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Drug Development and Approval Process, Part 2

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Contents

Phase 1 Trials

Phase 1 Trials: Objectives, Population, Sample Size, and Duration

- Objectives
  - Short-term safety and tolerability
  - Characterize pharmacokinetics and pharmacodynamics
  - Dose finding
- Population
  - Healthy volunteers or people with disease conditions
- Sample size
  - 20 to 100
- Duration
  - Several months

Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Key Concepts in Phase 1 Trials

- Pharmacodynamics
  - Quantitative relationship between drug exposure (i.e., concentration in a reference fluid) and drug effect
  - What the drug does to the body
- Pharmacokinetics
  - Quantitative description of drug disposition in the body over time
  - What the body does to the drug: ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

- Maximum tolerated dose (MTD)
  - The highest dose of a drug or treatment that does not cause unacceptable side effects
- Dose-limiting toxicity (DLT)
  - Toxic effects that are presumably related to the drugs that are considered unacceptable and limit dose escalation
- Half-life
  - The length of time required for the concentration of a drug to decrease to half its starting dose in the body

How to Find the Maximally Tolerated Dose in Phase 1 Trials

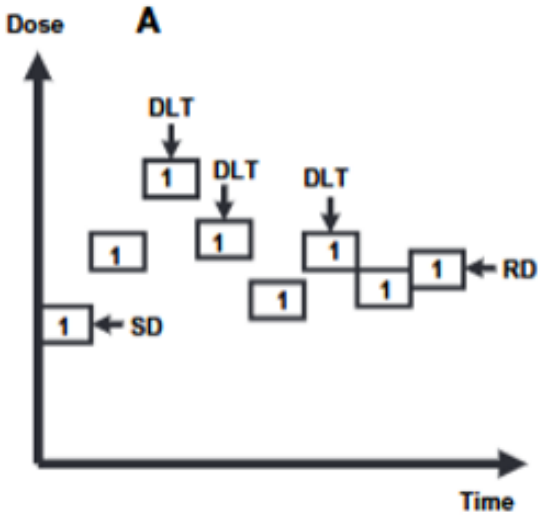
- One of the first steps is to identify the maximally tolerated dose

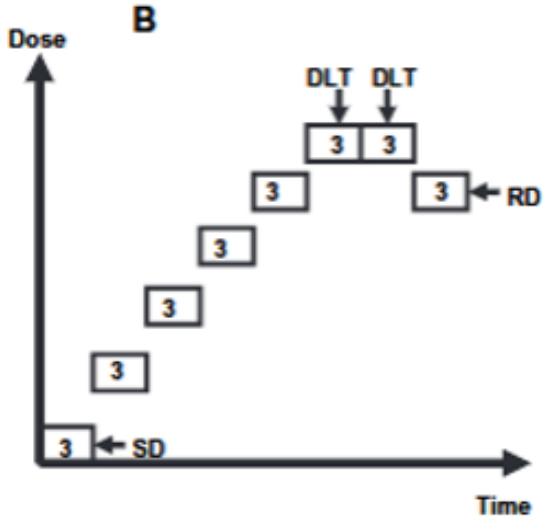
- Traditional design
  - Start with a very low dose and escalate until a prespecified level of toxicity is reached
  - One-third of the participants experience unacceptable toxicity—maximally tolerated dose is reached

- Other approaches
  - Specify a sampling scheme for dose escalation and a statistical model to estimate the maximally tolerated dose
  - Bayesian approaches to assess and escalate with overdose control schemes

Dose Escalation Methods in Phase 1 Trials—1

Simple up-and-down design	Traditional 3+3 design





Note: SD = starting dose; RD = recommended dose; DLT = dose-limiting toxicity

Dose Escalation Methods in Phase 1 Trials—2

- Accelerated titration design
- Pharmacologically guided dose escalation
- Modified continual reassessment method
- Escalation with overdose control

Source: Le Tourneau, C., Lee, J. J., & Siu, L. L. (2009). Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute, 101*(10), 708–720. https://doi.org/10.1093/jnci/djp079

Phase 1a vs. 1b Trials

Phase 1a	Phase 1b
▶ Single ascending dose ▶ Start with a single dose ▶ Pharmacokinetic data and tolerance to drug is determined ▶ Dose escalation occurs until maximally tolerated dose is identified ▶ Goal ▶ Maximally tolerated dose ▶ Pharmacokinetic and pharmacodynamic	▶ Multiple ascending dose ▶ Start with multiple doses ▶ Pharmacokinetic data and tolerance to drug is determined ▶ Provide information quickly as multiple doses are being tested simultaneously ▶ Goal ▶ Finding safe dose for Phase 2

Source: Vial. Retrieved December 5, 2024, from https://vial.com/blog/articles/what-are-the-differences-between-phase-ia-and-phase-ib-clinical-trials/

When to Move to Phase 2?

- Move to Phase 2
  - Once a dose or range of doses is determined
  - Preliminary safety and tolerability is established
  - Pharmacokinetic characteristics are characterized

- What proportion of drugs move from Phase 1 to Phase 2?
  - 52%

Source: BIO, PharmaIntelligence, & QLS. (2021, February). Clinical Development Success Rates and Contributing Factors 2011–2020. Retrieved December 5, 2024, from https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

Phase 2 Trials

Objectives, Population, Sample Size, and Duration of Phase 2 Trials

- Objectives
  - Initial evidence of beneficial activity
  - Medium-term safety, tolerability, and side effects
- Population
  - People with disease condition
- Sample size
  - Up to several hundred people
- Duration
  - Several months to two years

Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Phase 2a vs. 2b Trials

Phase 2a	Phase 2b
▶ Explore efficacy of drug and identify side effects ▶ Proof-of-concept studies ▶ Optimal dose finding—may test multiple doses based on Phase 1 trial ▶ Decide whether to proceed to Phase 2b	▶ Further evaluate the efficacy of the drug and identify side effects ▶ Use confirmed dose from Phase 2a to assess efficacy ▶ Could be considered as “mini–Phase 3” trials ▶ Decide whether to proceed to Phase 3

Endpoints in Phase 2 Trials

Clinical endpoints

- Directly measure the target of the intervention
- *Example: measuring rate of stroke when investigating therapeutic aimed to reduce risk of stroke*
- Phase 2 trials may use less definite clinical endpoints (unstable angina rather than stroke) due to power issues

Surrogate endpoints

- Measure that is expected to predict clinical benefit, but not directly measuring clinical outcome
- *Example: measuring blood pressure reduction when investigating therapeutic aimed to reduce risk of stroke*

Sources: FDA. Retrieved December 5, 2024, from https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development; Friedman, L. M., Furberg, C. D., DeMets, D. L., Reboussin, D. M., & Granger, C. B. (2015). *Fundamentals of clinical trials*. Springer International Publishing.

Uses of Phase 2 Trials

- Phase 2 trials are generally used to decide whether to proceed to Phase 3
- However, sometimes Phase 2 trials are used by regulatory agencies for drug approval—**accelerated approval pathway**

Image source: Microsoft stock image.

Accelerated Approval Pathway—1

- It can take several years (10–15) to develop a drug and learn if a drug has a real effect on how a patient survives, feels, or functions
- A positive therapeutic effect that is clinically meaningful in the context of a given disease is known as “clinical benefit”
- It can take years to measure a drug’s intended clinical benefit
- Sometimes, we can’t afford to wait that long to learn if a drug has a beneficial effect or not

Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Accelerated Approval Pathway—2

- Established by the United States Food and Drug Administration (FDA) in 1992 for approval of drugs during the HIV/AIDS epidemic
  - Allows the use of a surrogate endpoint rather than a clinical endpoint for serious conditions with unmet needs

- A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit
  - Surrogate endpoint: tumor shrinkage, overall response rate
  - Clinical endpoint: death

- Example
  - Pembrolizumab for hepatocellular carcinoma (2018)

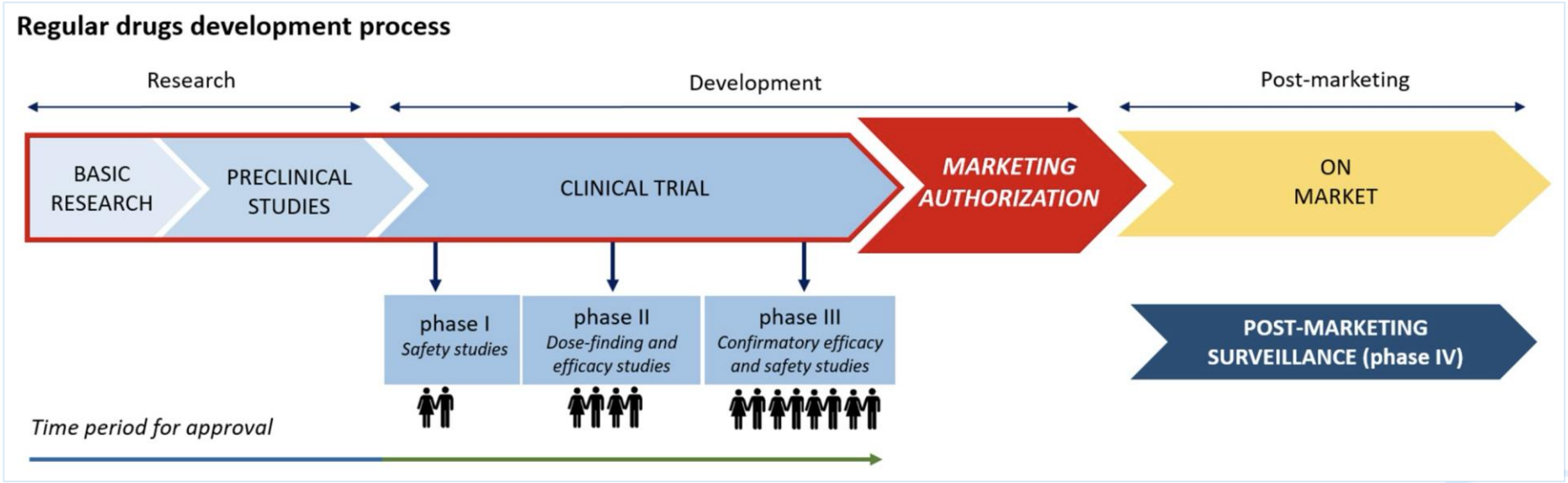
Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program and https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma

Example of Surrogate Endpoints in Cancer

Cancer: hematological malignancies	Cancer: solid tumors
▶ Major hematologic response	▶ Pathological complete response
▶ Durable complete remission rate	▶ Metastasis-free survival
▶ Minimal residual disease response rate	▶ Durable objective overall response rate (ORR)
▶ Event-free survival (EFS)	▶ Progression-free survival (PFS)
▶ Progression-free survival (PFS)	▶ Disease-free survival (DFS)
▶ Durable objective overall response rate (ORR)	

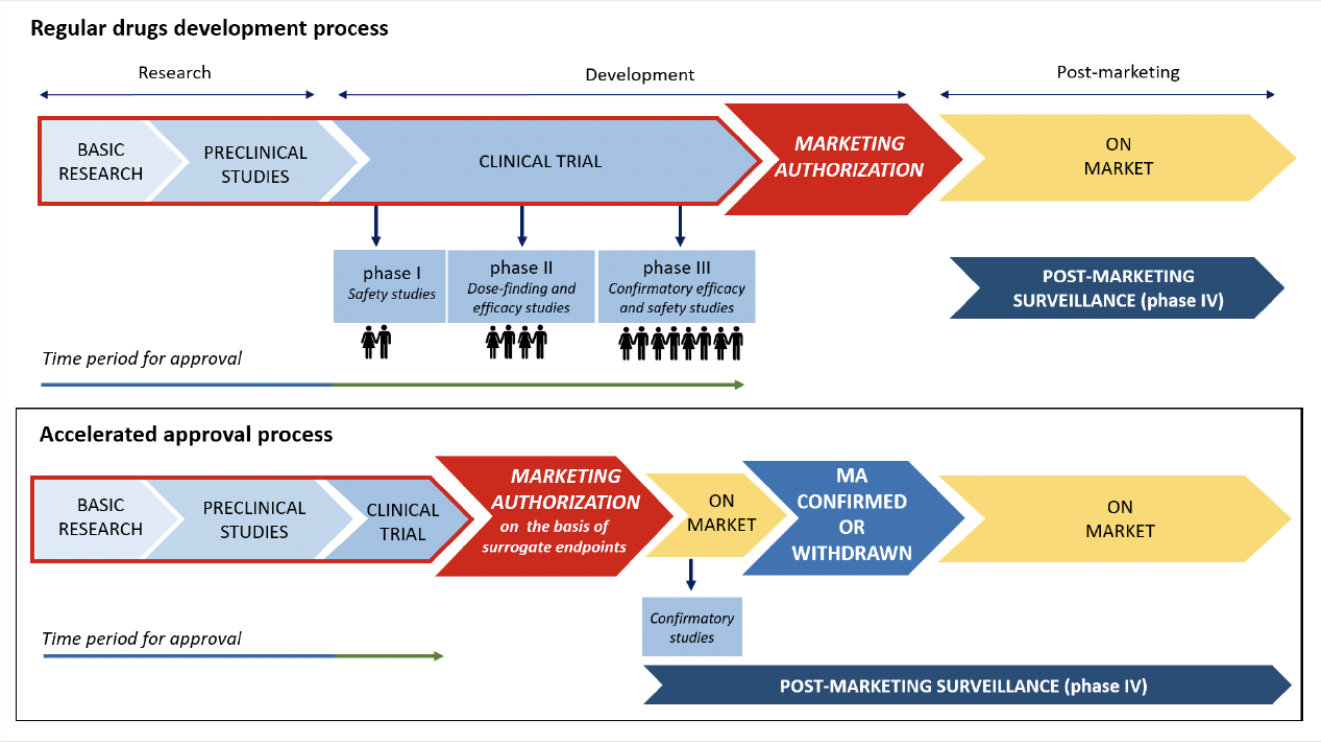
Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Traditional Approval



Source: Scavone, C., di Mauro, G., Mascolo, A., Berrino, L., Rossi, F., & Capuano, A. (2019). *Top portion (Regular drugs development process) of Figure 2. Traditional vs. accelerated development and approval process*. The new paradigms in clinical research: From early access programs to the novel therapeutic approaches for unmet medical needs. *Frontiers in Pharmacology, 10,* 111. https://doi.org/10.3389/fphar.2019.00111. Creative Commons BY.

Traditional vs. Accelerated Approval



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When to Move to Phase 3?

- Move to Phase 3
  - Once efficacy signal is found in Phase 2 trials
  - No major concerns regarding a drug's safety

- What proportion of drugs move from Phase 2 to Phase 3?
  - 28.9%

Source: BIO, PharmaIntelligence, & QLS. (2021, February). Clinical Development Success Rates and Contributing Factors 2011–2020. Retrieved December 5, 2024, from https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

Phase 3 Trials

Phase 3 Trials: Objectives, Population, Sample Size, and Duration

- Objectives
  - Assess the efficacy of interventions
  - Monitor the safety of interventions
- Population
  - People with disease condition
- Sample size
  - 300 to 3,000
- Duration
  - One to four years

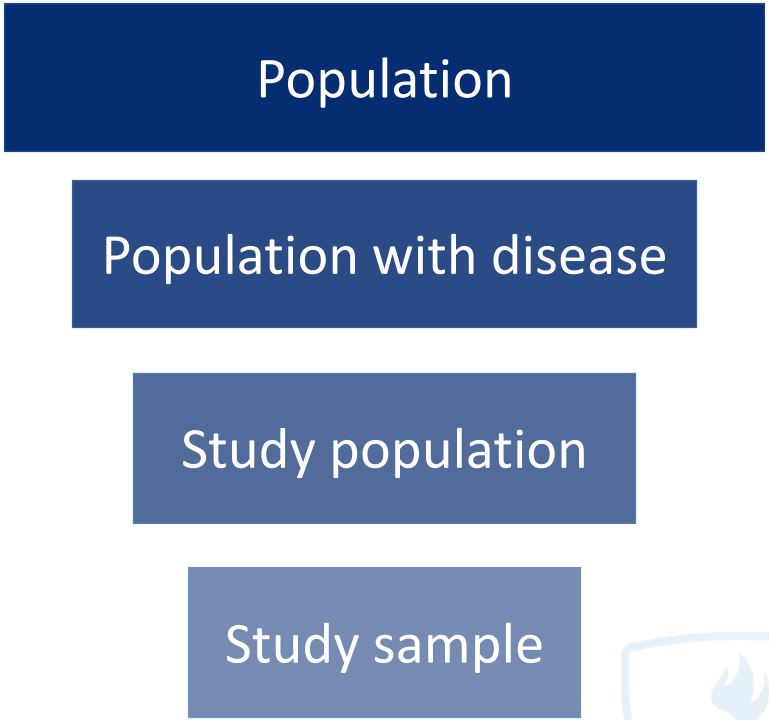
Source: FDA. Retrieved December 5, 2024, from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Phase 3 Clinical Trial

Population	Study design	Randomization
Masking	Data quality and reporting	Analysis

Population

- In clinical trials, a highly selective group of individuals who meet the eligibility criteria are included
  - More likely to benefit from an intervention
  - Less likely to experience adverse events
  - More likely to adhere to the protocol
- Due to highly selective populations in trials, they have high **internal validity**
- Less **external validity** or generalizability



Study Design

- Parallel design
  - Participants are assigned to one intervention for the entirety of the trial
  - Most common design
- Crossover design
  - Participants receive all interventions, but the order in which they receive them is assigned
  - A “washout” period helps isolate effects of interventions
- Factorial design
  - Multiple interventions are explored at the same time, allowing investigation of joint effects
  - Participants receive either treatment A, treatment B, treatment A & B, or no treatment
- Group allocation design
  - Interventions are allocated on the group level rather than on an individual participant level

Source: Kim S. (2024). Overview of clinical study designs. *Clinical and Experimental Emergency Medicine, 11*(1), 33–42. https://doi.org/10.15441/ceem.23.036

Visualization of Study Designs

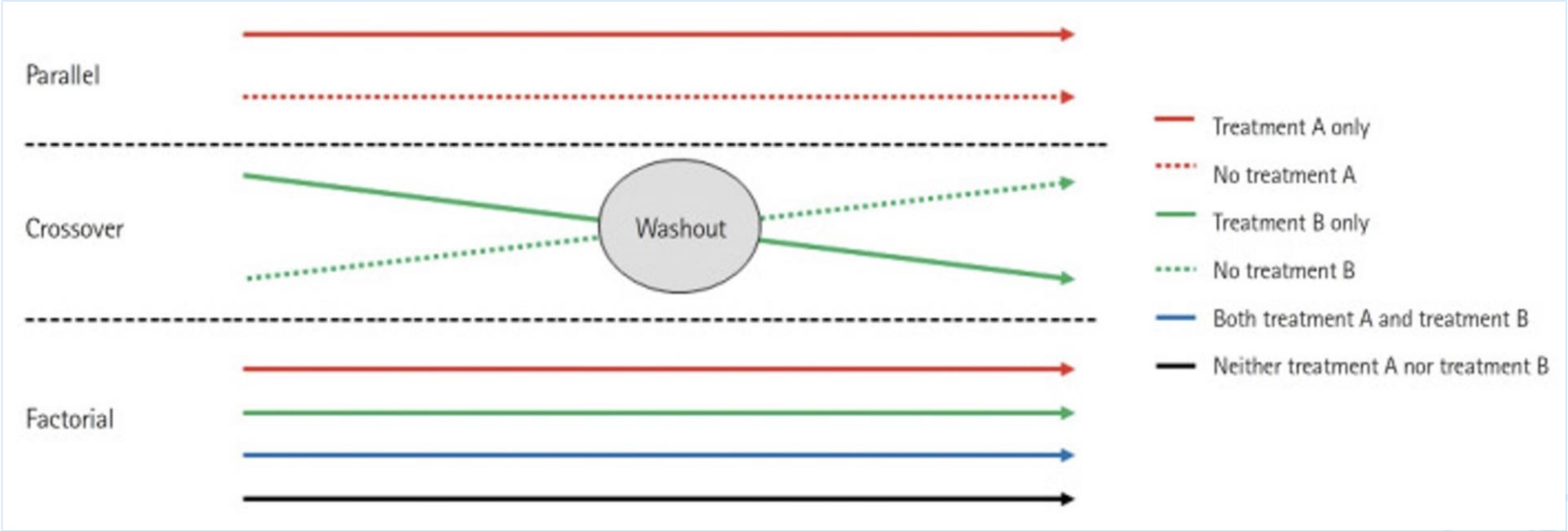


Image source: Kim S. (2024). *Figure 3. Parallel design trial, crossover design trial, and factorial design trial*. Overview of clinical study designs. *Clinical and Experimental Emergency Medicine, 11*(1), 33–42. https://doi.org/10.15441/ceem.23.036. Creative Commons BY-NC.

Randomization

- Randomization is the only factor for treatment assignment
  - Comparable study groups for both known and unknown risk factors
  - Remove investigator bias in the allocation of treatment
- Different methods of randomization
- Fixed allocation
  - Simple
  - Blocked
  - Stratified
- Adaptive
  - Covariate
  - Response

Fixed Allocation Randomization

Simple	Blocked	Stratified
▶ Toss a coin ▶ Random number table or digit generator ▶ With large N, equal people in both groups ▶ Imbalance at any point during trial; 20 people (12:8 or 7:13)	▶ Select a block size, assign patients to treatment based on some probability ▶ Block of four will have six combinations (AABB, ABAB, BAAB, BABA, BBAA, ABBA) ▶ Avoids serious imbalance in the number of participants assigned to each group	▶ Select a strata (age, sex) and perform blocked randomization within each strata ▶ Control the influence of possible characteristics by stratifying

Adaptive Randomization

Covariate	Response
▶ Based on covariate history, this method will assign new patient to the treatment arm to reduce imbalance among two treatment arms	▶ Response-adaptive randomization uses information on participant response to intervention during the course of the trial to determine the allocation of the next participant

Masking—1

- In clinical trial, determining “true” treatment effect is the goal
- Bias is a systematic error
  - Conscious or subconscious factors
  - Occur at design, data analysis, and reporting
- Masking
  - General solution
  - Different types of masking

Masking—2

Masking	Advantages	Limitations
Unblinded	• Necessary for some interventions • Investigators can make informed decisions	• Possibility of bias
Single (patients)	• Investigators can make informed decisions	• Possibility of bias (less than unblinded)
Double (patients, investigators)	• Less bias • Investigator effect is equivalent in both groups	• Complex
Triple (patients, investigators, analysts)	• Best form of blinding • Less bias	• Complex and difficult to blind everyone • Data committee may need to know about side effects

Other Considerations

Data quality and reporting

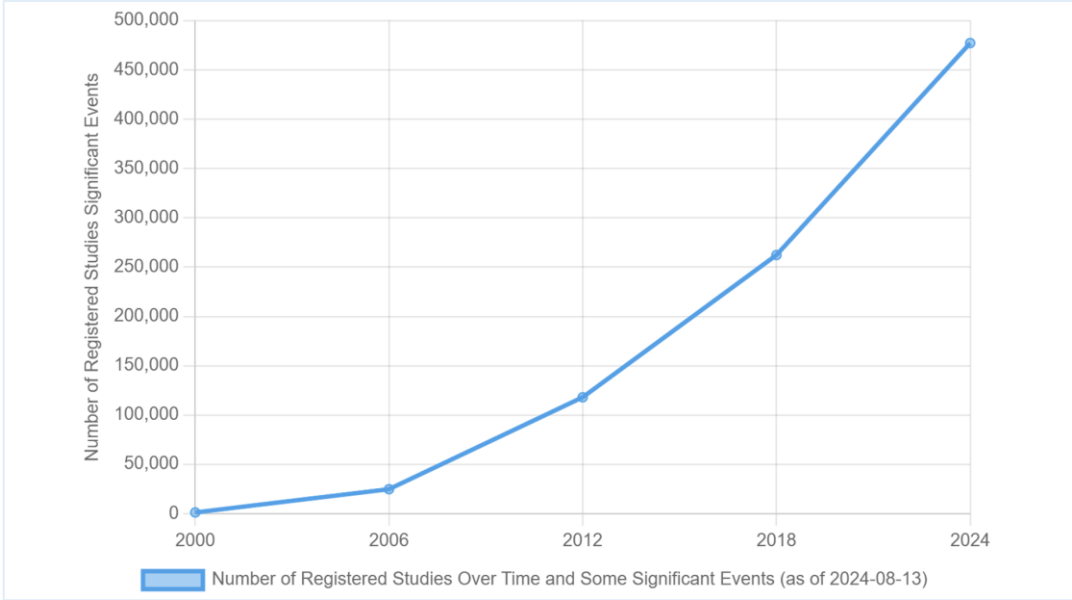
- Four common problems in data collection
  - Missing data
  - Incorrect data
  - Excess variability
  - Delayed submission
- Strategies to collect good-quality data
  - Protocols
  - Data entry tools
  - Training and certifications

Analysis

- Intention-to-treat analysis
  - Analyze study participants based on the treatment to which they were randomized, regardless of their adherence to, or whether they received, the intended treatment
- Per-protocol analysis
  - Analyze study participants who completed the trial as per the protocol

https://clinicaltrials.gov/

- Access to information about clinical trials is important to researchers, health care professionals, and patients
- In 2000, the National Institutes of Health (NIH) developed a web-based registry
  - Although this represents just the beginning of an evolving long-term project, we hope that it may be viewed as an important step toward providing better access to clinical trials information

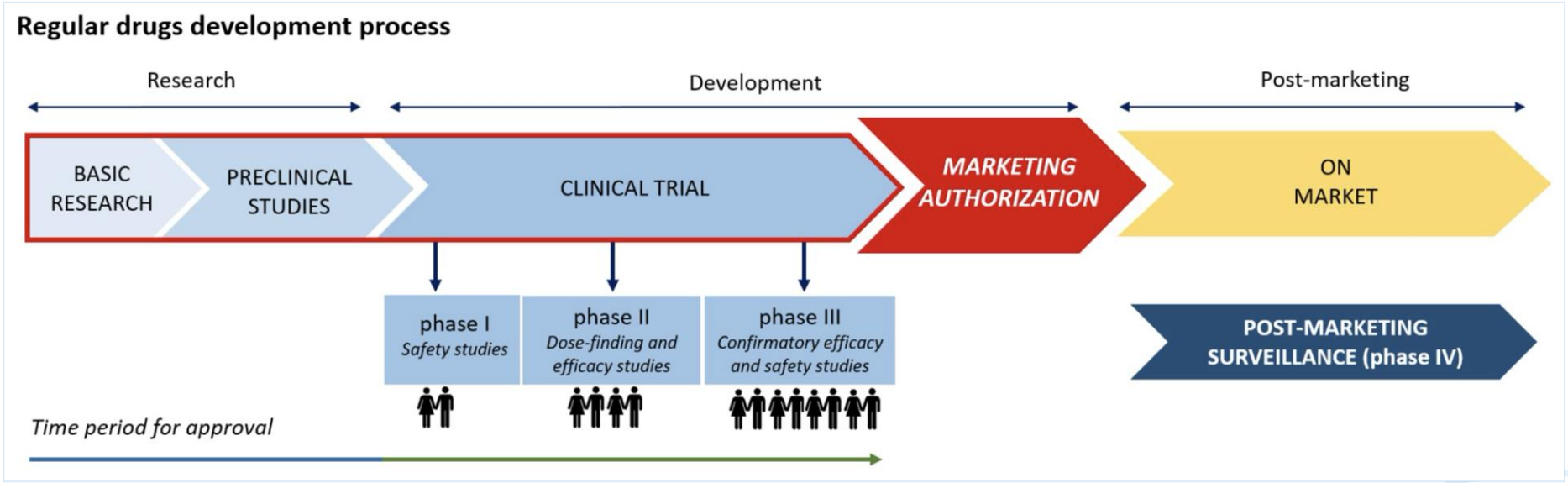


Total number of studies posted on ClinicalTrials.gov since 2000, based on the first posted date

Source: ClinicalTrials.gov. Retrieved December 6, 2024, from https://clinicaltrials.gov/about-site/trends-charts#registeredStudiesOverTime. Public domain.

Phase 4 Studies

Traditional Approval



Source: Scavone, C., di Mauro, G., Mascolo, A., Berrino, L., Rossi, F., & Capuano, A. (2019). *Top portion (Regular drugs development process) of Figure 2. Traditional vs. accelerated development and approval process*. The new paradigms in clinical research: From early access programs to the novel therapeutic approaches for unmet medical needs. *Frontiers in Pharmacology, 10,* 111. https://doi.org/10.3389/fphar.2019.00111. Creative Commons BY.

Phase 3 Provides Some Evidence on Safety, but It's Not Enough—Limitations of Phase 3 Trials Include …

- Trial population
  - Small sample size in a trial vs. thousands or millions of people using the drug in the real world
  - Very young or old people are generally not included in the clinical trial
  - People with comorbidities (who have other disease conditions) may not be included in the trial
- Indication for use
  - Patients at a complex disease stage are often excluded from trials
- Duration of trial
  - Relatively short-term use in the trial vs. long-term use in the real world

Source: FDA. Retrieved December 6, 2024, from https://www.fda.gov/media/103424/download

Institute of Medicine's Report on Drug Safety

Institute or Medicine Report 2006

- The future of drug safety report
- Identified several issues in drug safety
  - Regulatory authority of the the United States Food and Drug Administration (FDA)
  - Regulatory science
  - Financial resources
  - Organizational culture
  - Communication
- In response, the FDA made a number of changes

Food and Drug Administration Amendments Act of 2007 (FDAAA)

- FDA authority to require manufacturers to conduct post-marketing safety studies (Phase 4)
- Population-based surveillance system
- Implementation of risk evaluation and mitigation strategies (REMS), which can require physician certification, mandatory risk communication, or laboratory testing when specific high-risk medications are used

Source: FDA. Retrieved December 6, 2024, from https://www.fda.gov/files/drugs/published/The-Future-of-Drug-Safety---Promoting-and-Protecting-the-Health-of-the-Public.pdf

Phase 4 Studies: Types of Data

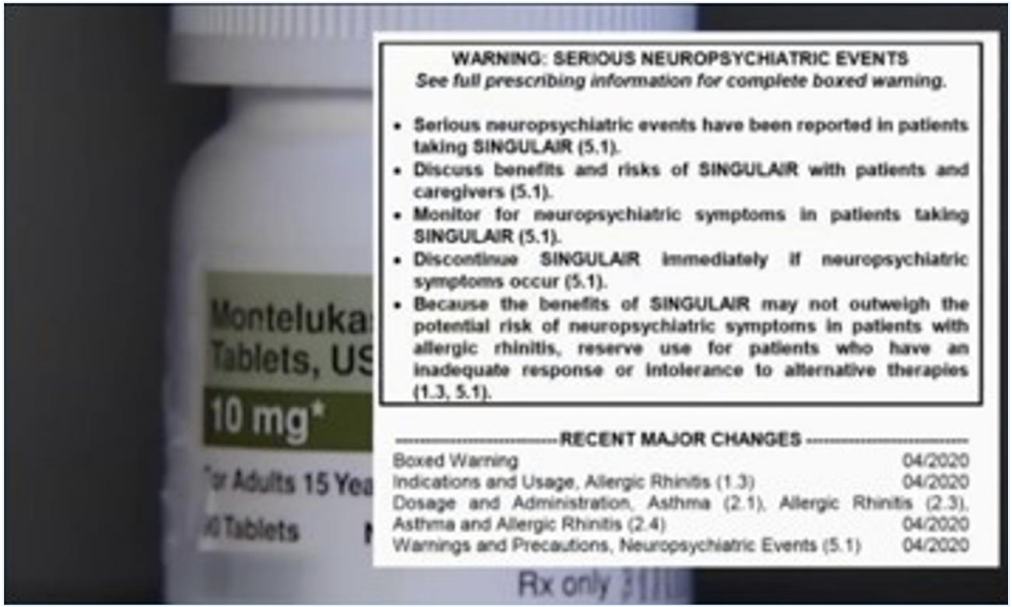
Randomized controlled trial data	▶ Randomized controlled trials ▶ Sibutramine Cardiovascular Outcomes Trial (SCOUT): trial for Meridia (sibutramine) for cardiovascular death
Observational data (primary collection)	▶ Disease-specific registry ▶ Prospective observational cohort study
****Observational data (secondary collection)****	▶ Real-world data ▶ Health care claims or electronic health records data

Source: FDA. Retrieved December 6, 2024, from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-against-continued-use-meridia-sibutramine

Example No. 1: Montelukast

- Phase 4 studies can lead to “black box warning” or “box warning” to warn of serious risks

- Story of Montelukast (Singulair and other generic names)
  - **1998:** approved for asthma and allergy
  - **2019:** FDA conducted an observational pharmacoepidemiologic study
  - **2020:** the FDA issued boxed warning indicating risk of serious neuropsychiatric events



“Serious neuropsychiatric events have been reported … Discuss benefits and risks of Singulair with patients and caregivers …”

Sources: Sentinel. Retrieved December 6, 2024, from https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/neuropsychiatric-events-following-montelukast-use-propensity; FDA. Retrieved December 6, 2024, from https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warning-about-risk-neuropsychiatric-events-associated-asthma-and-allergy
Image source: NBC Miami. Retrieved December 6, 2024, from https://www.nbcmiami.com/news/local/popular-asthma-medicine-being-linked-to-severe-mental-health-side-effects/2313966/

Example No. 2: Rofecoxib

- In rare circumstances, Phase 4 studies can lead to withdrawal of a drug

- Story of rofecoxib (Vioxx)
  - **1999:** the FDA approved Vioxx to treat osteoarthritis, rheumatoid arthritis, and other conditions causing pain
  - **Between 2000 and 2004:** several pharmacoepidemiological studies and one clinical trial showed increased risk of cardiovascular problems
  - **2004:** rofecoxib (Vioxx) was withdrawn from the market

- It is estimated that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died

Source: Prakash & Valentine. (2007, November 10). Timeline: The rise and fall of Vioxx. NPR. Retrieved December 6, 2024, from https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx
Image source: Getty Images. Retrieved from the BBC website December 6, 2024, at https://www.bbc.com/news/business-35328099

Case Study: From Phase 1 Trial to Phase 3 Trial

LCZ696: Phase 1 Clinical Trial

- Novel, dual-acting angiotensin receptor–neprilysin inhibitor (ARNi) (valsartan + sacubitril) for heart failure
- Dose escalation study: randomized, double-blind, placebo-controlled, parallel-group study among healthy volunteers
  - Eight cohorts of 10 individuals (eight drug and two placebo in each cohort)
    - Four cohorts received a single dose (200, 600, 900, 1200 mg)
    - Four cohorts received multiple doses (50, 200, 600, and 900 mg)
    - Escalation to the next dose was allowed given satisfactory safety and tolerability data
- LCZ696 was well tolerated when administered as a single doses of up to 1200 mg or as multiple doses of up to 900 mg once daily
- "These data support further clinical development of LCZ696, a novel, orally bioavailable, dual-acting ARNi for hypertension and heart failure"

Source: Gu, J., Noe, A., Chandra, P., et al. (2010). Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *Journal of Clinical Pharmacology, 50*(4), 401–414. https://doi.org/10.1177/0091270009343932

LCZ696: Phase 2 Clinical Trial (PARAMOUNT)

- **Design:** randomized, double-blind, parallel-group, active controlled trial
- **Population:** patients with New York Heart Association (NYHA) Class II–III heart failure
- **Treatment:** 308 patients treated for 36 weeks
  - 149: LCZ696 200 mg twice daily
  - 159: valsartan 160 mg twice daily
- **Outcome:** NT-proBNP, a marker of left ventricular wall stress, at 12 weeks
- "LCZ696 could have favorable effects in patients … further testing of the drug in this patient population might be warranted"

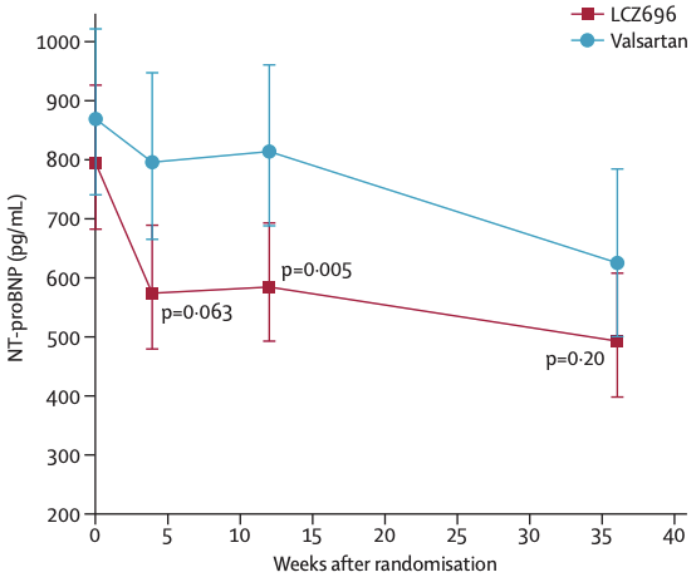


Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

Source: Solomon, S. D., Zile, M., Pieske, B., et al., & Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. (2012). *Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups*. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. *Lancet (London, England), 380*(9851), 1387–1395. https://doi.org/10.1016/S0140-6736(12)61227-6

LCZ696: Phase 3 Clinical Trial (PARADIGM-HF)—1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

Source: McMurray, J. J., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Shi, V. C., Solomon, S. D., Swedberg, K., Zile, M. R., & PARADIGM-HF Investigators and Committees (2014). Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England Journal of Medicine, 371*(11), 993–1004. https://doi.org/10.1056/NEJMoa1409077

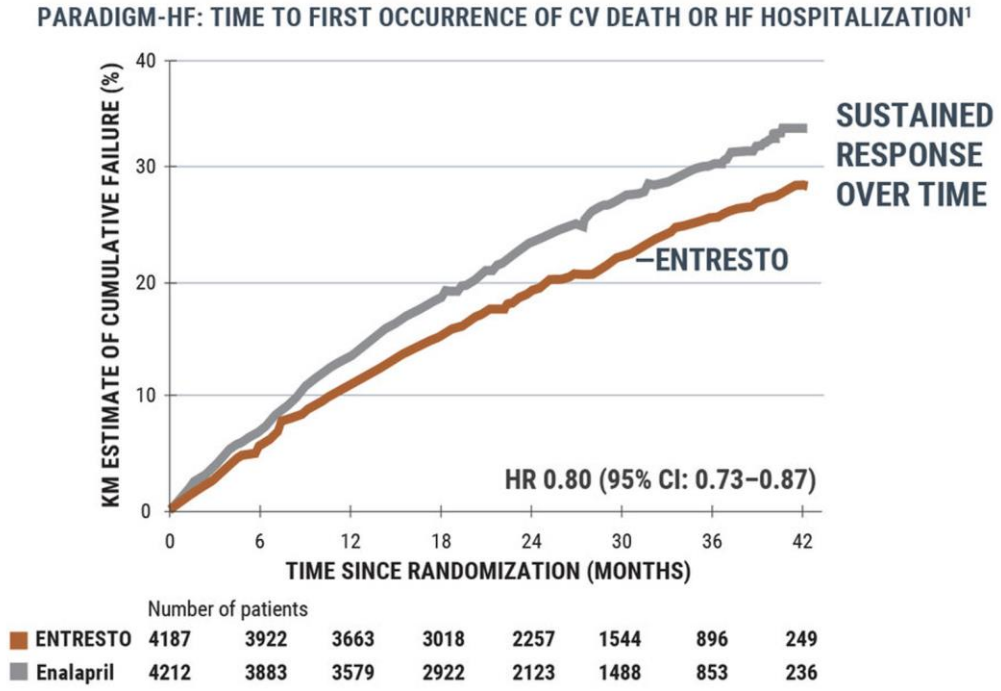
LCZ696: Phase 3 Clinical Trial (PARADIGM-HF)—2

- **Design:** randomized, double-blind, parallel-group, active controlled trial
- **Population:** symptomatic (NYHA Class II–IV) HFrEF* patients (LVEF† ≤40%)
- **Treatment**
  - 4,187: LCZ696 200 mg twice daily
  - 4,212: enalapril 10 mg twice daily
- **Outcome:** composite of death from cardiovascular causes or a first hospitalization for heart failure

- **Statistical analysis**
  - Intention-to-treat analysis by including all individuals who were randomized
  - Kaplan–Meier analysis to analyze primary outcome
    - A commonly used approach to analyze time-to-event data
  - Analysis among 18 prespecified subgroups

*Heart failure with reduced ejection fraction
†Left ventricular ejection fraction

LCZ696: Phase 3 Clinical Trial (PARADIGM-HF)—3

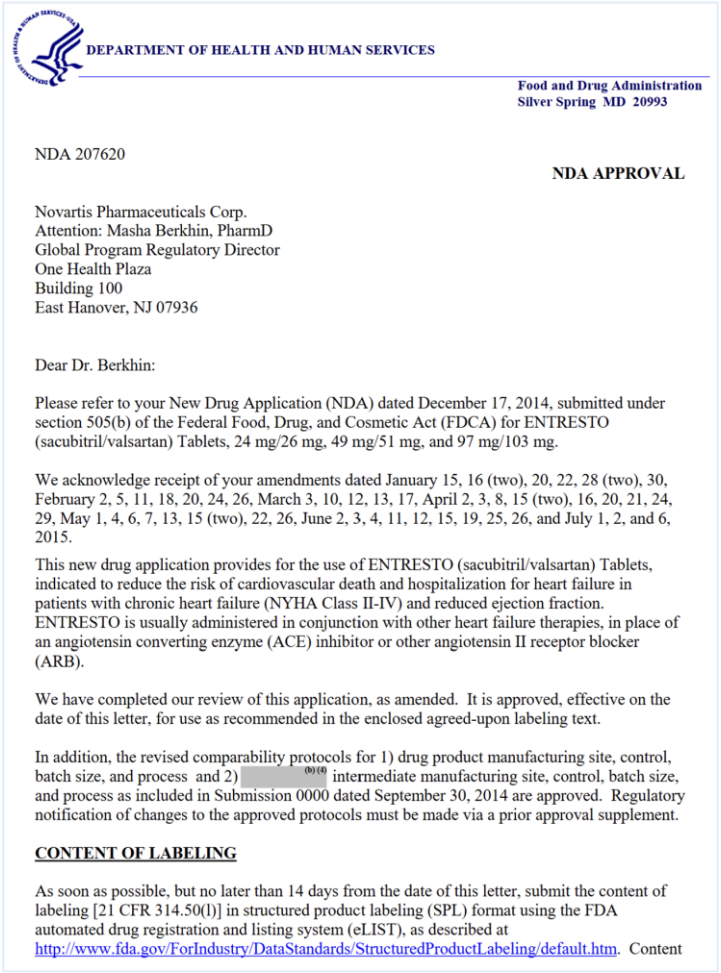


- The primary outcome occurred in …
  - 21.8% in the LCZ696 group
  - 26.5% in the enalapril group
  - Hazard ratio, 0.80 (95% CI, 0.73 to 0.87)
- No major safety concerns
- **“LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure”**

Image source: Retrieved December 6, 2024, from https://www.entrestohcp.com/hfref/clinical-trial-biomarker-data

FDA Approval

- FDA approved Entresto in July 2015
- NDA approval letter



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207620

NDA APPROVAL

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTRESTO (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of your amendments dated January 15, 16 (two), 20, 22, 28 (two), 30, February 2, 5, 11, 18, 20, 24, 26, March 3, 10, 12, 13, 17, April 2, 3, 8, 15 (two), 16, 20, 21, 24, 29, May 1, 4, 6, 7, 13, 15 (two), 22, 26, June 2, 3, 4, 11, 12, 15, 19, 25, 26, and July 1, 2, and 6, 2015.

This new drug application provides for the use of ENTRESTO (sacubitril/valsartan) Tablets, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

In addition, the revised comparability protocols for 1) drug product manufacturing site, control, batch size, and process and 2) (b)(4) intermediate manufacturing site, control, batch size, and process as included in Submission 0000 dated September 30, 2014 are approved. Regulatory notification of changes to the approved protocols must be made via a prior approval supplement.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

Image source: FDA. Retrieved December 9, 2024, from https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf

Summary

Lecture Summary

1. **Phase 1 trial:** primarily done to evaluate short-term safety and tolerability; dose-finding trial
2. **Phase 2 trial:** proof-of-concept studies to evaluate the efficacy of the drug; accelerated approval pathway for speedy drug approval
3. **Phase 3 trial:** pivotal clinical trial based on which drug is approved by the FDA; key design elements such as study design, randomization, and masking
4. **Phase 4 trial:** post-marketing safety surveillance studies to continuously monitor adverse events in the real world
5. **Case study:** example of a drug showing how it moved through different phases of clinical trials