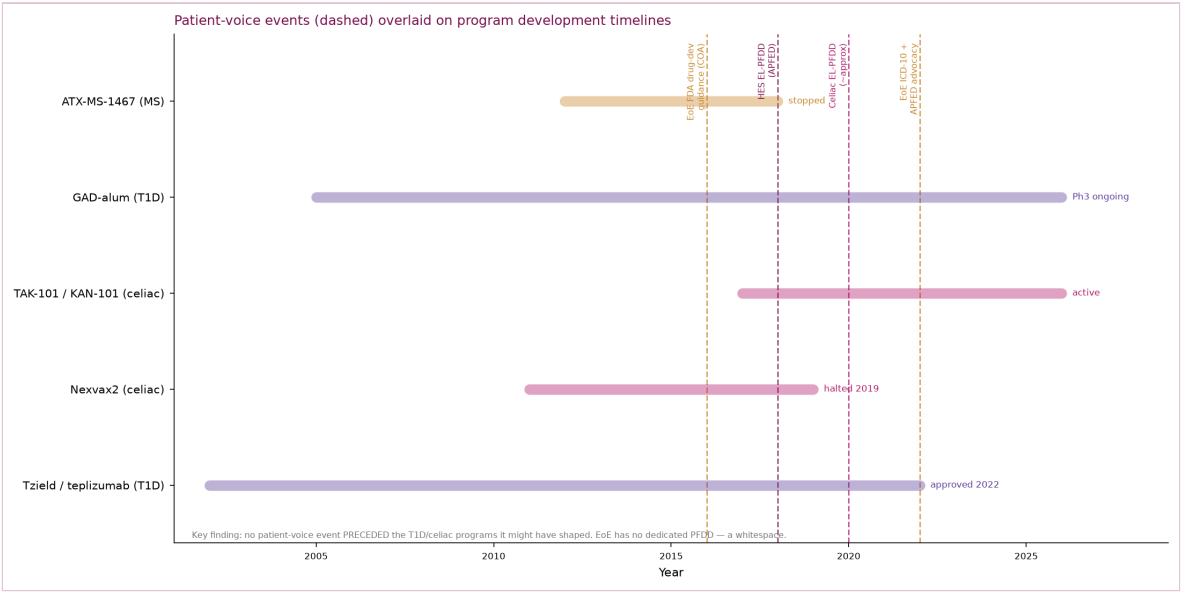

Figure 4. Patient-voice events (dashed) overlaid on program development timelines. No patient-voice event precedes the program it might have shaped; EoE has no dedicated PFDD.

Section 7B: Regulatory Pathways and Precedent

An antigen-specific or pMHC-based vaccine for eosinophilic esophagitis (EoE) will not be evaluated in a regulatory vacuum. It follows a trail already blazed by Tzield (teplizumab) in type 1 diabetes, KAN-101 in celiac disease, and dupilumab in EoE itself — and it will need to navigate the same categorical tension that has shaped each of those programs: how to credential a disease-modifying, immune-mediated mechanism to a regulator whose institutional muscle memory is built around symptom relief. The strategic lessons are as much about endpoint architecture and diagnostic infrastructure as they are about designation-seeking.

Expedited-Program Options

The FDA's toolkit for immune-mediated and antigen-directed therapies offers several non-mutually-exclusive routes, each with different evidentiary triggers:

- **Breakthrough Therapy Designation (BTD)** requires preliminary clinical evidence that the drug may offer substantial improvement over available therapy on a clinically significant endpoint. Tzield's BTD was anchored in delay-of-onset data — a hard, objective endpoint — and the designation bought it intensive FDA interaction and rolling review. An EoE pMHC vaccine would need analogous early signal, most plausibly a biomarker or histologic effect size that credibly predicts downstream symptomatic and structural benefit.
- **Fast Track**, already granted to KAN-101 in celiac disease, is the lower-bar entry point: it requires only that the drug address an unmet need in a serious condition, with nonclinical or mechanistic rationale sufficient to open rolling submission and more frequent FDA touchpoints. This is the more realistic near-term target for an EoE antigen-specific program prior to human proof-of-concept.
- **Orphan Drug Designation** is available if the sponsor's target EoE population (e.g., a specific pMHC/allele-restricted subgroup) is defined narrowly enough to fall under prevalence thresholds — a strategic choice with downstream consequences for label breadth and market exclusivity.
- **Accelerated Approval**, built around a surrogate reasonably likely to predict clinical benefit, is the pathway most structurally suited to an antigen-specific

vaccine, since immunologic desensitization or antigen-specific tolerance biomarkers are unlikely to constitute a direct measure of clinical benefit on first pass.

- **RMAT** designation, though built for cell and gene therapies, extends to some regenerative and reprogramming immunotherapies; whether a pMHC-based tolerizing vaccine qualifies depends on how the mechanism is characterized (durable immune reprogramming vs. repeat-dosed biologic), and is worth testing with FDA early rather than assuming.

None of these designations substitutes for endpoint strategy; they accelerate interaction and review timelines but do not lower the evidentiary bar for approval itself.

Endpoint Selection Lessons

Tzield's approval rested on a single, objective, disease-modification endpoint — time to Stage 3 (clinical) diabetes in an at-risk, autoantibody-positive population. That endpoint worked because it was unambiguous, hard, and directly tied to an accepted natural history model of disease staging. It did not require the FDA to accept a subjective patient-reported measure as sufficient on its own.

Celiac disease illustrates the opposite failure mode. There is no approved drug for celiac disease and no FDA-endorsed single primary endpoint. Nexvax2's reliance on protection from symptoms induced by a gluten challenge proved to be a fragile foundation — symptom response to acute challenge is noisy, driven by heterogeneous mechanisms (some non-immune), and does not cleanly map onto the chronic, cumulative mucosal injury that defines the disease. The lesson for EoE is that a symptom-only or challenge-only endpoint, chosen for trial convenience, invites exactly the kind of endpoint controversy that has stalled celiac drug development for over a decade.

EoE sits closer to Tzield than to Nexvax2 in one respect (an objective histologic correlate exists) but is bound by its own disease-specific guidance in a way neither precedent fully anticipated.

The Co-Primary Challenge for EoE

FDA's EoE-specific guidance requires co-primary endpoints: a validated patient-reported dysphagia/symptom instrument (such as a DSQ-type measure) together with histologic response, defined as reduction in peak eosinophil count on esophageal biopsy. Dupilumab's 2022 EoE approval demonstrates that this dual bar is clearable, but it also demonstrates the operational burden — the pivotal program had to show statistically robust separation on both a subjective, patient-experienced axis and an objective, biopsy-

dependent axis simultaneously, with neither endpoint permitted to compensate for a shortfall in the other.

For an antigen-specific pMHC vaccine, this is a materially harder co-primary problem than for a broad anti-inflammatory biologic like dupilumab. An antigen-specific mechanism may plausibly produce durable histologic and immunologic change on a delayed timeline relative to symptom improvement — tolerization is not degranulation blockade, and eosinophil count normalization may lag or lead symptom resolution depending on mechanism of action. Trial designs will need to prespecify a timepoint (or multiple timepoints) at which both axes are assessed, and sponsors should engage FDA early on whether histologic remission alone, in a population with prior objective diagnosis, can serve as a registration-enabling surrogate under Accelerated Approval with dysphagia-symptom confirmation as a post-marketing requirement — an approach that would borrow Tzield's disease-modification logic while still respecting EoE's guidance-mandated symptom axis.

Companion Diagnostic Strategy

A pMHC-restricted vaccine is inherently genotype-dependent: efficacy is only interpretable, and possibly only present, in patients carrying the relevant HLA allele(s). This makes a companion diagnostic not an optional commercial add-on but a regulatory precondition — analogous to HLA-restricted therapies in other indications where label and diagnostic are co-reviewed. Three strategic issues follow. First, the diagnostic development timeline must run in parallel with, not behind, clinical development, since late-stage trials will need prospective HLA-based enrollment or stratification to generate a clean efficacy signal in the labeled population. Second, sponsors must decide early whether to pursue a single-allele label (narrower population, cleaner effect size, easier orphan-drug qualification) or a multi-allele panel (broader reach, more complex diagnostic and statistical burden). Third, the commercial and access implications of a mandatory genetic screen — testing infrastructure, payer coverage of the companion diagnostic, and equitable access across populations with variable HLA allele frequency — should be modeled well before Phase 3, since diagnostic bottlenecks have historically slowed launch uptake for genotype-restricted therapies more than the therapeutic approval itself.

Proposed Regulatory Roadmap for an EoE pMHC Vaccine

A phase-appropriate strategy, informed by the precedents above, would proceed as follows:

- **Phase 1 (safety/pharmacodynamics):** Establish safety and tolerability in HLA-genotyped participants; use this stage to generate the preliminary mechanistic and biomarker evidence needed to support a Fast Track (and potentially Breakthrough) designation request, and to open early dialogue with FDA on endpoint architecture and companion diagnostic co-development.
- **Phase 2 (biomarker plus symptom signal):** Enroll genotype-stratified patients; assess peak eosinophil count change alongside a validated dysphagia/symptom instrument to generate the dose-response and effect-size data needed to negotiate the Phase 3 co-primary or Accelerated Approval structure, and to test timepoint assumptions about the relative kinetics of histologic versus symptomatic response.
- **Phase 3 (progression/co-primary confirmation):** Design around FDA's mandated co-primary framework (histology plus patient-reported symptom outcome), while incorporating a longer-term disease-modification or progression endpoint — analogous in spirit to Tzield's delay-of-onset model — to differentiate an antigen-specific tolerizing mechanism from symptom-suppressing standard of care, with companion diagnostic validation completed in parallel to support simultaneous drug/diagnostic filing.

Engagement with EMA under PRIME should track this same staged logic; Tzield's progression through EMA's PRIME scheme (with EU marketing authorization anticipated around 2026) suggests that disease-modification and delay-of-onset framing can be credentialed under EMA's parallel expedited scheme, making transatlantic alignment on endpoint definitions — particularly around what constitutes an acceptable co-primary or surrogate structure for EoE — a priority for sponsor engagement well before pivotal trial design is locked.

Section 8: Cross-Program Synthesis, Whitespace & EoE Strategic Implications

This section integrates the five evidence streams — origins, trials, results, patient voice, PFDD timing — into a strategy for an EoE peptide-MHC (pMHC) vaccine. It is written for decision-making: each lesson maps to a concrete EoE design choice.

8.1 The landscape in one matrix

The landscape matrix figure plots every program on two axes — **clinical stage reached** (preclinical → approved) and **mechanistic fidelity to a true pMHC vaccine** (anti-CD3 → antigen+adjuvant → peptide/nanoparticle → pMHC complex) — with marker size encoding **patient-input maturity**. Three facts jump out:

1. **The only approved agent (Tzield) has the *lowest* mechanistic fidelity** — it is antigen-nonspecific. Approval was won on regulatory strategy (delay-of-onset in an at-risk population), not on antigen specificity.
2. **The clinically-advanced antigen-specific programs cluster at peptide/nanoparticle fidelity, Phase 2** (Nexvax2, TAK-101, KAN-101, ATX-MS-1467) — proving the *modality* can enter mid-stage trials.
3. **The high-fidelity pMHC corner at clinical proof-of-concept is empty.** Navacim (the truest pMHC platform) sits at preclinical. **No true pMHC therapeutic has demonstrated clinical efficacy in any disease.** This is the whitespace an EoE pMHC vaccine would enter — high scientific novelty, high risk, no direct competitor.

8.2 Competitive whitespace for EoE specifically

- **No antigen-specific tolerance therapy exists for EoE.** The approved/late EoE pipeline is anti-inflammatory biologics (dupilumab, approved 2022; and IL-5/IL-13 agents) — they suppress eosinophilic inflammation but **do not induce antigen-specific tolerance** and require indefinite dosing. A tolerance vaccine is mechanistically differentiated.

- **The EoE antigen problem is the central scientific risk and the central opportunity.** Unlike celiac (one antigen, gluten) or T1D (defined autoantigens), EoE is driven by **multiple, patient-variable food allergens** (milk, wheat, egg, soy most common). A pMHC vaccine must decide: single dominant allergen, personalized allergen panel, or a shared-epitope strategy. This is where the project's EoE omics + pMHC/HLA analysis streams feed directly in.
- **No dedicated EoE PFDD and no pMHC EoE program** = the chance to make EoE the first indication where **patient voice precedes trial design**.

8.3 The transferable lessons, mapped to EoE design decisions

#	Lesson (source program)	EoE pMHC design decision
1	Lead with a validated pharmacodynamic tolerance biomarker (TAK-101 succeeded, Nexvax2 didn't)	Define an EoE tolerance PD marker (e.g., allergen-specific T-cell / esophageal eosinophil / cytokine readout) and validate it **before** betting on a symptom endpoint
2	A therapy made of the antigen can reproduce the disease (Nexvax2)	For food allergens, **anaphylaxis/reactogenicity risk is paramount** — favor a tolerogenic delivery context (pMHC scaffold, nanoparticle, liver-targeting) over bare allergen peptide; build in dose-escalation safety
3	Redefine population toward early/at-risk (Tzield TN-10 approval)	Consider **early / pre-fibrostenotic EoE** or newly-diagnosed pediatric EoE, where tolerance induction is most plausible, rather than established fibrostenotic disease
4	HLA/genetic responder stratification rescued a failed antigen (GAD DIAGNODE)	Build **HLA typing + allergen-sensitization stratification** into the trial from Phase 1 — directly enabled by the project's pMHC/HLA analysis
5	Delay-of-progression is an approvable endpoint (Tzield)	An EoE endpoint of **preventing progression to fibrostenosis** may be more attainable and payer-relevant than symptom cure
6	Screening/companion-diagnostic is the real access bottleneck (Tzield)	Co-develop and fund the **allergen/HLA screening pathway**; partner with patient orgs to build it
7	Administration burden gates adoption in asymptomatic patients (Tzield 14 infusions)	Design for **few doses, outpatient, low-burden route** — a core question for the patient survey
8	Patient voice arrived too late everywhere (PFDD timing)	Put the **EoE patient survey and an EL-PFDD FIRST**, before trial design

8.4 Risk register

Risk	Severity	Mitigation
Antigen heterogeneity — no single dominant EoE allergen	High	Omics-driven epitope prioritization; personalized or multi-allergen pMHC; start with milk/wheat-dominant subset
Anaphylaxis / reactogenicity from allergen exposure	High	Tolerogenic delivery (pMHC NP), dose-escalation, exclusion of high-anaphylaxis-risk patients early
No validated tolerance PD biomarker for EoE	High	Biomarker-first development; leverage esophageal histology + allergen-specific T-cell assays
pMHC modality unproven clinically anywhere	Med-High	De-risk with Navacim/celiac-NP read-across; strong preclinical package
Symptom-COA co-primary is demanding (FDA EoE guidance)	Medium	Early COA strategy; PRO instrument co-designed with patients
Slow adoption / screening bottleneck (Tzield precedent)	Medium	Companion-diagnostic + patient-org access partnership from day one
Small addressable early-disease population	Medium	Health-economic case built on preventing fibrostenosis/ endoscopy burden

8.5 The strategic thesis

An EoE pMHC vaccine would be the first true peptide-MHC therapeutic to pursue clinical proof-of-concept, in an indication with no antigen-specific competitor and no prior patient-voice capture. Its success probability is maximized by doing what the winners did and avoiding what the losers did: lead with a validated tolerance biomarker, deliver allergen in a tolerogenic (non-reactogenic) context, stratify by HLA/sensitization, target early disease with a progression-prevention endpoint, co-build the screening pathway — and, uniquely, capture patient needs and concerns *before* designing the trial. That final step is the follow-on survey.

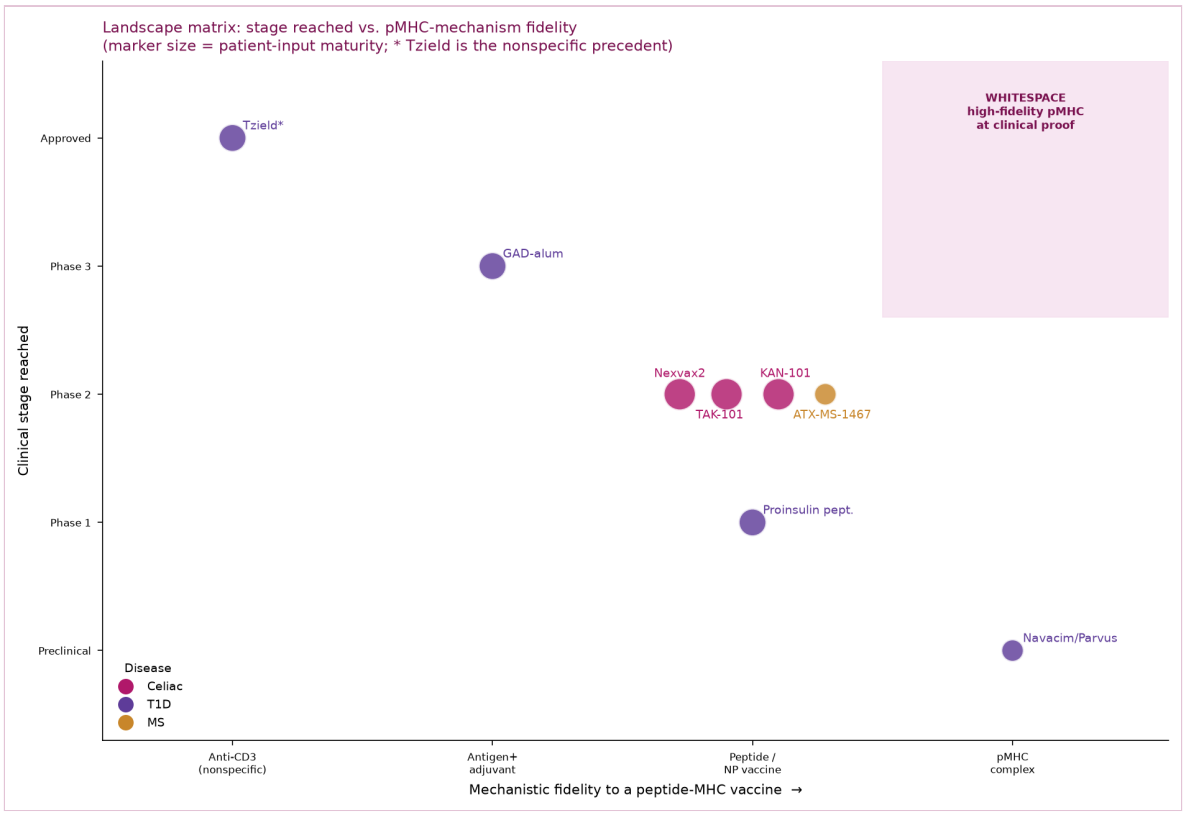

Figure 5. Landscape matrix — clinical stage reached vs. mechanistic fidelity to a pMHC vaccine; marker size = patient-input maturity. The high-fidelity/clinical-proof corner is empty (whitespace).

Section 8B: The Broader EoE Competitive Pipeline

Standard of Care Today

Eosinophilic esophagitis is currently managed with a small set of tools that either reduce acid exposure, suppress local inflammation, remove inciting antigens from the diet, or blunt a specific cytokine signal — none of which address the underlying antigen-driven immune response.

Proton pump inhibitors (PPIs) remain a first-line intervention, reflecting the substantial overlap between EoE and acid-mediated esophageal pathology and the fact that a meaningful subset of patients achieve histologic remission on PPI therapy alone, likely through effects on epithelial barrier function and cytokine signaling rather than acid suppression per se. Swallowed topical corticosteroids are a second pillar: budesonide oral suspension (marketed as EOHILIA) has received formal regulatory approval for EoE, and fluticasone delivered via inhaler-swallowed technique is widely used off-label. Both approaches suppress local eosinophilic and Th2-driven inflammation but require ongoing administration to maintain effect. Dietary elimination therapy — empiric or targeted removal of common trigger foods (milk, wheat, egg, soy, and others) — offers a non-pharmacologic route to remission by removing the antigenic trigger itself, but it is burdensome, requires sequential food reintroduction and repeat endoscopy/biopsy to identify triggers, and adherence is a persistent challenge.

The most significant recent addition to this landscape is dupilumab (Dupixent), an anti-IL-4Rα monoclonal antibody that blocks both IL-4 and IL-13 signaling. Its approval for EoE in 2022 marked the first biologic sanctioned for this indication and validated the Th2 axis as a druggable target in EoE. Dupilumab is administered as a chronic injectable therapy; like the other standard-of-care options, it manages disease activity rather than resolving the underlying antigen-specific immune drive.

The Biologic Wave

Dupilumab's approval has catalyzed a broader wave of biologic development aimed at various nodes of the type 2 inflammatory cascade implicated in EoE pathogenesis. These programs share a common conceptual architecture: identify a cytokine or receptor upstream or downstream of the eosinophil/Th2 axis and block it systemically.

Anti-IL-5 and anti-IL-5 receptor agents (mepolizumab and benralizumab, respectively) target eosinophil survival and maturation directly; both have been investigated in eosinophilic gastrointestinal diseases, including EoE, given the centrality of eosinophils to tissue pathology, though their role and positioning relative to dupilumab in EoE specifically continues to evolve. Anti-IL-13 approaches, such as cendakimab, aim at the cytokine most directly implicated in esophageal epithelial remodeling and eotaxin-3 induction. Anti-TSLP strategies target further upstream, at the epithelial alarmin thought to initiate the type 2 cascade in response to allergen or irritant exposure — an approach with precedent in asthma that is being explored in eosinophilic esophageal disease. Anti-Siglec-8 therapy (lirentelimab) has been studied in EoE and related eosinophilic GI disorders as a mechanism to deplete or inhibit eosinophils and mast cells directly, with results across this program's trials described as mixed; its ultimate role in EoE, if any, remains unsettled. Sphingosine-1-phosphate (S1P) receptor modulators, which limit lymphocyte trafficking, represent a further mechanistic category under exploration, drawing on precedent from inflammatory bowel disease and other immune-mediated conditions. For several of these agents, EoE-specific development status, trial outcomes, and regulatory pathways remain in flux, and this section does not assert specific results or approval timelines beyond what is well established for dupilumab and the topical/PPI standard of care.

What None of Them Do: The Tolerance Gap

Despite mechanistic diversity — spanning acid suppression, corticosteroid-mediated immune suppression, cytokine blockade at multiple nodes, and eosinophil/mast cell depletion — every therapy described above shares a defining structural feature: it is anti-inflammatory, not tolerogenic. Each works by continuously suppressing a downstream or upstream node of the immune response, and none is designed to retrain the adaptive immune system's antigen-specific recognition of the food or environmental triggers that drive disease.

The practical consequence is that all of these therapies require indefinite dosing to maintain effect. Discontinuation — whether of a PPI, a topical steroid, an elimination diet, or a biologic — is typically followed by histologic and symptomatic relapse, because the underlying antigen-specific T cell and IgG4/IgE responses that perpetuate esophageal eosinophilic inflammation remain intact and are simply being masked or dampened rather than corrected. Elimination diets come closest to addressing antigen exposure directly, but they act by avoidance rather than by inducing tolerance, and they carry no mechanism for enabling a patient to safely reintroduce a trigger food.

This is the whitespace: no approved or late-stage EoE therapy today is designed to induce durable, antigen-specific immune tolerance. The field has developed an increasingly sophisticated toolkit for suppressing the consequences of the immune response, but nothing that addresses its cause at the level of antigen-specific T cell education.

Positioning a pMHC Vaccine

An antigen-specific pMHC-based vaccine approach occupies a category distinct from every therapy described above: it is positioned as disease-modifying rather than chronic-suppressive. Rather than continuously blocking a cytokine or depleting an effector cell population, the intent is to re-educate the antigen-specific T cell response directly, with the goal of durable remission that persists after dosing is reduced or stopped — the inverse of the relapse-on-discontinuation pattern that characterizes the current standard of care and the biologic pipeline alike.

This positioning also suggests combination and sequencing opportunities rather than pure substitution. A pMHC vaccine could plausibly be introduced after biologic- or steroid-induced remission, using anti-inflammatory therapy to quiet active eosinophilic disease while the tolerizing intervention re-shapes the underlying antigen-specific response, with anti-inflammatory agents subsequently tapered as tolerance is established. This complementary framing — chronic-suppressive therapy for induction, antigen-specific therapy for durable maintenance — differentiates the mechanism from a head-to-head competitive threat to dupilumab or the emerging biologics, and instead frames it as addressing the one gap none of them were designed to close.

Section 9: The EoE Patient Journey — Why This Program Exists

Every disease has a clinical narrative and a lived one. For eosinophilic esophagitis, those two stories rarely match. The clinical narrative is a chronic, immune-mediated inflammatory condition of the esophagus, driven largely by food antigens, characterized by eosinophilic infiltration of the esophageal mucosa. The lived narrative is years spent learning how to eat around a body that has turned swallowing into something that must be managed rather than trusted. This program exists because those two narratives need to be brought closer together, and because our team includes people for whom that gap is not theoretical.

The Odyssey to Diagnosis

For many patients, the path to an EoE diagnosis is long and indirect. Children may present with feeding difficulty, food refusal, or failure to thrive — symptoms that are easy to misattribute to picky eating or reflux. Adolescents and adults more often present with dysphagia and, in a substantial number of cases, an episode of food impaction requiring emergency intervention. Because these symptoms overlap with far more common conditions, and because EoE is confirmed only through esophageal biopsy at endoscopy, diagnosis is frequently delayed by years and often follows multiple procedures — each requiring sedation, each a small ordeal in its own right, each layered onto the anxiety of not knowing what is wrong.

Living With a Disease That Is Managed, Not Cured

Once diagnosed, patients face a treatment landscape that is genuinely effective for many but fundamentally incomplete. Proton pump inhibitors, swallowed topical corticosteroids, food elimination diets, and biologic therapy such as dupilumab can each reduce eosinophilic inflammation and improve symptoms. But none of these approaches is curative. They require ongoing adherence — daily medication, repeated food reintroduction trials, or continued injections — and inflammation and symptoms typically return when treatment stops. Elimination diets, while drug-free, carry their own burden: they demand vigilance at every meal, complicate social eating, and often require serial endoscopies to test whether a reintroduced food is tolerated. Patients are, in effect, asked

to manage this disease indefinitely, with periodic biopsies to confirm that the management is still working.

Left inadequately controlled over time, chronic esophageal inflammation can progress to fibrostenotic disease — strictures and narrowing of the esophagus caused by tissue remodeling that does not reverse with anti-inflammatory treatment alone. This is why patients so often describe not just current symptoms but a quieter, ongoing fear of this disease's future: the possibility of needing esophageal dilation, a mechanical procedure to stretch a narrowed esophagus, sometimes repeatedly, sometimes for the rest of one's life.

The Burden That Doesn't Show Up in a Biopsy

None of this captures what EoE actually feels like day to day. Patients describe learning to chew every bite an unusual number of times, avoiding foods by texture rather than taste, drinking liquid with every mouthful, and quietly watching how fast others at the table are eating so as not to fall behind or draw attention. Meals — ordinarily a site of connection — can become a site of vigilance. Many patients limit restaurant dining, travel, or social occasions built around food, not because they cannot manage their disease but because managing it in public is exhausting. Anxiety around choking or impaction is common and rational, given how many patients have experienced it. This is a disease that asks for constant, low-grade attention, meal after meal, for life.

Why an Antigen-Specific Tolerance Approach Matters

Current therapies work by suppressing or blocking the downstream inflammatory response. An antigen-specific tolerance vaccine takes a different aim: retraining the immune system's response to the specific food antigens driving disease, rather than continuously countering the inflammation those antigens provoke. If successful, such an approach could offer something patients consistently say they want most — not just fewer symptoms, but less vigilance. Fewer doses, delivered less frequently than a daily pill or biologic injection, addressing a cause rather than only a consequence, could mean fewer moments of the day organized around managing disease.

That promise is also why patients cannot be a downstream audience for this work. The symptoms worth measuring, the outcomes worth calling success, the burden of a trial's endoscopy schedule, the real-world meaning of "improvement" — these are things patients understand from the inside in ways that no amount of external consultation replaces. Involving patients at every stage of development, from trial design through

outcome selection to eventual delivery, is not a gesture. It is how this program stays honest about what it is actually trying to fix.

Section 10: EoE pMHC-Vaccine Patient Survey — Design Plan & Instrument Blueprint

Purpose and guiding principles (patient-partnership-first)

This section commits the working group to a concrete next step: fielding a patient survey to ground pMHC (peptide-MHC) tolerance vaccine development for eosinophilic esophagitis (EoE) in the lived experience of the people it is meant to serve, rather than in assumptions made on their behalf. The lead investigator's own standing as an EoE patient is not incidental to this plan — it is the organizing principle. Every design choice below follows from a single conviction: instruments and development pathways built without patients at the table tend to measure what is convenient to measure, not what patients experience as burden, risk, or benefit.

Four principles govern this design:

1. **Nothing about us without us.** Patients and caregivers co-design the instrument, not merely respond to it. Draft items in this document are a starting point for patient-advisor revision, not a final survey.
2. **Anchor to lessons already paid for.** The Nexvax2 experience (a celiac gliadin-peptide immunotherapy halted after triggering allergic-type reactions in trials) and the Tzield post-market adoption problem (14 daily IV infusions proving a hard sell to asymptomatic at-risk individuals) are treated as empirical priors, not hypotheticals. This survey is designed to detect analogous failure modes for EoE — especially anaphylaxis risk from food-antigen-derived peptides and schedule/route burden — before they are designed into a program.
3. **Measure what patients feel, using tools patients helped build.** Wherever validated instruments exist (DSQ, EEsAI, PROMIS), we anchor to them for comparability and regulatory relevance. Where they do not — patient willingness to accept anaphylaxis risk in exchange for reduced avoidance burden, for instance — we build new items transparently and iteratively.
4. **This is a companion, not a replacement, for a formal Patient-Focused Drug Development (PFDD) meeting.** No dedicated EoE PFDD currently exists. This survey generates the quantitative and qualitative substrate that can seed one, convened jointly with APFED and CURED.

Nothing in this document constitutes medical advice, and no item here is final; all items require review by the patient advisory panel and IRB approval before fielding.

Research questions

1. What is the current burden of EoE and its management (dietary, endoscopic, pharmacologic) as patients themselves rank it?
2. How well do patients understand the concept of a pMHC/antigen-based tolerance vaccine, and what explanatory framing is needed for informed response?
3. What efficacy profile (symptom relief vs. histologic remission vs. diet liberalization) would patients consider worth pursuing, and what is the minimum acceptable benefit?
4. What routes, schedules, and administration burdens are patients willing to tolerate, and how does this vary by symptom severity and life stage (child, adolescent, adult)?
5. What level of risk — particularly anaphylaxis and other immune-mediated reactions — are patients willing to accept, and how does this trade off against potential benefit?
6. How does prior treatment history (biologics, steroids, diet elimination, dilation) shape fatigue, trust, and willingness to enroll in novel trials?
7. What information, consent processes, and trust-building steps do patients need before considering participation?
8. Is HLA-typing or other companion-diagnostic screening acceptable, and what equity barriers might it introduce?
9. What forms of ongoing involvement do patients want in the development pipeline itself?

Target population and sampling (incl. pediatric/caregiver considerations)

Target population: Individuals with a clinician-confirmed diagnosis of EoE (self-reported diagnosis acceptable with a confirmatory screening question), age 8 and up, across the disease spectrum — newly diagnosed, well-controlled, and refractory/fibrostenotic. Given that a large share of EoE patients are diagnosed in childhood, the sample must include both pediatric patients (via caregiver-assisted or caregiver-proxy response) and adults who were diagnosed as children, whose retrospective perspective on years of dietary and procedural burden is distinct and valuable.

Sampling strata: - Age at survey: child (8–12, caregiver-assisted), adolescent (13–17, assent + caregiver), adult (18+) - Age at diagnosis: pediatric-onset vs. adult-onset - Current disease control status: active symptoms vs. histologic/clinical remission - Current management: elimination diet only, topical steroids, biologic therapy, dilation history, combination - Geographic and sociodemographic diversity, with deliberate oversampling outreach to underrepresented racial/ethnic groups and lower-income/rural respondents, given known disparities in specialist access

Target sample size: Minimum n=400 adults and n=150 caregiver-proxy pediatric responses to support subgroup analysis (informed by prior EoE registry survey response patterns); powered as a descriptive/exploratory study, not a hypothesis-testing trial.

Caregiver considerations: For children under 13, caregivers complete the survey with the child; for adolescents 13–17, a dual instrument (adolescent self-report + caregiver report) captures both the patient's own risk tolerance and the caregiver's, since these may diverge meaningfully on questions like anaphylaxis risk acceptance.

Recruitment strategy (patient organizations: APFED, CURED; clinical networks: CEGIR)

Recruitment will be led by trusted patient-community channels rather than cold clinical outreach, consistent with the patient-partnership principle:

- **APFED (American Partnership for Eosinophilic Disorders):** primary distribution partner via newsletter, member portal, and social channels; APFED's existing patient registry (if consented for research contact) as a sampling frame.
- **CURED Foundation:** parallel distribution, particularly valuable for reaching pediatric-diagnosed and caregiver populations given CURED's family-support focus.
- **CEGIR (Consortium of Eosinophilic Gastrointestinal Disease Researchers):** clinical-site recruitment through participating academic centers, providing a clinically-verified (vs. self-reported) diagnosis subgroup and access to patients with more severe/refractory disease who may be underrepresented in patient-organization-driven samples.
- **Snowball and social recruitment:** shareable survey link with plain-language explainer video, encouraging forwarding within patient communities.
- **Incentive design:** modest, equitable incentive (e.g., gift card) to reduce participation burden without being coercive, reviewed by IRB for appropriateness across income levels.

All recruitment materials will be drafted with patient advisors and will disclose the survey's purpose, sponsor, voluntary nature, and data use plainly before consent.

Survey domains and sample items

All items below are illustrative drafts for patient-advisor and IRB revision — not a final instrument.

Domain 1: Disease and treatment burden / current experience 1. In the past month, how often did swallowing difficulty (dysphagia) affect what or how you ate? (Never / Rarely / Sometimes / Often / Every day) 2. How much does fear of a food getting stuck (impaction) affect your food choices? (Not at all — A great deal, 5-point Likert) 3. Rank the following burdens from most to least disruptive to your daily life: dietary restriction, fear of food impaction, endoscopy frequency, medication routine, symptom unpredictability. 4. In the past year, approximately how many upper endoscopies have you had? (0 / 1 / 2 / 3 / 4+) 5. Open text: "Describe, in your own words, what living with EoE costs you day to day."

Domain 2: Understanding of the pMHC/tolerance vaccine concept 1. Before today, had you heard of a "tolerance vaccine" or antigen-based immunotherapy approach for allergic or immune conditions? (Yes / No / Not sure) 2. After reading the plain-language explanation provided, how clear is your understanding of how this approach is intended to work? (1=Not at all clear – 5=Very clear) 3. What questions do you still have about how this type of treatment would work? (open text)

Domain 3: Efficacy expectations and acceptable outcomes 1. If a treatment reduced your swallowing symptoms but did not fully normalize esophageal tissue (histology), would you consider that worthwhile? (Yes / No / Depends on degree of symptom relief) 2. Which outcome matters most to you personally? (Choose one: fewer swallowing symptoms / ability to eat previously avoided foods / fewer endoscopies / reduced medication use / normal biopsy results) 3. What is the minimum symptom improvement that would make ongoing treatment worth it to you? (0–25% / 25–50% / 50–75% / 75–100% improvement)

Domain 4: Route and schedule tolerance 1. Which administration route would you find most acceptable? (Oral pill / Under-the-skin injection / IV infusion in a clinic / Patch or skin-based / No preference) 2. If effective, how many clinic visits per year would you be willing to accept for treatment administration? (1–2 / 3–6 / 7–12 / more than 12 / none — would require self-administration only) 3. Would a multi-dose induction schedule (e.g.,

several visits in the first month) affect your willingness to start treatment? (Yes, less willing / No effect / Yes, more willing) with open-text follow-up on why.

Domain 5: Risk tolerance, including anaphylaxis and immune-related risk 1. How concerned would you be about a treatment made from the same food-protein fragments that trigger your EoE causing an allergic reaction, including anaphylaxis? (Not at all concerned – Extremely concerned, 5-point) 2. What is the highest level of risk of a serious allergic reaction you would accept in exchange for a meaningful reduction in your EoE symptoms? (No added risk / Small risk, e.g., similar to routine allergy shots / Moderate risk, requiring in-clinic monitoring / Would accept regardless of risk level / Not sure) 3. Would you want treatment administered only in a setting equipped to treat anaphylaxis (e.g., clinic with emergency equipment), even if less convenient? (Yes / No / Depends) 4. Open text: "What would make you feel a new treatment was being tested safely?"

Domain 6: Prior-treatment history and fatigue 1. Which treatments have you tried for EoE? (checklist: elimination diet, topical/swallowed steroids, biologic injection, dilation procedure, other) 2. How many different treatment approaches have you tried in total? (1 / 2–3 / 4–5 / 6+) 3. How "burned out" do you feel by ongoing EoE management and trying new treatments? (1=Not at all – 5=Extremely) 4. Has treatment fatigue ever led you to stop or delay a recommended treatment or trial participation? (Yes / No / Prefer not to say)

Domain 7: Trust, consent, and information needs 1. How much do you trust that a new EoE treatment developed from research would be tested thoroughly for safety before being offered to patients? (1–5 scale) 2. What information would you want before agreeing to try an experimental tolerance vaccine? (checklist: how it was tested in animals/early trials, specific risks including allergic reaction, what monitoring would occur, who developed it and funding source, other — specify) 3. Would knowing that EoE patients helped design the trial increase your trust in participating? (Yes, a lot / Somewhat / No difference / Not sure)

Domain 8: Screening/HLA-typing acceptability 1. Would you be willing to undergo a blood test (e.g., genetic/HLA typing) to determine if this treatment might work for you or carries elevated risk? (Yes / Yes, with concerns / No / Not sure) 2. What concerns, if any, would you have about genetic or immune-marker testing as an eligibility requirement? (open text) 3. Would cost or travel required for this testing affect your willingness to participate? (Yes, significantly / Somewhat / No)

Domain 9: Desire for involvement in development; Demographics 1. How interested are you in being involved in future stages of this treatment's development (e.g., advisory panels, reviewing trial materials, giving feedback on study design)? (Not interested – Very interested, 5-point) 2. Which forms of involvement appeal to you? (checklist: joining a patient advisory board, reviewing plain-language study materials, participating in a PFDD-style meeting, being contacted for future surveys, none at this time) 3. Demographics: age, age at diagnosis, sex, race/ethnicity, geographic region, insurance status, household income bracket (optional/skippable), caregiver-vs-self-report indicator.

Validated-instrument anchors (map domains to DSQ/EEsAI/ PROMIS)

- **Domain 1 (burden/current experience)** anchors to the **Dysphagia Symptom Questionnaire (DSQ)**, the FDA-recognized symptom COA for EoE trials, and the **EEsAI (EoE Symptom Activity Index)** for composite symptom/ impact scoring. Using DSQ-consistent recall periods and phrasing allows direct comparability to regulatory-grade endpoints.
- **Domain 3 (efficacy expectations)** cross-references EEsAI domains (dysphagia frequency, avoidance/modification behaviors, associated symptoms) so that patient-defined "meaningful improvement" can eventually be benchmarked against EEsAI score changes used in trials.
- **Domain 6 (fatigue, burden of prior treatment)** and general quality-of-life items draw on **PROMIS** short forms (Fatigue, Global Health, Anxiety) to allow comparison with broader chronic-disease populations and existing PROMIS normative data.
- Domains 2, 4, 5, 7, 8, and 9 (concept understanding, route/schedule, risk tolerance, trust, screening, engagement) have no existing validated instrument in EoE — these are the novel contribution of this survey, and a priority candidate set for future psychometric validation, potentially through a formal EoE PFDD process.

Analysis plan (quantitative + qualitative/thematic; segmentation)

Quantitative: Descriptive statistics (frequencies, means, medians) for all closed-ended items; comparison across pre-specified segments (pediatric-onset vs. adult-onset, active vs. controlled disease, treatment-naive vs. treatment-experienced, biologic-exposed vs. not) using chi-square/Fisher's exact tests for categorical items and Kruskal-Wallis for

ordinal Likert items given expected non-normality. Composite burden and risk-tolerance scores will be constructed and correlated with DSQ/EEsAI-anchored items to test convergent validity. Where sample size allows, latent class or cluster analysis will be used to identify patient segments (e.g., "risk-averse/high-vigilance," "high-burden/high-risk-tolerance," "diet-fatigued/procedure-averse") to inform differentiated trial-design and communication strategies.

Qualitative: Open-text responses will undergo inductive thematic coding by at least two coders (including a patient co-analyst) with a reconciled codebook, focused especially on Domains 1, 2, 5, and 7 where nuance is expected to exceed closed-ended capture. Illustrative de-identified quotes will be retained for the eventual PFDD briefing document.

Segmentation reporting: All findings will be reported by pediatric/caregiver vs. adult, and by disease severity strata, to avoid masking divergent needs within an averaged "EoE patient" profile.

Ethical considerations & health-literacy/plain-language design

All survey materials will be written at a 6th–8th grade reading level, reviewed with a health-literacy checklist, and piloted with a small patient-advisor group (including at least one adolescent and one caregiver) for comprehension before full fielding. The pMHC/tolerance-vaccine explainer (Domain 2) requires particular care: it must convey mechanism honestly, including the Nexvax2-informed anaphylaxis-risk context, without inducing undue alarm or, conversely, false reassurance. Consent language will be layered (short summary plus expandable detail), translated into languages reflecting the recruitment population, and reviewed for accessibility (screen-reader compatibility, plain visual design). Pediatric assent will use age-appropriate language distinct from the adult/caregiver instrument. The full instrument, recruitment materials, and consent forms require IRB approval prior to fielding, and no data collection will begin without it. Nothing in this survey or its resulting report is intended as individual medical advice; respondents will be reminded of this, and directed to their own clinicians for treatment decisions.

Patient-engagement model — embedding patients at each development stage

Patient involvement is not a single survey event but a standing structure:

- **Advisory board (ongoing):** A standing EoE Patient Advisory Board (recruited via APFED/CURED, including pediatric-diagnosed adults and caregivers) reviews and approves all survey instruments, recruitment materials, and consent language before fielding, and reconvenes at each subsequent development milestone.
- **Co-design (pre-fielding):** Draft items in this document go through at least two rounds of patient-advisor revision and cognitive-interview pilot testing (5–10 respondents) before the survey is

Appendix B: Verified Reference Library

All DOIs validated against CrossRef.

- **2002** — Anti-CD3 Monoclonal Antibody in New-Onset Type 1 Diabetes Mellitus. *NEJM*. doi:10.1056/NEJMoa012864
- **2005** — Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *NEJM*. doi:10.1056/NEJMoa043980
- **2010** — Comprehensive, quantitative mapping of T-cell epitopes in gluten. *Sci Transl Med*. doi:10.1126/scitranslmed.3001012
- **2012** — Microparticles bearing encephalitogenic peptides induce T-cell tolerance. *Nat Biotechnol*. doi:10.1038/nbt.2434
- **2012** — GAD65 Antigen Therapy in Recently Diagnosed Type 1 Diabetes. *NEJM*. doi:10.1056/NEJMoa1107096
- **2013** — Teplizumab (Anti-CD3 mAb) Treatment Preserves C-Peptide Responses (AbATE). *Diabetes*. doi:10.2337/db13-0345
- **2016** — Expanding antigen-specific regulatory networks to treat autoimmunity with pMHC nanoparticles. *Nature*. doi:10.1038/nature16962
- **2017** — Epitope-specific immunotherapy targeting CD4+ T cells in coeliac disease (Nexvax2 Ph1). *Lancet Gastroenterol Hepatol*. doi:10.1016/S2468-1253(17)30110-3
- **2017** — Peptide-MHC-based nanomedicines for autoimmunity. *Nat Nanotechnol*. doi:10.1038/nnano.2017.56
- **2017** — Metabolic and immune effects of immunotherapy with proinsulin peptide (MonoPepT1De). *Sci Transl Med*. doi:10.1126/scitranslmed.aaf7779
- **2018** — Effects of ATX-MS-1467 immunotherapy over 16 weeks in relapsing MS. *Neurology*. doi:10.1212/WNL.0000000000005118
- **2019** — An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *NEJM*. doi:10.1056/NEJMoa1902226
- **2019** — Randomised clinical trial: a placebo-controlled study of subcutaneous or intradermal Nexvax2, an epitope-specific immunotherapy for coeliac disease. *Aliment Pharmacol Ther*. doi:10.1111/apt.15435
- **2019** — Antigen-specific therapeutic approaches for autoimmunity. *Nat Biotechnol*. doi:10.1038/s41587-019-0015-4

- **2021** — Teplizumab improves and stabilizes beta cell function in at-risk (TN-10 extended). *Sci Transl Med*. doi:10.1126/scitranslmed.abc8980
- **2021** — TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized Trial. *Gastroenterology*. doi:10.1053/j.gastro.2021.03.014
- **2021** — Intralymphatic GAD-alum + Vitamin D in T1D (DIAGNODE-2). *Diabetes Care*. doi:10.2337/dc21-0318

Appendix A: Full Trial Register (ClinicalTrials.gov harvest)

59 core relevant trials across 8 programs. Full machine-readable version: trials_master.csv.

ATX-MS-1467 (2 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT01097668	PHASE1	COMPLETED	43	Non Randomized, None mask	2010-03	Safety and Tolerability
NCT01973491	PHASE2	COMPLETED	37	—	2014-02-28	Change From Baseline in the Average Number of Time Constant 1 (T1) Contrast-enhanced Lesions (CELs) Over On-treatment Scans

GAD-alum/Diamyd (18 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT00456027	PHASE2	COMPLETED	160	—	2004-12	The development over time of safety variables, i.e. injection site discomfort, vital signs, laboratory values and AEs/SAEs as well as development of d

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT00435981	PHASE2	COMPLETED	70	Randomized, Double mask	2005-01	To evaluate the efficacy of Diamyd® 20ug versus placebo with respect to preserving residual insulin secretion as measured by C-peptide levels. The eff
NCT00723411	PHASE3	TERMINATED	334	Randomized, Quadruple mask	2008-07	Meal stimulated C-peptide (area under the curve)
NCT00751842	PHASE3	TERMINATED	331	Randomized, Quadruple mask	2008-09	Meal Stimulated C-peptide (area under the curve)
NCT00529399	PHASE2	COMPLETED	145	Randomized, Triple mask	2009-02	The Primary Outcome is the Area Under the Stimulated C-peptide Curve (AUC) at the One Year Visit
NCT00837759	PHASE2	TERMINATED	7	—	2009-02	Change in C-peptide
NCT01122446	PHASE2	COMPLETED	50	Randomized, Triple mask	2009-04	Adverse Events

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT01129232	PHASE2	TERMINATED	6	Randomized, Quadruple mask	2011-01	Intensity of insulitis in proportion to living, insulin-staining beta cells in pancreatic biopsies // Prevalence of virus infected islets in pancreati
NCT01785108	PHASE2	COMPLETED	60	Randomized, Quadruple mask	2013-02	Change in C-peptide (90 minute value and AUC mean 0-120 min) during a Mixed Meal Tolerance Test from baseline to month 6, 15 and 30
NCT02352974	PHASE1	COMPLETED	12	—	2015-01	Number of Subjects With Injection Site Reactions Month 1 // Number of Subjects With Injection Site Reactions Month 2 // Number of Subjects With Inject
NCT02002130	PHASE1	COMPLETED	101	Randomized, Quadruple mask	2015-01	Compare the effect of oral GABA or oral GABA/GAD combination administration on pancreatic beta cell function by quantitative C-peptide secretion

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT02387164	PHASE2	TERMINATED	26	Randomized, Quadruple mask	2015-03-09	Type 1 Diabetes Month 24 // Type 1 Diabetes Status Overall
NCT02464033	PHASE2	COMPLETED	20	—	2015-05	Number of Patients With Reactions of the Injection Site as an Assessment of the Tolerability // Number of Patients With Reactions of the Injection Sit
NCT03345004	PHASE2	COMPLETED	109	Randomized, Quadruple mask	2017-12-20	Change in Stimulated C-peptide During a MMTT
NCT04262479	PHASE2	COMPLETED	14	—	2020-03-02	Injection Site Skin Reactions // Occurrence of Adverse Events (AEs) During 5 Months From Baseline. // Occurrence of Adverse Events (AEs) During the St

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT05351879	PHASE1/ PHASE2	COMPLETED	6	—	2022-05-09	Number of Clinically Significant Abnormal Results from Physical examinations, including neurological and Vital Signs assessments // Injection site rea
NCT05018585	PHASE3	ACTIVE_NOT_RECRUITING	321	Randomized, Quadruple mask	2022-05-19	Beta cell function // Glycemic control
NCT05683990	PHASE2	ACTIVE_NOT_RECRUITING	5	Randomized, None mask	2024-07-09	Occurrence of AEs (including Injection site reactions) and SAEs // Number of Clinically Significant Abnormal Results from Physical examinations, inclu

KAN-101 (3 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT04248855	PHASE1	COMPLETED	41	Randomized, Double mask	2020-01-21	Incidence and Severity of Treatment-emergent Adverse Events (TEAEs)
NCT05574010	PHASE1/ PHASE2	TERMINATED	128	Randomized, Triple mask	2022-11-15	Incidence and Severity of TEAEs as Assessed by Common Terminology Criteria for Adverse Events (CTCAE) in Part A // Change in Pre- and Post-Gluten Chal

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT06001177	PHASE2	COMPLETED	55	Randomized, Triple mask	2023-12-13	Changes From Baseline in Villous Height to Crypt Depth (Vh:Cd) as Assessed by Esophagogastroduodenoscopy With Biopsy After 2-week Gluten Challenge (GC

Nexvax2 (4 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT00879749	PHASE1	COMPLETED	34	Randomized, Quadruple mask	2009-04	—
NCT02528799	PHASE1	COMPLETED	38	Randomized, Quadruple mask	2015-08	Incidence of toxicity and safety of Nexvax2 according to the "Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0"
NCT03543540	PHASE1	COMPLETED	14	Randomized, Quadruple mask	2018-05-01	Safety of Nexvax 2 administered subcutaneously (SQ) // Evaluate bioavailability of the constituents of Nexvax2 after SQ versus intradermal (ID) admini
NCT03644069	PHASE2	UNKNOWN	146	Randomized, Quadruple mask	2018-08-06	Efficacy of Nexvax2 compared to placebo in reducing Celiac Disease (CeD) associated GI symptoms.

Proinsulin peptide (3 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT01536431	PHASE1/ PHASE2	COMPLETED	27	Randomized, Quadruple mask	2012-01	Safety

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT02620332	PHASE1	COMPLETED	27	Randomized, Quadruple mask	2015-10-20	Assessment of MultiPepT1De safety profile
NCT02837094	PHASE1	COMPLETED	6	—	2016-09-29	To examine the risk of C19A3 GNP administration in terms of general safety and induction of hypersensitivity.

TAK-101/TIMP-GLIA (3 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT03486990	PHASE1	COMPLETED	23	Non Randomized, None mask	2018-01-23	Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) // Number of Participants Wit
NCT03738475	PHASE2	COMPLETED	34	Randomized, Quadruple mask	2018-11-11	Change From Baseline in Interferon-Gamma Spot Forming Units (IFN-gamma SFUs) in a Gliadin-specific Enzyme-linked Immunospot (ELISpot) at Day 20
NCT04530123	PHASE2	COMPLETED	102	Randomized, Triple mask	2022-06-23	Change From Baseline in Interferon-gamma Spot Forming Units (IFN-γ SFUs) in Human Leukocyte Antigens Density Quotient (HLA-DQ2.5-positive) Participant

TPM502/Topas (1 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT05660109	PHASE2	COMPLETED	28	Randomized, Quadruple mask	2022-12-12	Incidence, severity, causality, and outcomes of treatment-emergent adverse events

Tzield/teplizumab (25 trials)

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT00806572	PHASE2	TERMINATED	10	Randomized, None mask	2002-05	4-hour C-peptide AUC
NCT00129259	PHASE2	COMPLETED	83	Randomized, Single mask	2005-09	Change in Mean C-peptide Area Under the Curve (AUC) Response to a Mixed Meal Tolerance Test (MMTT)
NCT00239720	PHASE2	TERMINATED	4	Randomized, Double mask	2006-03-16	Proportion of Participants Who Received at Least Two Cycles of Treatment and Who Showed Predefined Levels of Improvement in Primary Efficacy Parameter

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT00378508	PHASE2	COMPLETED	63	Randomized, Triple mask	2006-09	C-peptide Area Under the Curve (AUC) Response to a Mixed Meal Tolerance Test (MMTT) at 12 Months // C-peptide Area Under the Curve (AUC) Response to a
NCT00385697	PHASE2/ PHASE3	COMPLETED	554	Randomized, Triple mask	2006-10	Number of Subjects in Segment 2 With Both a Total Daily Insulin Dose of Less Than 0.5 U/kg/Day and Hemoglobin A1c (HbA1c) Level of Less Than 6.5%. //
NCT00920582	PHASE3	TERMINATED	254	Randomized, Triple mask	2009-09	Proportion of Subjects With Both a Total Daily Insulin Dose of Less Than 0.5 U/kg/Day and Hemoglobin A1c (HbA1c) Level of Less Than 6.5%. // Mean Chan
NCT00954915	PHASE1/ PHASE2	TERMINATED	1	—	2009-12	Adverse Events (AE)
NCT01189422	PHASE1	TERMINATED	1	Randomized, Quadruple mask	2010-08	Dose regimen
NCT01030861	PHASE2	COMPLETED	76	Randomized, Quadruple mask	2010-08	Rate of New Diabetes Per Year

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT03751007	PHASE1/ PHASE2	COMPLETED	45	Randomized, Quadruple mask	2018-10-24	Incidence of Treatment-emergent Adverse Events (TEAE)
NCT03875729	PHASE3	COMPLETED	328	Randomized, Quadruple mask	2019-04-05	Change in C-peptide ln(AUC+1) Standardized by Duration of the Mixed Meal Tolerance Test (MMTT)
NCT04270942	PHASE2	COMPLETED	6	—	2020-02-26	Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Adverse Events of Special Interest (TEAESIs) and Treatment-e
NCT04598893	nan	ACTIVE_NOT_RECRUITING	188	—	2020-10-26	Incidence of adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs), including infections and malignancies

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT05757713	PHASE4	ACTIVE_NOT_RECRUITING	20	—	2023-07-25	Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), TEAEs leading to withdrawal, and serious adverse events (SAEs)
NCT06338553	EARLY_PHASE1	RECRUITING	24	Randomized, Quadruple mask	2024-06-12	Investigate the impact of GLP-1Ra on postprandial glycemia in a pilot study // Study the impact of GLP-1Ra on the disposition index (DI) in a pilot st
NCT06481904	nan	RECRUITING	200	—	2024-09-27	Number of adverse events of special interests (AESI) // Number of serious adverse events (SAE) // Number of adverse events (AE) in mothers, fetuses, a

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT06892002	nan	COMPLETED	110	—	2025-02-11	Participant demographic characteristics at teplizumab initiation // Participants' family history of T1D and autoimmune diseases // Presence of T1D sus
NCT06791291	PHASE2	RECRUITING	10	Randomized, None mask	2025-07-25	Number of participants with Stage 3 Type 1 Diabetes based on American Diabetes Association criteria // Change from baseline in area under the curve (A
NCT07088068	PHASE3	RECRUITING	723	Randomized, Quadruple mask	2025-08-06	For United States (US) and non-European Union (EU) countries: Glycated hemoglobin (HbA1c) change from baseline // For US and non-EU countries: Total n

NCT	Phase	Status	N	Design	Start	Primary outcome(s)
NCT07260110	nan	RECRUITING	550	—	2025-10-31	Change in participant and caregiver-reported outcomes from survey responses: ease of diabetes management questions // Change in participant and caregi
NCT07457580	nan	RECRUITING	60	—	2026-03-16	Participant demographics at teplizumab initiation // Participants' family history of T1D and autoimmune diseases // Presence of T1D susceptibility gen
NCT07360080	nan	RECRUITING	1000	—	2026-03-19	Time from teplizumab infusion start to the onset of Stage 3 T1D
NCT07216391	PHASE2	NOT_YET_RECRUITING	60	Randomized, None mask	2026-07-30	Change in DPTRS at six months
NCT07610213	PHASE1	NOT_YET_RECRUITING	60	Randomized, Single mask	2027-01-01	Change in Stimulated C-peptide AUC
NCT00008801	PHASE1/ PHASE2	UNKNOWN	—	Non Randomized, None mask	—	—

Appendix D: Program Quick-Reference Fact Sheets

Fact Sheet — Tzield (teplizumab)

Disease	Type 1 diabetes
Sponsor(s)	Provention Bio / Sanofi (orig. MacroGenics, Lilly, NIH/Herold)
Modality	Anti-CD3 mAb (antigen-nonspecific immunomodulator)
Key antigen	None (pan-T-cell CD3)
Mechanism	FcR-nonbinding anti-CD3 induces partial exhaustion/anergy of autoreactive T cells, expands Tregs
Lead stage	Approved (Nov 2022, US)
Status	Marketed
Registered trials (harvest)	25 (EARLY_PHASE1, PHASE1, PHASE1|PHASE2, PHASE2, PHASE2|PHASE3, PHASE3, PHASE4)
Trial span	2002–2027
Total enrollment (sum)	4,430

Pivotal outcomes:

- **NCT00129259 (AbATE)** — C-peptide preservation: ✓ *met*
- **NCT00385697 (Protégé)** — Composite insulin+HbA1c: × *missed/halted*
- **NCT01030861 (TN-10, NEJM 2019)** — Time to clinical T1D: ✓ *met*
- **NCT03875729 (PROTECT)** — C-peptide at 78 wk: ✓ *met*

Fact Sheet — Nexvax2

Disease	Celiac disease
Sponsor(s)	ImmusanT (Bob Anderson / Walter+Eliza Hall)
Modality	Peptide immunotherapy (3 immunodominant gluten peptides)
Key antigen	Gliadin/glutenin HLA-DQ2.5-restricted peptides
Mechanism	Antigen-specific tolerance via repeated intradermal peptide dosing (SGIT)
Lead stage	Phase 2 (halted 2019)
Status	Discontinued
Registered trials (harvest)	4 (PHASE1, PHASE2)
Trial span	2009–2018
Total enrollment (sum)	232

Pivotal outcomes:

- **NCT03644069 (RESET CeD)** — Gluten-challenge symptom protection: × *missed/halted*
- **Goel 2017 Ph1** — Safety/immunogenicity: ✓ *met*

Fact Sheet — TAK-101 / TIMP-GLIA

Disease	Celiac disease
Sponsor(s)	Cour Pharmaceuticals / Takeda
Modality	Tolerogenic nanoparticle (PLGA encapsulating gliadin)
Key antigen	Gliadin (whole protein in NP)
Mechanism	Tolerogenic NP taken up by liver/spleen APCs -> Treg induction, deletion
Lead stage	Phase 2
Status	Active/various
Registered trials (harvest)	3 (PHASE1, PHASE2)
Trial span	2018–2022
Total enrollment (sum)	159

Pivotal outcomes:

- **NCT03738475** — Gluten-induced IFN-γ+ T cells: ✓ *met*
- **NCT04530123** — Mucosal protection on challenge: ~ *partial/subgroup*

Fact Sheet — KAN-101

Disease	Celiac disease
Sponsor(s)	Anokion
Modality	Glycosylation-tag liver-targeting antigen conjugate
Key antigen	Deamidated gliadin peptide-Fc/glycan conjugate
Mechanism	Liver-targeted tolerance (ASGPR) -> antigen-specific Treg/anergy
Lead stage	Phase 2 (ACeD/SynCeD)
Status	Active
Registered trials (harvest)	3 (PHASE1, PHASE1|PHASE2, PHASE2)
Trial span	2020–2023
Total enrollment (sum)	224

Pivotal outcomes:

- **NCT04248855 (ACeD)** — Safety + cytokine response: ✓ *met*
- **NCT06001177 (SynCeD)** — Gluten-challenge protection: ~ *partial/subgroup*

Fact Sheet — GAD-alum / Diamyd

Disease	Type 1 diabetes
Sponsor(s)	Diamyd Medical
Modality	Antigen + adjuvant (recombinant GAD65 in alum)
Key antigen	GAD65 autoantigen
Mechanism	Antigen-specific immune modulation; intralymphatic delivery in DIAGNODE
Lead stage	Phase 3 (DIAGNODE-3)
Status	Active
Registered trials (harvest)	18 (PHASE1, PHASE1|PHASE2, PHASE2, PHASE3)
Trial span	2004–2024
Total enrollment (sum)	1,777

Pivotal outcomes:

- **Ph3 (NCT00723411/751842)** — C-peptide at 15 mo: × *missed/halted*
- **DIAGNODE-2 (2021)** — C-peptide (intralymphatic): ~ *partial/subgroup*

Fact Sheet — Navacims / Parvus

Disease	Type 1 diabetes / autoimmune
Sponsor(s)	Parvus Therapeutics
Modality	pMHC-II nanoparticle (peptide-MHC on iron oxide NP)
Key antigen	Disease-relevant peptide-MHCII
Mechanism	pMHC-NP re-programs cognate CD4 T cells into Tr1 regulatory cells
Lead stage	Preclinical/early
Status	Preclinical
Registered trials (harvest)	0 ()
Trial span	—
Total enrollment (sum)	0

Pivotal outcomes:

- Preclinical / not yet in pivotal trials

Fact Sheet — Proinsulin peptide / MonoPepT1De

Disease	Type 1 diabetes
Sponsor(s)	King's College London / UCL (Peakman)
Modality	Peptide immunotherapy (proinsulin C19-A3)
Key antigen	Proinsulin peptide (HLA-DR4)
Mechanism	Intradermal peptide tolerance
Lead stage	Phase 1
Status	Academic
Registered trials (harvest)	3 (PHASE1, PHASE1|PHASE2)
Trial span	2012–2016
Total enrollment (sum)	60

Pivotal outcomes:

- **MonoPepT1De (2017)** — Safety + immune markers: ✓ *met*

Fact Sheet — ATX-MS-1467

Disease	Multiple sclerosis
Sponsor(s)	Apitope / Merck KGaA
Modality	Peptide immunotherapy (4 MBP peptides)
Key antigen	Myelin basic protein peptides
Mechanism	Apitope tolerogenic peptide design (native APL)
Lead stage	Phase 2
Status	Discontinued
Registered trials (harvest)	2 (PHASE1, PHASE2)
Trial span	2010–2014
Total enrollment (sum)	80

Pivotal outcomes:

- **Chataway 2018** — Gd-enhancing MRI lesions: ~ *partial/subgroup*

Appendix C: Glossary

Anergy A state of functional unresponsiveness in T or B lymphocytes induced when an antigen receptor is engaged without adequate costimulatory signals. Anergic cells remain alive but fail to proliferate or produce effector cytokines upon subsequent antigen exposure, serving as a peripheral tolerance mechanism.

Antigen-Specific Immunotherapy (ASIT) A therapeutic approach designed to selectively modulate the immune response to a defined disease-relevant antigen (e.g., an autoantigen or allergen) rather than broadly suppressing immune function. The goal is to restore or induce tolerance to the specific target while preserving protective immunity elsewhere.

APC (Antigen-Presenting Cell) A cell type—including dendritic cells, macrophages, and B cells—that processes protein antigens into peptide fragments and displays them on MHC molecules for recognition by T cells. APCs also provide costimulatory signals that determine whether the resulting T cell response is activating or tolerizing.

Autoantibody An antibody produced by the immune system that erroneously targets one of the host's own proteins or cellular components. Autoantibodies (e.g., anti-GAD65) are frequently used as biomarkers of autoimmune disease activity or risk, though they are not always directly pathogenic.

Autoantigen A self-protein or self-molecule that becomes the target of an inappropriate adaptive immune response in autoimmune disease. Identification of relevant autoantigens (such as insulin or GAD65 in type 1 diabetes) underpins the design of antigen-specific tolerizing therapies.

C-Peptide A byproduct cleaved from proinsulin during insulin biosynthesis, released into circulation in equimolar amounts with endogenous insulin. Serum or urinary C-peptide level is a standard clinical biomarker of residual beta-cell function and is commonly used as an endpoint in type 1 diabetes intervention trials.

CD3 A multi-subunit protein complex associated with the T cell receptor (TCR) on the surface of T lymphocytes, essential for transmitting activation signals following antigen recognition. CD3 is the molecular target of therapeutic antibodies such as teplizumab.

Clonal Deletion A central tolerance mechanism occurring primarily in the thymus in which developing T cells (or in the bone marrow for B cells) that react strongly to self-antigens are eliminated via apoptosis. This process removes the most overtly autoreactive lymphocytes before they enter the peripheral circulation.

Companion Diagnostic An assay or device co-developed with a therapeutic to identify patients likely to respond, require dose adjustment, or be at risk of adverse events, often required by regulators as a condition of the drug's approved label. In antigen-specific immunotherapy, companion diagnostics may include autoantibody panels or HLA genotyping tests.

DSQ (Dysphagia Symptom Questionnaire) A validated patient-reported outcome instrument used to quantify the frequency and severity of swallowing difficulty, most notably as a primary or key secondary endpoint in eosinophilic esophagitis clinical trials. Scores are typically derived from daily patient diary entries over a defined recall period.

EoE (Eosinophilic Esophagitis) A chronic, antigen/immune-mediated inflammatory disease of the esophagus characterized by eosinophil-predominant infiltration, often triggered by food antigens, leading to symptoms of dysphagia and, over time, esophageal fibrostenosis. It is a key indication of interest for antigen-specific and food-allergen-targeted therapeutic approaches.

Epitope The specific molecular region of an antigen—typically a short peptide sequence or a conformational surface—that is recognized and bound by a T cell receptor, B cell receptor, or antibody. Epitope specificity determines which immune cells are engaged and is central to designing precisely targeted antigen-specific therapies.

Epitope Spreading A phenomenon in which an immune response initially directed against a single dominant epitope broadens over time to target additional, previously unrecognized epitopes on the same or related antigens. It is implicated in the progressive amplification of autoimmune and allergic responses and is a consideration in the durability of antigen-specific interventions.

Fibrostenosis A pathological process of tissue scarring and narrowing resulting from chronic inflammation, particularly relevant in eosinophilic esophagitis, where persistent eosinophilic inflammation can lead to esophageal strictures requiring dilation. It represents a key long-term disease complication that antigen-specific and anti-inflammatory therapies aim to prevent.

GAD65 (Glutamic Acid Decarboxylase 65) An enzyme expressed in pancreatic beta cells and neurons that is a major autoantigen target in type 1 diabetes. Anti-GAD65 autoantibodies are widely used as a diagnostic and risk-stratification biomarker, and GAD65 itself has been investigated as a tolerizing antigen in therapeutic vaccines.

Gliadin A component protein fraction of gluten found in wheat that contains immunogenic peptide epitopes responsible for triggering the pathological T cell response

in celiac disease. Gliadin-derived peptides are a primary target antigen for tolerizing and antigen-specific therapeutic strategies in celiac disease.

HLA / MHC (Human Leukocyte Antigen / Major Histocompatibility Complex) The MHC is the general term for the gene family encoding cell-surface molecules that present peptide antigens to T cells; HLA is the human-specific designation of this system. Specific HLA alleles (e.g., HLA-DQ2/DQ8 in celiac disease) confer differential genetic susceptibility to autoimmune and allergic diseases and are often used to stratify patients for antigen-specific therapy trials.

Immune Tolerance The state in which the immune system does not mount a destructive response against a particular antigen, encompassing central mechanisms (thymic/bone marrow deletion) and peripheral mechanisms (anergy, regulatory T cells, suppression). Restoring lost tolerance to self- or food-antigens is the core therapeutic objective of antigen-specific immunotherapy.

Nanoparticle (Tolerogenic) A synthetic or biodegradable particle engineered to co-deliver a target antigen (and sometimes an immunomodulatory signal) to antigen-presenting cells or lymphoid tissue in a manner that promotes a tolerogenic rather than immunogenic outcome. These platforms are an active area of antigen-specific drug delivery innovation across autoimmune and allergic disease programs.

pMHC (Peptide-MHC Complex) The physical complex formed when a processed antigenic peptide is bound within the groove of an MHC molecule on the cell surface, constituting the actual ligand recognized by a T cell receptor. pMHC complexes are the molecular unit of specificity exploited in engineered antigen-specific therapeutics and diagnostic tetramer assays.

PFDD (Patient-Focused Drug Development) An FDA initiative and regulatory framework for systematically incorporating