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Review Article

**Navigating Global Regulatory Frameworks: A Review of Submission Frameworks, Approvals and Timelines Across the FDA, EMA and MHRA**

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Abstract

Launching new pharmaceutical drugs is a complex, multi-phase process involving years of research and development. Regulatory approval is critical for ensuring that medicinal products meet rigorous standards of safety, efficacy, and quality. In the drug development lifecycle, clinical trial and marketing authorisation submissions represent pivotal regulatory milestones in the journey of a drug from research to commercialisation. This review focuses on navigating the regulatory submission frameworks, documentation, and timelines for the approval of clinical trials and marketing authorisation across the FDA, EMA and MHRA. Real-world clinical trials of some drugs have been analysed in this review as case studies, and the regulatory authority decisions have been compared to identify the key requirements for successful clinical trial and marketing authorisation applications. The review reveals that the FDA, EMA and MHRA are regulated globally by the ICH guidelines, specific regional regulations, and similar documentation requirements, but differ in their submission, review processes, approaches to evidence/endpoints, risk tolerance and timelines. The FDA adopts a relatively flexible approach, accepting single-arm trials with surrogate endpoints to support accelerated approval, with subsequent confirmatory studies required to verify clinical benefit. In contrast, the EMA operates a conservative, evidence-based framework that generally favours comparator-controlled trials and robust clinical endpoints, with conditional approvals subject to stringent obligations and annual review. Post-Brexit, the MHRA operates a hybrid model that combines EMA-style conditional approvals and reliance pathways that facilitate the recognition of decisions from other regulatory authorities, thereby increasing both regulatory agility and review efficiency.

Conclusion: Differences in regulatory agency approvals have important implications for global drug development programs, and efforts are underway to harmonise drug approval processes globally.

Keywords: Clinical Trials; IND submission; CTA submission; NDA approvals; MAA approvals; Timelines; FDA; EMA; MHRA

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1. Introduction

Pharmaceutical investigational drug regulatory submissions for approval of clinical trials ensure patient safety, ethical compliance, data integrity, and enable the legal authorisation to test and market new drugs. Compliance with regulations and guidelines is mandatory for successful regulatory submissions, ensuring that drug development meets the established safety and efficacy standards. Regulatory submissions occur at various stages of drug development and are subject to the specific requirements of the regulatory bodies in each region. The health regulatory agencies, namely the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Medicines and Healthcare products Regulatory Agency (MHRA), regulate the use of investigational drugs within the United States, the European Union (EU), and the United Kingdom (UK), respectively. In addition, Institutional review boards

(IRBs) in the United States and Ethics committees (ECs) in the EU and UK must approve the use of drugs in humans, and their primary responsibility is to ensure the protection of the participating human subjects. The submission required to commence clinical trials in the United States is the Investigational New Drug Application (IND). In contrast, in the European Union and the United Kingdom, it is the Clinical Trial Authorisation (CTA). (1-3)

For marketing authorisation approval, it is the New Drug Application (NDA)/Biologics Licensing Application (BLA-for biologics) for the FDA and Marketing Authorisation Application (MAA) for the EMA and MHRA. (4-6)

This review focuses on the regulatory frameworks, submission methods, documentation, approval processes, and timelines for clinical trial applications, as well as marketing authorisation, across the FDA, EMA, and

MHRA. To achieve this, four real-world drug clinical trials were analysed, one with a similar approval status across all agencies, and the other three with divergent approval statuses across the different agencies. Comparing regulatory authorities decisions on drug authorisation based on trial results will provide a sound understanding of the regulatory requirements of different agencies for successful clinical trial approval and drug authorisation for marketing.

2. Regulatory Frameworks Overview

IND as well as CTA's adherence to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (ICH E6) and regional regulations are pivotal for conducting clinical trials. The ICH GCP guideline establishes an international standard for design, conduct, recording, and reporting clinical trials involving human subjects, so that participant rights are protected and the data are reliable. (7)

21 CFR 312 (US-FDA), EU CTR 536/2014 (EU-EMA) and SI 2006/1928 (UK-MHRA) are the regional regulations governing clinical trials, ensuring the safety of

Table 1. Features described in the regional regulatory frameworks

Documents described	Sponsor responsibilities	Investigator responsibilities
Clinical Trial Protocol	Protocol design	Obtain subject-informed consent
Investigator's brochure	Study plan	Report on the progress and adverse effects encountered by the subjects during the trial to the sponsor
Informed consent form	Monitoring study sites to determine if the sites are following the standard of care established by the GCP guidelines	Maintain proper records and inform the IRB and the sponsor about any unexpected problems or serious adverse events that may happen during the trial
Safety reporting		
Labelling formats		

3. Comparative Review of IND and CTA Submission Process, Documentation and Regulatory Timelines

3.1. Submission Process and Documentation

While the non-clinical data required for both IND and CTA are similar, the submission process and formats are different. While the FDA accepts an eCTD format for the IND applications submitted through the electronic gateway ESG NextGen, the CTAs require an Investigational Medicinal Product Dossier (IMPD) submission via CTIS for EMA and through the Integrated Research Application System (IRAS portal) for MHRA. (1-3) Once an IND has been submitted for a specific drug and condition, all future studies, data, and documents for that drug and condition are submitted as additions to the same IND. In contrast, CTAs require a separate documentation submission whenever a new clinical trial is initiated for a given drug or indication. The regulatory agencies check for the validation of the documents and review the submissions to assess the safety of the proposed clinical trial. The details regarding the application form and an elaborate list of documentation required by the different agencies are given in Table 2.

3.2 IND and CTA Review Timeline

The FDA follows a "silent approval" process for IND applications, whereby the study may proceed if no clinical hold is issued by the FDA within 30 calendar days. However, for the CTAs, EMA has a 10-working-day

participating subjects, data integrity and ethical standards. (1-3)

21 CFR 312 focuses on FDA-IND requirements; Clinical Trial Directive (CTD) (2001/20/EC) initially regulated clinical trials in the EU and was subsequently replaced by the Clinical Trials Regulation CTR (EU No 536/2014) on 31 Jan 2022. EU CTR 536/2014 harmonises trial submissions through the Clinical Trial Information System (CTIS). Brexit, the UK's departure from the EU (Jan 31, 2020), reshaped the regulatory environment for clinical trials in the UK. Before 2020, the UK relied on EU directives, enabling smooth collaboration and data exchange across Europe. Post-Brexit, MHRA operates independently. It was regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) until April 2026, and the new MHCTR 2025 (SI 2006/1928) has been effective from April 28, 2026.

All three regional regulations, 21 CFR 312, EU CTR 536/2014, and SI 2006/1928 share core GCP principles but differ in application procedures, reporting and oversight. The common aspects described in all the regional regulatory frameworks are as mentioned in Table 1.

validation period followed by a 45-working-day review, and an approval letter from EMA is vital for commencing the trials. The MHRA CTA validation period is 1 or 2 days, followed by a 30-working-day review period and an approval letter from the MHRA is required to commence the clinical trial.

3.3. Transparency, Safety reporting and Labelling requirements

All agencies maintain transparency of trial data and publish detailed information on regulatory decisions. The IND trial details and results are publicly available through Clintrials.gov, whereas the CTA details are available through CTIS for EMA and ISRCTN for MHRA. (1-3) Constant safety monitoring and robust reporting of adverse events are mandatory across all regions (Table 2).

In summary, the comparison of clinical trial submission requirements across the FDA, EMA, and MHRA indicates that the fundamental trial documentation, including non-clinical data, CMC information, the Investigator's Brochure (IB), Informed Consent Form (ICF), and Case Report Form (CRF), is largely consistent across these regulatory agencies, with ICH guidelines being universally adopted. Nevertheless, IND and CTA submissions differ in terms of regional regulatory frameworks, submission processes, review timelines, labelling requirements, and safety reporting procedures.

Table 2. Comparison of documentations, safety and labelling requirements across FDA, EMA and MHRA for IND and CTA

ASPECT	FDA	EMA	MHRA
Submission Portal	Electronic gateway system as eCTD	Clinical Trial Information System (CTIS)	Integrated Research Application System (IRAS)
Application forms	IND Form 1571: IND Form IND form 1572: Statement of Investigator Facilities data IND Form 3654: Certificate	Part 1 (Scientific features) Part 2 (National features) Scientific Advice letter Documents concerning the clinical trial sites Statement by the Sponsor on compliance with EU data protection rules GMP compliance form	Application Form Medicines form Qualified person declaration GMP compliance form
Documents	Investigational study plan Clinical Trial Protocol Investigators Brochure Informed Consent form Case Report Form Trial-specific Labelling eCTD format: Chemistry, Manufacturing and Control data (CMC), Pharmacology and Toxicology data	Investigational study plan Clinical Trial Protocol Investigators Brochure Informed Consent form Case Report Form Trial-specific Labelling Investigational Medicinal Product Dossier (IMPd) Auxiliary medicinal product (AxMP) dossier (If applicable)	Investigational study plan Clinical Trial Protocol Investigators Brochure Informed Consent form Case Report Form Trial-specific Labelling Investigational Medicinal Product Dossier (IMPd)
Ethical Committee Review	A separate submission is made to the IRB and requires approval before the trial	A single submission, reviewed in parallel by the regulatory authority and ethics committee	A single submission, reviewed in parallel by the regulatory agency and ethics committee
Safety reporting Suspected unexpected serious adverse reactions (SUSARs): Non-fatal Fatal or Life-Threatening SUSARs Safety reporting and Development Safety Update report (DSUR)	Reported at the earliest and not later than 15 calendar days Reported at the earliest but in no case later than 7 calendar days. IND safety forms submitted Form 3500A/FAERS. DSUR is submitted annually	Reported at the earliest and not later than 15 calendar days Reported promptly, but in no case later than 7 calendar days. Reported via the Eudravigilance database. DSUR is submitted annually	Reported at the earliest and not later than 15 calendar days Reported promptly but no later than 7 calendar days ICSR/MHRA gateway route. DSUR is submitted annually.
Labelling Requirements	Labelling in English Labels to include “Caution: New Drug—Limited by Federal (or United States) law to investigational use,” Drug name or code, dosage, administration mode, storage conditions and identifier to ensure traceability. Expiration date on label is not mandatory if provided elsewhere (IB or protocol).	Multilingual requirement Labels must include “For clinical trial use only” Trial reference code, name and address of the sponsor, batch number, protocol number, storage condition and instructions for use. Expiration dates are mandatory on the label.	Labelling in English Labels must include the phrase “For clinical trial use only” . Trial reference code, name and address of the sponsor, batch number, protocol number, storage condition and the instructions for use. Expiration dates are mandatory on the label.

4. Comparative Regulatory Perspectives on NDA/BLA(FDA), MAA (EMA) and MAA (MHRA)

Once the clinical trials are completed, the trial results and essential documents are submitted to the regulatory agency for approval to market the drug. The FDA requires an NDA for small molecules/chemical drugs and a BLA for biologic drugs such as monoclonal antibodies. (4) However, for both EMA and MHRA, a Marketing

Authorisation Application (MAA) is submitted for small molecules, biologics, as well as Advanced Therapy Medicinal Products (ATMPs). (5,6)

4.1 Documentation Requirements for NDA/BLA and MAA

The electronic Common Technical Document (eCTD) is a globally recognised format, designed to streamline the

regulatory application submission and review process. eCTD enables pharmaceutical companies to submit data in a structured, consistent and electronic format. The documentation for NDA and MAA is broadly similar because both follows the eCTD formats proposed by ICH.

The CTD consists of Module 1: Administration information

Module 2: Non-clinical and clinical summaries

Module 3: Quality information

Module 4: Nonclinical studies

Module 5: Clinical studies

Modules 2 to 5 largely remain the same across the agencies, and the main differences between agencies are in module 1 (administrative information) as listed below in Table 3.

Table 3. Module 1 comparison between FDA, EMA and MHRA

Module1 comparison	FDA	EMA	MHRA
Administration information	FDA Form 356h Cover letter Patent certification (Para I–IV)	EU Application Form Cover letter No patent required	MHRA Application Form Cover letter Patent not included
Labelling	Prescribing Information (PI) Carton / container labels (English)	SmPC- Summary of Product Characteristics Package Leaflet (PIL) (multi-language)	SmPC-Summary of Product Characteristics Package Leaflet (PIL) (English)
Pharmacovigilance	Risk Evaluation and Mitigation Strategy (REMS if required)	Risk management plan (RMP-mandatory) Qualified Person for Pharmacovigilance	Risk management plan (RMP- mandatory) Qualified Person for Pharmacovigilance
Environmental	Environmental Assessment (EA) or exclusion	Environmental Risk Assessment is mandatory	Environmental Risk Assessment is mandatory
Manufacturing/ Quality	Description of Establishment FDA inspection readiness	QP declaration GMP certificates Manufacturing authorization	QP declaration GMP certificates Manufacturing authorization

4.2. NDA and MAA review process: Geographical scope and the decision-making hierarchy

The FDA covers the entire United States with a single, centralised process and grants the marketing authorisation. EMA oversees the centralised evaluation of certain drugs, in collaboration with the national agencies and issues a scientific recommendation, and the legal decision is taken by the European Commission based on this assessment. For other procedures (decentralised and mutual recognition), marketing authorisation remains the responsibility of national authorities. MHRA, post-Brexit, has moved from collaboration with the EU to an independent body with a nationalised approach for the

entire UK. It also employs International Recognition Procedures to stay competitive. A comparison of the marketing authorisation process across different agencies is presented in Table 4.

In summary, NDA, a single centralised FDA process, includes FDA-specific forms, patent certifications and REMS (if required). Whereas, the MAA requires EU/UK-specific documents such as SmPC, PIL, mandatory RMP, multi-language labelling and a QP declaration. Overall, the EU submission is more extensive in risk management and patient-facing documentation. MHRA-MAA is structurally similar to EMA.

Table 4. Comparison of Marketing authorisation review process and timelines across FDA, EMA and MHRA

Review Process	FDA	EMA	MHRA
Review method	Single centralised FDA process 60-day filing review to accept or refuse to file. The FDA issues complete response letters if deficiencies exist	Centralised via EMA Multi-country scientific review	Direct via MHRA Independent review or Reliance-based
Types of review process	Single agency (FDA) review	Centralised Decentralised National Mutual recognition	National route Reliance route International recognition Procedure IRP
Timeline	6–10 months	~210 days (+clock stops)	67-120 days
Faster Review Methods	Priority Review-6 months	Accelerated review-150 days	IRP (67 to 110days)
Early support	Breakthrough therapy	Priority Medicines (PRIME)	Innovative Licensing and Access Pathway (ILAP)

Early Approval	Accelerated Approval	Conditional MAA	Conditional MAA
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5. Real World Case Studies in Global Regulatory Submissions

Four real-world clinical trials submitted to the FDA, EMA and MHRA have been analysed as case studies in this review. The trial details, documentation, study protocols, results, and approval status of these trials were compared across the FDA, EMA and MHRA. The trials chosen were: Dupilumab (Dupixent) for Chronic Obstructive Pulmonary Disease (COPD), Donanemab (Kisunla) for Alzheimer's disease, Adagrasib (Krazati) for Non-Small Cell Lung Cancer (NSCLC) and Melflufen (Pepaxti) for Multiple Myeloma. The regulatory authority decisions for these drugs were compared to identify the key requirements for successful clinical trial and marketing authorisation applications.

5.1 Case Study 1: Dupilumab clinical trial for COPD

Dupilumab, marketed as Dupixent®, is a human monoclonal antibody directed against the interleukin IL-4 receptor α (IL-4R α) subunit. By blocking this receptor subunit, Dupilumab inhibits the signaling of the type 2 cytokines, IL-4 and IL-13, which are key drivers of type 2 inflammation. (8)

In March 2017, Dupilumab received its first global approval by the US-FDA for the treatment of adult patients with moderate-to-severe atopic dermatitis. Ever since, it's been globally approved for some types of asthma, chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis with nasal polyposis, eosinophilic oesophagitis and chronic spontaneous urticaria. Patients

with these conditions produce high levels of IL-4 and IL-13, which cause inflammation of the skin, airways and oesophagus, leading to symptoms of these diseases.

Dupilumab blocks receptors (targets) for IL-4 and IL-13 and thus prevents IL-4 and IL-13 from working and relieves disease symptoms. Dupilumab, co-developed by Regeneron Pharmaceuticals and Sanofi, has been approved by global agencies for various indications mentioned above.

This review aims to explore and compare the clinical trial submission and marketing authorisation approval process of Dupilumab for COPD by the US-FDA, EU-EMA and UK-MHRA. To characterise the efficacy and safety of Dupilumab in patients with COPD and type 2 inflammation, two replicate multicentric clinical trials, BOREAS (FDA Trial ID: NCT03930732, EMA Trial ID: EudraCT 2018-001953-28) and NOTUS (NCT04456673, EudraCT 2018-001954-91), were performed in 38 countries across Europe, Asia, North America, South America, Africa and Australia. To commence the phase III trials, submissions were made to the respective regulatory agencies for approval. The documentation submitted is as mentioned earlier in Table 2. The clinical trial protocol is as presented in Figure 1; the results and approval status of the FDA, EMA and MHRA for these trials have been compared (Figure 2). All three agencies approved Dupilumab as an add-on maintenance therapy of COPD with inflammation in adults who have increased levels of eosinophils and whose disease is not controlled well enough with a combination of other available drugs. (9-11)

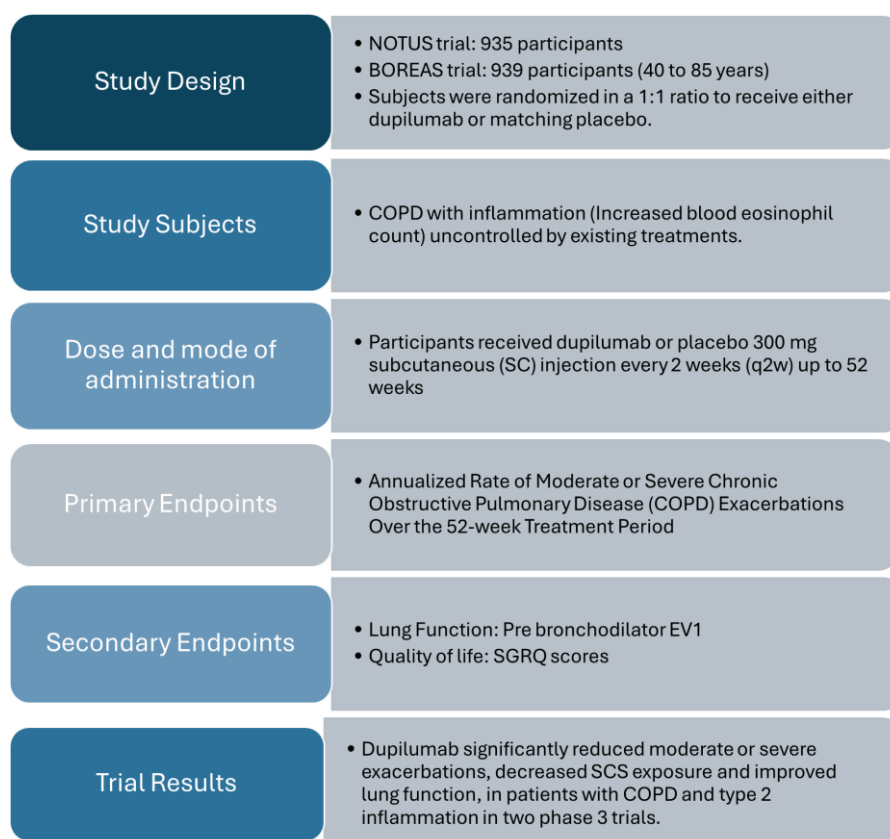


Figure 1. Study Protocol for the NOTUS and BOREAS Trial of Dupilumab for COPD

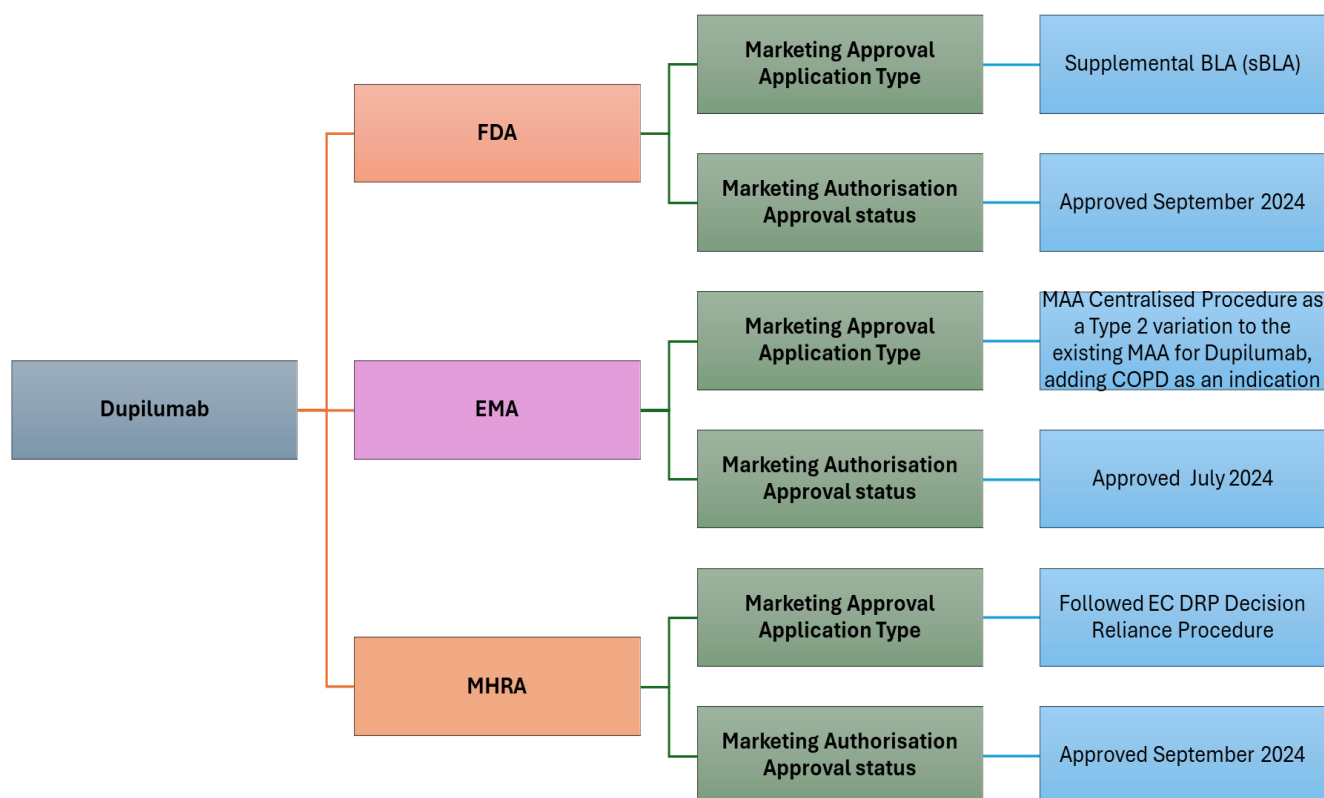


Figure 2. Approval status of the Dupilumab trial by different agencies

5.2 Case Study 2: Donanemab clinical trial for Alzheimer's

Alzheimer's disease (AD), the most common cause of Dementia, is an age-related, progressive neurodegenerative disorder characterised by progressive decline in cognitive and functional abilities, ultimately resulting in a fatal outcome. The amyloid cascade hypothesis of AD suggests that the production and deposition of amyloid beta A β plaques in the brain is an early and necessary event in the pathogenesis of AD. (12)

Donanemab (Kisunla™) is an emerging class of amyloid-targeting therapies whose mechanisms of action are intended to modify the pathology and slow the cognitive and functional decline in patients with AD. It is a monoclonal antibody directed against the insoluble, modified, N-terminal truncated form of amyloid beta (N3pG A β) present only in brain amyloid plaques. Donanemab binds to the deposited amyloid plaque and aids its removal through microglial-mediated phagocytosis. Eli Lilly and Company, Indianapolis, IN, developed Donanemab, and after successful preclinical studies, clinical trials were undertaken in different countries. There was a Phase 2 trial called TRAILBLAZER ALZ, a randomised, placebo-controlled, double-blinded trial conducted in the USA and Canada and the results were submitted to the FDA for accelerated approval. In this trial, participants were allowed to stop treatment when they reached a predefined level of amyloid plaque clearance. While the trial enrolled more than 100

participants, many stopped taking the drug after six months due to the speed of amyloid plaque reduction. This resulted in fewer than 100 participants receiving 12 months of Donanemab. Hence, the FDA rejected the accelerated approval in 2023 and issued a complete response letter requesting additional data. The FDA sought results from a minimum of 100 participants who received at least a year of continued treatment with Donanemab. The company then submitted results from the TRAILBLAZER-ALZ 2 Phase 3 study for traditional FDA approval (Trial ID: NCT 04437511). The Phase 3 trial was conducted in European countries as well, and the results were submitted to EMA as well (EudraCT 000077-25, CTIS 2023-507303-55-00). The clinical trial applications, documentation submitted, and approval status for Donanemab TRAILBLAZER-ALZ2 have been analysed, comparing and contrasting FDA, EMA and MHRA requirements. The documentation submitted was as described earlier (Table 2). The trial details, study protocol (Figure 3), results and marketing approval status have been analysed and presented (13-15) (Figure 4,5). The trial results revealed Donanemab to slow the clinical progression as well as removed amyloid plaques, and the data were submitted to regulatory agencies for approval to market the drug.

Thus, Donanemab was authorised first by the FDA, followed by the MHRA. EMA initially refused authorisation and approved after re-examination.

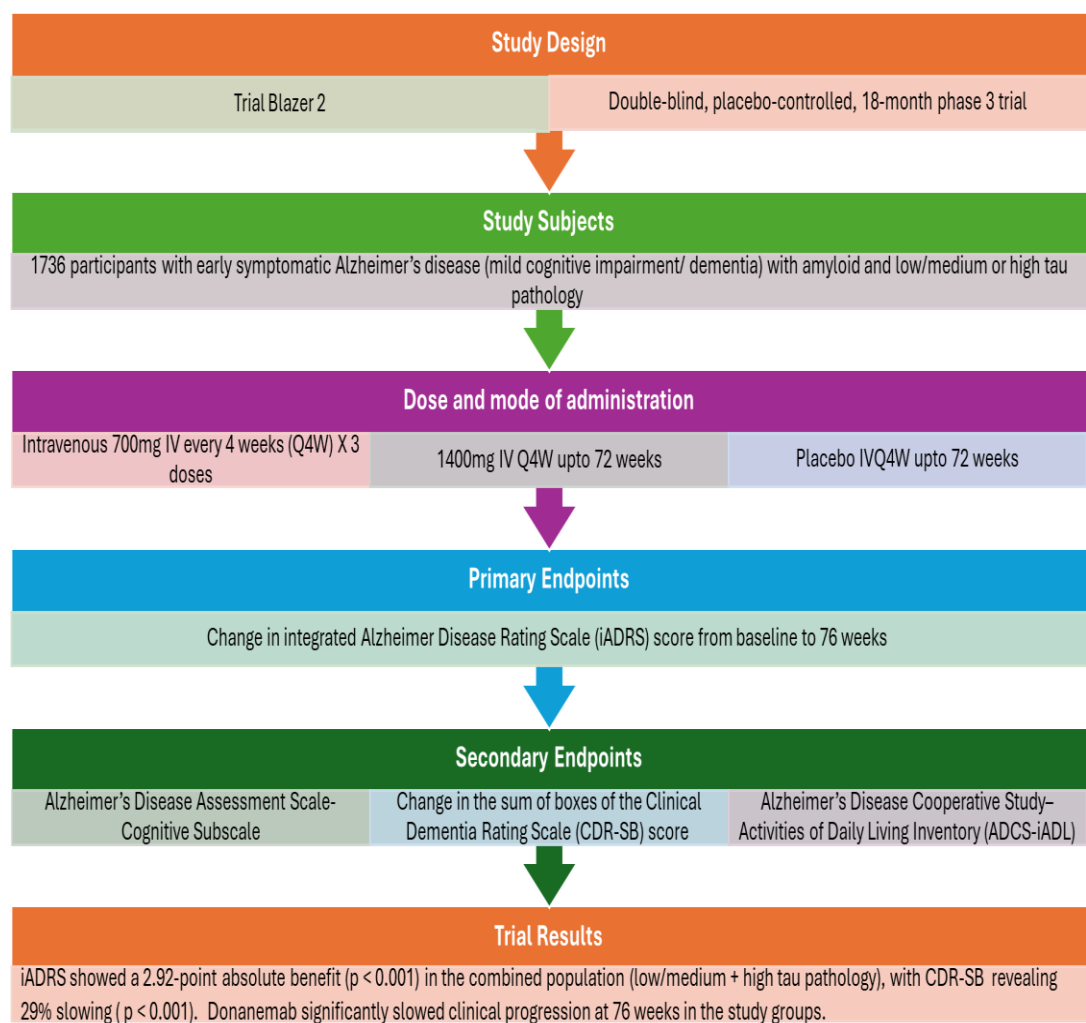


Figure 3. A flowchart of the study design, protocol and results of the Donanemab Phase 3 trial

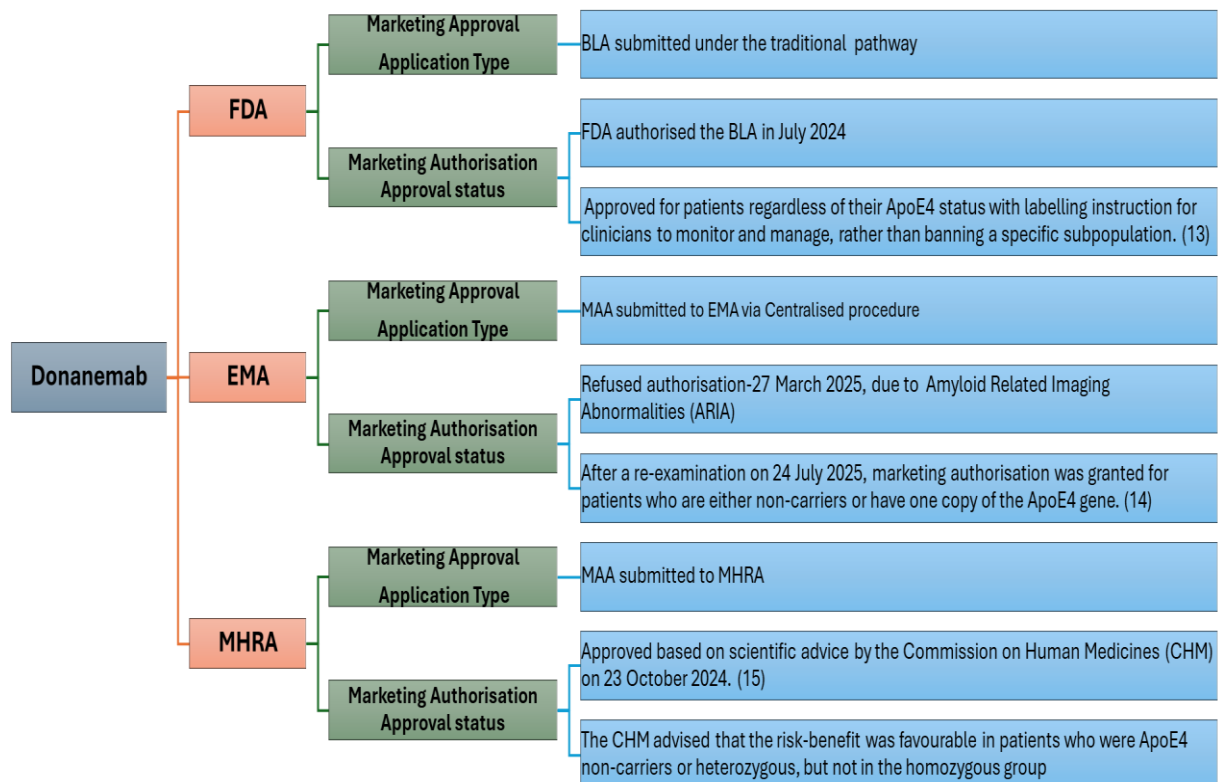


Figure 4. Marketing Authorisation submission and approval status of Donanemab by FDA, EMA and MHRA

Reasons for EMA Rejection

- EMA was concerned about ARIA that occurred in 36.8% of those who received Donanemab compared with 14.9% of them who received placebo. 1.6% of people treated with Donanemab experienced serious ARIA events, including some deaths.
- EMA noted that the benefits of Donanemab were not large enough to outweigh the risks to patients due to ARIA and hence refused its marketing authorisation.

Data submitted to EMA for Re-examination

- Additional safety data submitted from the ongoing phase 3 study revealed that 33.0% of those in the group of ApoE4 noncarriers and those with just one copy of ApoE4 had an ARIA while the rate in those with two copies of the gene was 55.9%.
- A different dosing regimen to reduce the risk of ARIA was proposed based on Phase 3b TRAILBLAZER-ALZ 6 study. This involved administration of lower dose initially.
- The dosing schedule demonstrated that the incidence of ARIA-E was significantly lowered at 24 and 52 weeks using a more gradual titration dosing. This gradual dosing increase still achieved similar levels of amyloid plaque removal and P-tau217 reduction.

Approval conditions

- Taking account of the subject selection restrictions, new dosing regimen and the additional measures to reduce the risk of ARIA, EMA granted marketing approval of Donanemab.
- EMA also mandated additional measures to manage the risk, including more stringent rules for stopping treatment and excluding patients at risk.

Figure 5. EMA Re-examination and Approval of Donanemab

5.3. Case Study 3: Adagrasib/Krazati Clinical Trials For NSCLC

Adagrasib (MRTX849) is an investigational drug studied for the treatment of various cancers, particularly those with KRAS G12C mutations. Genetic changes to the KRAS gene can produce an altered form of the KRAS protein, which causes the uncontrolled growth of cancer cells. Adagrasib, marketed as Krazati, is a targeted KRAS G12C inhibitor that attaches to the altered protein inside cancer cells, interrupting the protein from functioning and thereby slowing the growth and spread of the cells. It also encourages processes that kill the cancer cells. Adagrasib, developed by Mirati Therapeutics, is being studied primarily for the treatment of Non-Small Cell Lung Cancer (NSCLC), Colorectal cancer and other solid tumours with KRAS G12C mutations. (16)

A Phase 1/2 Study of Krazati in patients with cancer having a KRAS G12C Mutation (KRYSTAL-1 Trial: NCT 03785249) was conducted in various locations in the USA and Canada, and the trial results were submitted for approval to the FDA, EMA and MHRA. The documents submitted were as mentioned earlier (Table 2). The KRYSTAL-1 trial study protocol (Figure 6), results and the marketing approval status of different agencies for Adagrasib have been analysed and presented. (Figure 7,8) (17-19)

Various clinical trials are underway assessing combination therapy with Adagrasib. A combination of Adagrasib with

Cetuximab has been given accelerated approval for colorectal cancer by the FDA based on the earlier Phase 1/2 KRYSTAL1 trial data. Confirmation of safety and efficacy, along with clinical benefit, is to be submitted from Phase 3 trials. However, EMA has not yet approved this combination for colorectal cancer.

5.4 Case Study 4: Melphalan Flufenamide Clinical Trial for Multiple Myeloma

Melphalan flufenamide (Pepaxti), also known as Melflufen, is a peptide drug conjugate. It is a lipophilic derivative of melphalan, an older chemotherapy drug used to treat myeloma. Adding a peptide to Melphalan helps Melphalan to rapidly and efficiently find and enter myeloma cells, resulting in a more effective drug. Once Pepaxti is inside myeloma cells, it is broken down into its active form, releasing the Melphalan, which inhibits DNA and RNA synthesis, causing tumour cell death. Pepaxti, developed by Oncopeptides AB, has a different regulatory status in the US and Europe for the treatment of multiple myeloma. (20-22) A Phase 3 trial of the Melflufen-Dexamethasone combination compared with the Pomalidomide-Dexamethasone combination in patients with relapsed, refractory multiple myeloma was submitted to regulatory agencies (FDA: NCT0315811, EMA: EudraCT 2016-003517-95). The OCEAN trial protocol (Figure 9), results and authorisation comparison between different agencies have been represented in Figures 10 and 11.

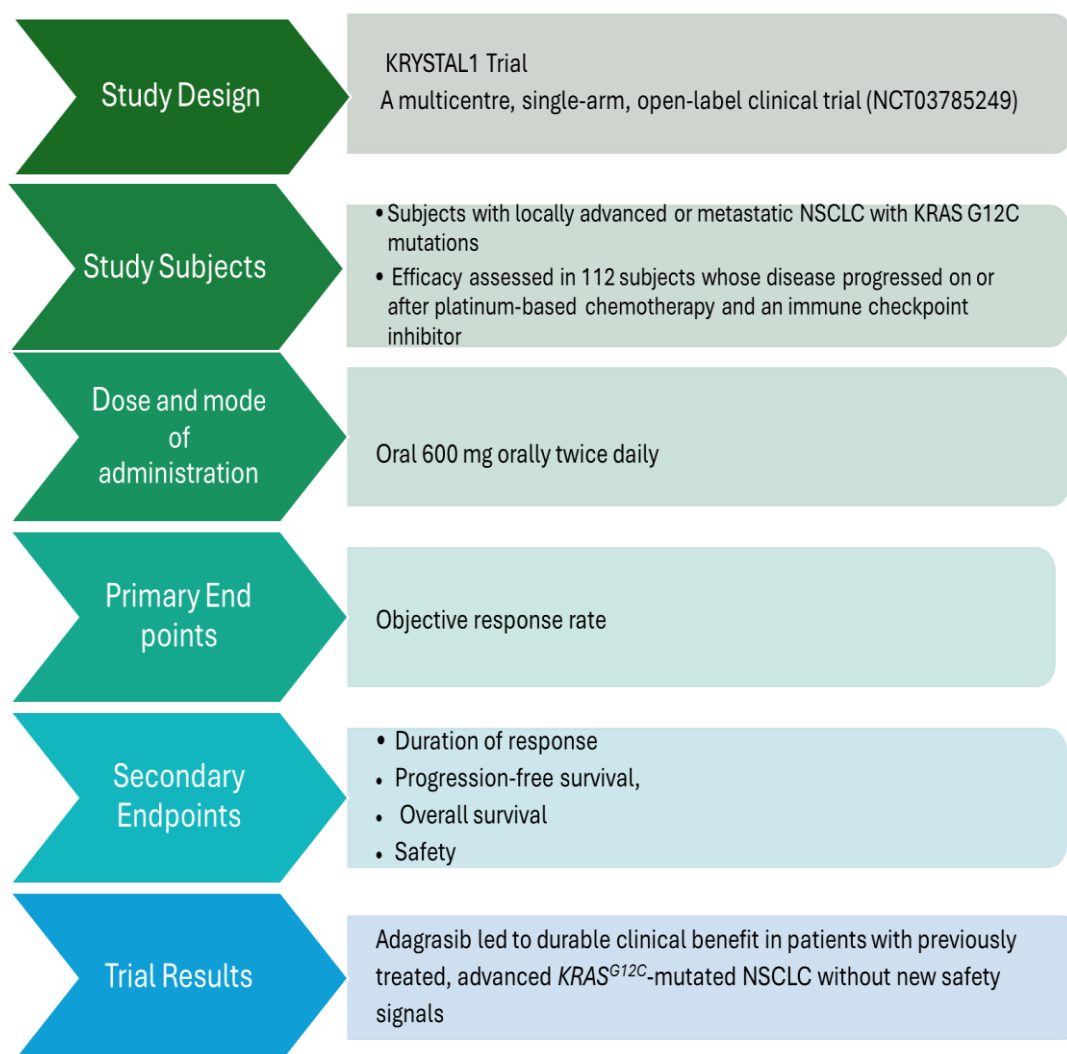


Figure 6. KRYSTAL-1 Trial Study design, Protocol and Results

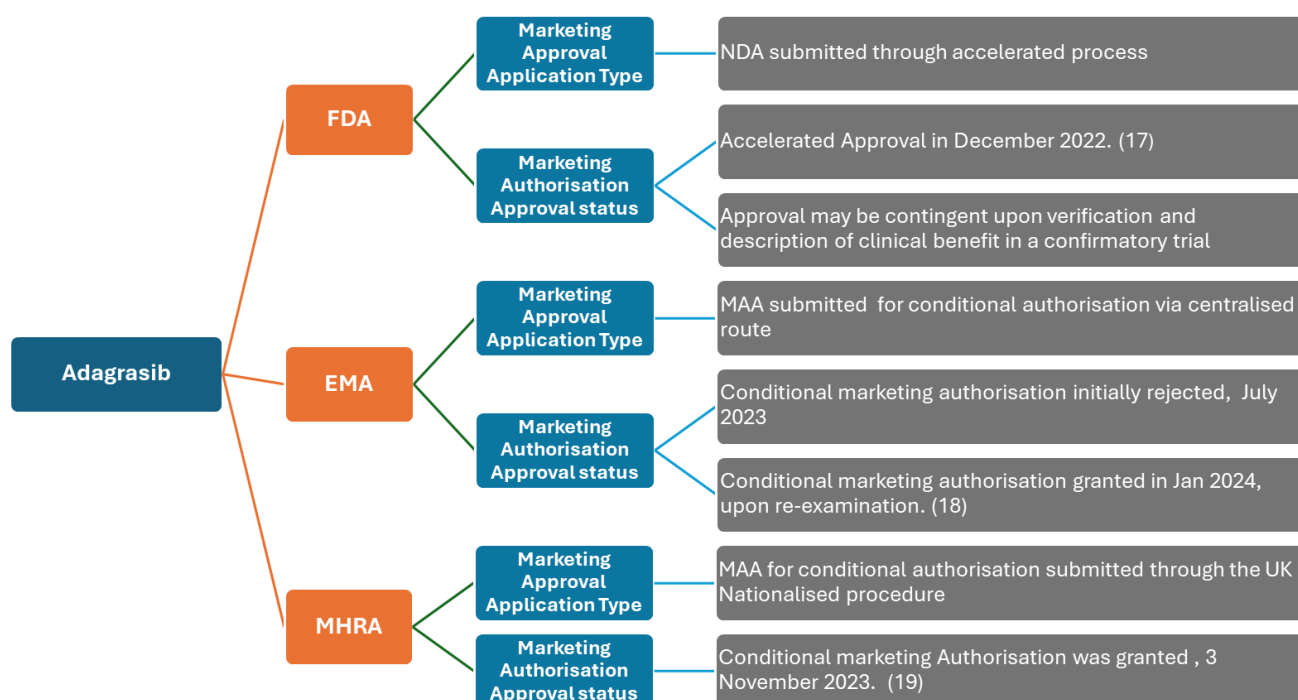


Figure 7. Marketing approval status of Adagrasib/Krazati for NSCLC by FDA, EMA and MHRA

Reasons for EMA Rejection	Data submitted to EMA for Re-examination	Approval conditions
- EMA felt that unmet need, which is essential for conditional authorisation, has not been justified - CHMP took into account preliminary results from a study (CodeBreak 200) with a similar medicine, sotorasib, that cast doubt on the potential benefits of Krazati, as Sotorasib has conditional authorisation for NSCLC. - The study was single-arm; no comparator was assessed. - The absence of an established major therapeutic advantage of Krazati and in view of the non-comprehensive data on efficacy and safety, it is considered that the benefits to public health do not outweigh the risks, and hence additional data are still required.	- On re-examination, the Committee noted that although Sotorasib and Krazati work in a similar way, there are differences between the two medicines. Therefore, the results of the CodeBreak 200 study are not necessarily relevant for Krazati. - In addition, the main study showed that Krazati is of benefit for patients with NSCLC with a KRAS G12C mutation, despite it being a small study with no comparator. - Krazati's different safety profile compared to Sotorasib and Docetaxel (the standard of care for patients with NSCLC whose disease worsened after previous treatment) - Oral administration of adagrasib has advantages over docetaxel (which is given by infusion into a vein)	- Conditional authorisation granted - To further confirm the effectiveness and safety of Krazati, the results of an ongoing study comparing Krazati with Docetaxel in patients with NSCLC with a KRAS G12C mutation who have received at least one prior treatment have to be submitted to the EMA. - Periodic Safety Update Reports are essential.

Figure 8. EMA Re-examination and approval of Adagrasib/Krazati for NSCLC

	FDA	EMA	MHRA
Marketing Approval Application Type Marketing Authorisation Approval status	- NDA application - Granted accelerated approval in February 2021 based on a phase 2 HORIZON clinical trial - Final decision to withdraw approval in Feb 2024 based on the results of OCEAN trial	- MAA centralised procedure - Granted marketing authorisation August 17, 2022.	- MAA national procedure - Granted marketing Authorisation, 11 November, 2022

Figure 9. Marketing Approval status of Pepaxti for Multiple Myeloma by FDA, EMA, and MHRA

a) Marketing authorisation submission and outcome:

The trial results were submitted to the regulatory agencies for marketing authorisation. The trial was approved by the EMA and MHRA, while the FDA rejected approval.

b) Pepaxti approval status:

There was an initial Phase 2 trial called HORIZON, a single-arm study of Melflufen in combination with Dexamethasone in patients with Relapsed Refractory Multiple Myeloma (RRMM) who had received a minimum of 2 prior lines of therapy. These trial data revealed clinical benefits and hence accelerated approval by the FDA in 2021. However, the results of the confirmatory Phase 3 OCEAN trial revealed detrimental OS in the overall population and hence were rejected by the FDA. (19) However, EMA and MHRA based their decision on post hoc analysis restricted to patients without prior ASCT or those with the time to progress at least 3 years from transplantation. The results of this subgroup

analysis were considered clinically relevant and hence approved for this unmet medical need.

5.5: Cancer Drug Trials Rejected or Withdrawn by Regulatory Agencies

While the FDA and EMA agree on approximately 94% of cancer drug approvals, some treatments are rejected or withdrawn by both agencies when confirmatory phase 3 clinical trials fail to confirm the clinical benefit or overall survival (OS) or fail to prove that the potential benefits outweigh the risks. Some examples of cancer drugs that were either rejected by the regulatory agencies or initially approved and later withdrawn from the market are as follows:

a) Olarutumab (Lartuvo) for soft tissue sarcoma: Phase 3 trial (ANNOUNCE) for this drug failed to show an improvement in OS compared to standard chemotherapy and hence resulted in the drug's withdrawal from the global markets in 2019. (23)

b) Romidepsin (Istodax) for peripheral T cell Lymphoma: Ro-CHOP confirmatory trials failed to show clinical benefit, hence withdrawn in 2021 from the US market, while EMA and MHRA refused authorisation. (24)

c) Domvanalimab for gastric and oesophageal cancer: Failure of the Phase 3 STAR-221 trial to improve OS resulted in drug withdrawal from all the agencies. (25)

d) Ukoniq (Umbralisib) for Marginal Zone Lymphoma and Follicular Lymphoma: The UNITY-CLL trial revealed an increased risk of death, and hence, the FDA withdrew its approval in June 2022 after an initial accelerated approval. The drug has not yet been authorised by EMA or the MHRA. (26)

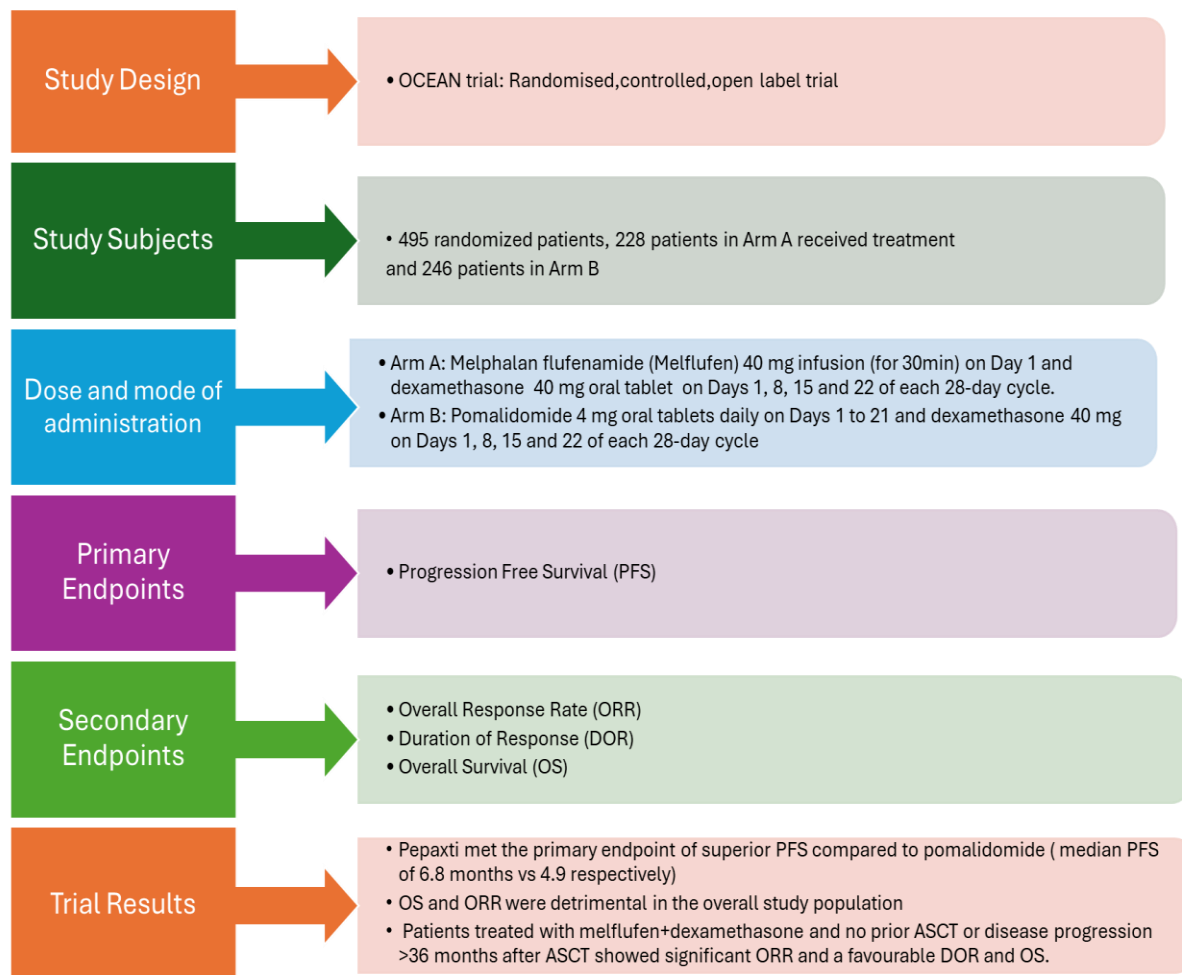


Figure 10. Study Protocol and results of the OCEAN trial for Multiple Myeloma

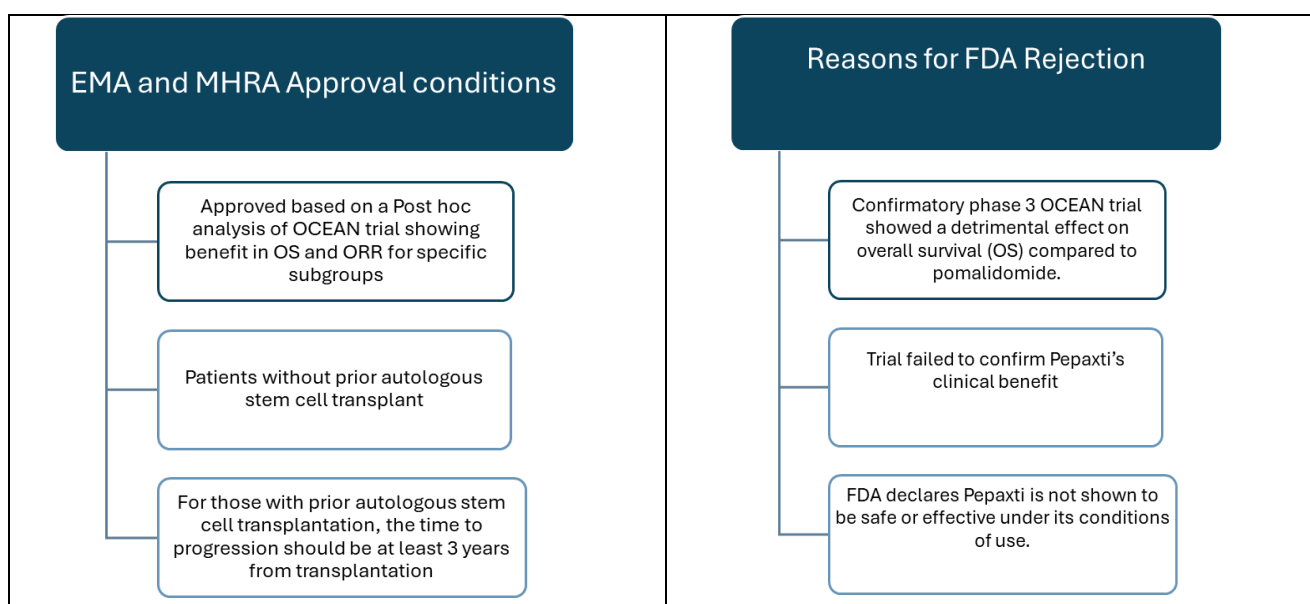


Figure 11. Regulatory divergence in Pepaxti approval status between agencies

6. Evaluation of the Clinical Trial Case Studies:

The global regulatory agencies share the common underlying objective of ensuring safety, efficacy and quality of drugs before they are marketed. The organisations base their decisions on rigorous scientific data from controlled clinical trials. The FDA operates a

fully centralised system; the EMA coordinates a decentralised, multi-country regulation with multiple approval routes; and the MHRA, post-Brexit, is a standalone national authority that combines centralised decision-making with international reliance mechanisms. A summary of the regulatory decisions of the four drug trials analysed in this review is presented in Table 5:

Table 5. Summary of the approval status of the clinical trial case studies

Drug	Condition	Approval status		
		FDA	EMA	MHRA
Dupilumab	COPD	Approved September 2024	Approved July 2024	Approved September 2024
Donanemab	Alzheimer's	Approved July 2024	Rejected March 2025, Approved with subject selection restrictions in July 2025	Approved October 2024
Adagrasib/ Krazati	NSCLC	Accelerated Approval 2022	Rejected Conditional Authorisation July 2023 Granted Conditional authorisation January 2024	Conditional Authorisation November 2023
Melphalan flufenamide	Myeloma	Accelerated Approval 2021 Approval withdrawn February 2024	Approved August 2022	Approved November 2022

6.1 Regulatory Summary of the case studies

From these case studies, it is evident that the FDA, EMA and MHRA differ primarily in their approach to evidence/trial results/endpoints, speed and risk tolerance.

- Dupilumab has been approved by all the regulatory agencies as an add-on maintenance therapy for COPD, and all agencies agreed on common endpoints for approval.
- For Donanemab, the FDA prioritised rapid access based on surrogate markers like amyloid plaque reduction and modest clinical benefits. Conversely, the EMA and MHRA emphasised long-term safety and clear evidence of therapeutic benefit before granting market authorisation. Moreover, EMA and MHRA approval was restricted to a specific genetic subset of individuals (ApoE non-carriers or heterozygotes).
- The FDA approval for Adagrasib and its combination focused on rapid access based on objective response rate from single-arm data, while the EMA necessitates a detailed dossier focused on long-term safety and superiority over standard-of-care. This reveals a significant difference in expectations regarding active comparators in clinical trials. EMA generally expects comparison against existing treatments. FDA traditionally has been more accepting of placebo-controlled trials, even when active treatments exist, provided the trial design is ethical and scientifically sound.
- For Pepaxti, EMA and MHRA authorised the unmet medical need for patients with Multiple Myeloma, who no longer improve with the available therapies. Despite some limitations,

EMA and MHRA considered the results clinically relevant, except for the subgroup of patients who had an autologous stem cell transplant and whose disease progressed within three years of transplantation. Though the FDA granted accelerated approval initially, it withdrew the drug as the results of the confirmatory trial revealed detrimental overall survival in the overall population.

There are some earlier studies which align with the views of our review. A review of regulatory requirements revealed that drug approval in different countries has similarities in the information submitted about safety, efficacy and quality of the drug, but differences occur in the review time, registration and review process. (27)

A study comparing drug approvals of the FDA and EMA between 2013 and 2023 revealed that the FDA significantly authorised more novel drugs than the EMA. The study suggested that the FDA tends to use faster and more flexible approval with greater tolerance for uncertainty in benefit-risk assessments. For accelerated approvals, it relies on surrogate endpoints and limited clinical data. In contrast, the EMA focuses on long-term safety and public health. Minor timing differences were observed, with the FDA authorising drugs earlier. (28)

A review on regulatory frameworks of the US-FDA, EMA and CDSCO elucidated an increasing adoption of harmonised guidelines, electronic submissions and reliance-based approaches. This reflects a global shift towards regulatory convergence. Continued collaboration among regulatory agencies, supported by international organisations such as the ICH, is vital to address the emerging challenges posed by innovative therapies and global health crises. (29)

7. Conclusion

The regulatory divergence between the FDA, EMA and MHRA has created a fragmented regulatory environment for pharmaceuticals. The FDA adopts a flexible and rapid approach to drug approval. Its accelerated approval allows earlier drug access for rare conditions with unmet medical needs but introduces greater uncertainty, which is later addressed through confirmatory trials. In contrast, EMA is conservative, expects an evidence-driven approach and prefers robust clinical endpoints. Although it offers conditional approvals, these are granted with stricter requirements and ongoing annual reassessment. As a result, approvals in the EU tend to occur later but with greater certainty in clinical benefit. Studies designed primarily to satisfy EMA requirements may include active comparators that add complexity and cost, while the FDA might have accepted placebo controls in the trials. The MHRA, post-Brexit, combines elements of both systems by allowing early access through the Early Access to Medicines Scheme (EAMS), while also maintaining conditional approvals like the EMA. Additionally, the MHRA has reliance pathways to recognise decisions from other regulators, which increases its flexibility and speed. In the current scenario of a complex regulatory landscape, a harmonised global drug development strategy is essential. Navigating the requirements of the FDA, EMA, and MHRA through integrated planning, alignment of clinical trial endpoints, mutual reliance initiatives, and strategic first-launch decisions will significantly augment the possibility of successful, effective and timely market entry of pharmaceutical drugs. It is advisable to harness opportunities for collaboration and streamline the processes, ultimately benefiting global public health.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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