

THE PATH TO FDA APPROVAL

Preclinical Research—Before a drug is tested in humans, laboratory and animal testing is performed to determine whether it's likely to be safe and work well in humans. This stage can last approximately 3 to 4 years.

Clinical Research Phases 1 to 3—When a drug compound has shown promise in preclinical research and the decision is made to proceed to clinical testing in humans, an Investigational New Drug Application (IND) is filed by the sponsor or drug company with the United States Food and Drug Administration (FDA). Clinical studies of the drug can be initiated 30 days after the FDA receives the IND unless the FDA places a clinical hold on the investigation. Clinical studies generally occur in three separate phases:

Phase 1: A small study usually involving healthy adult volunteers that requires approximately 12 to 18 months to complete. Phase 1 studies are used to determine the drug's basic properties and its safety when given to humans.

Phase 2: A medium-sized study involving patients with the disease or condition under study that may require at least 2 years to complete. Phase 2 studies are used to test the effectiveness of the drug and to collect additional safety information.

Phase 3: A large study that may require 3 or more years to complete. In Phase 3 studies, more information on the drug's safety and effectiveness is collected from a larger and more diverse patient population.

FDA Review Process—When the drug company has obtained sufficient preclinical and clinical information to allow the FDA to assess the safety and effectiveness of the study drug, the company submits a New Drug Application (NDA) or Biologics License Application (BLA) to the FDA for marketing approval. NDAs/BLAs include detailed information on topics such as the drug's proposed use or uses, chemistry/manufacturing/controls, and clinical information. Once the FDA receives an NDA/BLA, a team of scientists independently reviews the application to determine if the drug's health benefits outweigh its known risks. The FDA review process can take variable lengths of time, depending on the drug, but the process may require months to years until a decision is reached. Even if the FDA approves a drug for sale over the counter or by prescription, the FDA might require additional clinical studies to be performed to further address the drug's safety and effectiveness.

Phase 4—After a drug or treatment has been approved by the FDA and is being marketed, Phase 4 studies might be performed to continue to assess its safety and effectiveness over a longer period of time and in a larger number of people.

ORPHAN DRUG PROGRAMS

In 1983, the United States Congress passed the "Orphan Drug Act" to encourage the development of treatments for rare diseases and conditions, which are defined as those affecting fewer than 200,000 Americans. This law provides a number of business incentives for drug companies to develop orphan drugs, such as:

- ❖ Seven years of market exclusivity after approval
- ❖ Tax incentives for clinical research
- ❖ Research study design assistance
- ❖ Grant funding to defray costs of clinical trials

In order to obtain orphan designation for a drug, a company must submit an application to the FDA's Office of Orphan Products Development (OOPD) prior to its submission of a marketing application of the drug for the intended orphan use.

Drugs that have been approved for orphan status generally must travel the same regulatory development path as any other pharmaceutical product, and their safety and effectiveness must be established through adequate and well-controlled studies. However, clinical trials for rare diseases might involve different types of study designs, some of which allow for only a fraction of the number of patients used in larger-scale trials for drugs that treat more common diseases. For example, orphan drug regulations might provide a waiver of the required 1,000 patients for a Phase 3 clinical trial when fewer than 1,000 people can participate in the trial.

FAST-TRACK DESIGNATION

The FDA Modernization Act (FDAMA) of 1997 included the "fast-track designation," a new process designed to speed the development and expedite the review of certain drugs. To qualify for fast-track designation, a drug must be used for a serious or life-threatening disease and must have the potential to address an unmet medical need. Fast-track designation can be granted early in the clinical development process and if granted, emphasizes close and early communication between FDA and the drug company. Marketing applications for drugs granted fast-track designation are commonly given a priority review and accelerated approval by the FDA.

RESOURCES AND REFERENCES

- Buckley BM. Clinical trials of orphan medicines. *Lancet*. 2008 Jun 14;371(9629):2051-5.
- Graul AI. Promoting, improving and accelerating the drug development and approval processes. *Drug News Perspect*. 2009 Jan-Feb;22(1):30-8.
- Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA; Rare Diseases Clinical Research Network. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab*. 2009 Jan;96(1):20-6.
- Haffner ME. Adopting orphan drugs—two dozen years of treating rare diseases. *N Engl J Med*. 2006 Feb 2;354(5):445-7.
- Moore SW. An overview of drug development in the United States and current challenges. *South Med J*. 2003 Dec;96(12):1244-55.
- U.S. Food and Drug Administration: <http://www.fda.gov>



ABOUT ENOBIA PHARMA, INC.

Enobia Pharma, Inc. is a private Montreal-based company focused on the development of therapeutics to treat serious bone disorders for which there are no drug therapies currently approved. ENB-0040, an investigational drug for the treatment of hypophosphatasia (HPP), is the Company’s lead program.

ENB-0040 OVERVIEW

There are currently no therapies approved for hypophosphatasia (HPP), a rare, inherited, and sometimes fatal metabolic bone disease characterized by poor bone mineralization and profound skeletal defects. ENB-0040, a type of enzyme replacement therapy, is an investigational treatment for HPP. ENB-0040 was awarded orphan designation in the United States in 2008 and fast-track designation in 2009 and is currently in Phase 2 clinical development.

CLINICAL STUDIES WITH ENB-0040

Clinical Studies

Approx. Age

(at enrollment): 0–5 yrs

6–13 yrs

13–18 yrs

18 + yrs

Phase 1				001-08 Study (6 pts enrolled)

Phase 2	002-08 Infant Study (11 pts enrolled)	006-09 Juvenile Study (13 pts enrolled)	009-10 Adolescent & Adult Study (18 pts enrolled)	
	003-08 Infant Extension Study (10 pts enrolled)	008-10 Juvenile Extension Study (12 pts enrolled)		
	010-10 Infant Study (~35 pts expected)			
Phase 3/4	As necessary			

Enrolling	Ongoing	Complete
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Phase 1 Clinical Trial

Study 001-08: A Multicenter, Open-Label, Dose Escalating Study of the Safety, Tolerability and Pharmacology of Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein (ENB-0040) in Adults With Hypophosphatasia (HPP)

Patients enrolled: 6

Status: Completed; successfully met primary endpoint(s)

Phase 2 Clinical Trials

Study 002-08: A Multicenter, Open-Label Study of the Safety, Tolerability and Pharmacology of ENB-0040 (Enobia's Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in up to 10 Severely Affected Patients With Infantile Hypophosphatasia (HPP)

Patients enrolled: 11

Status: Completed; successfully met primary endpoint(s)

Study 003-08: Extension Study of Protocol 002-08 of ENB-0400 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Severely Affected Infants and Young Children With Hypophosphatasia (HPP)

Patients enrolled: 10

Status: Ongoing, but not recruiting participants

Study 006-09: A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Historical Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Children With Hypophosphatasia (HPP)

Patients enrolled: 13

Status: Completed; successfully met primary endpoint(s)

Study 008-10: Extension Study of Protocol ENB-006-09 Evaluating the Long-term Safety and Efficacy of ENB-0040 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Children With Hypophosphatasia (HPP)

Patients enrolled: 12

Status: Ongoing, but not recruiting participants

Study 009-10: A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Concurrent Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Adolescents and Adults With Hypophosphatasia (HPP)

Patients enrolled: 18

Status: Ongoing, but not recruiting additional participants

Study 010-10: An Open-Label, Multicenter, Multinational Study of the Safety, Efficacy and Pharmacokinetics of ENB-0040 in Infants and Children < 5 Years of Age With Hypophosphatasia (HPP)

Estimated enrollment: 35

Status: Currently recruiting participants

GLOSSARY

Biologics - A wide range of products such as vaccines, blood and blood components, gene therapy, tissues/cells, and proteins created by biological processes used in the prevention or treatment of disease.

Bone mineralization - The process by which the body uses minerals to build bone structure.

Clinical study/trial - A research study that uses consenting human subjects to test the safety and efficacy of new therapeutic interventions and diagnostic tests.

ENB-0040 - A subcutaneous enzyme replacement therapy with affinity for bone that is currently in clinical trials.

Endpoint - Occurrence of a disease, symptom, sign, or laboratory abnormality that is one of the target outcomes of the trial.

Enzyme - A molecule that catalyzes or triggers biochemical reactions.

Enzyme replacement therapy - A medical treatment that replaces an enzyme in patients who either lack or have a deficient form of the particular enzyme.

Fast-track designation - A process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need.

Hypophosphatasia (HPP) - A rare, inherited, and sometimes fatal metabolic bone disease characterized by poor bone mineralization and profound skeletal defects.

Orphan drug - A pharmaceutical agent that has been developed specifically to treat a rare medical condition.

Preclinical studies - Research done prior to a clinical study.

ADDITIONAL INFORMATION

MedlinePlus Health Information: <http://ghr.nlm.nih.gov>

National Institutes of Health Office of Rare Diseases Research: <http://rarediseases.info.nih.gov>

Orphan Net: <http://www.orpha.net>

U.S. National Institutes of Health clinical trial registry: <http://www.clinicaltrials.gov>

Enobia Pharma: <http://www.enobia.com>

PATIENT SUPPORT

NORD: National Association for Rare Disorders (USA): <http://www.rarediseases.org>

Soft Bones: The US Hypophosphatasia Foundation: <http://www.softbones.org>

The MAGIC Foundation: <http://www.magicfoundation.org>