Third Generation EGFR TKI for the Treatment of Non-small Cell Lung Cancer

With Strong Inhibitory Effect on EGFR T790M Mutations

Overview

Drug Name	FHND41
Description	Acquired T790M mutation is the most common cause of resistance for patients with epidermal growth factor receptor (EGFR) mutations to progress after treatment with first-line EGFR tyrosine kinase inhibitors (TKIs) in advanced non-small cell lung cancer (NSCLC). Because of the limited effectiveness of second-generation TKIs in circumventing the resistance of T790M to first-generation TKIs, the development of third-generation TKIs is needed. FHND41 is a third-generation TKI that selectively inhibits EGFR mutations, especially the T790M mutation. It is administered orally in capsule form. FHND41 is being developed in phase 3 clinical trials for first-line treatment of EGFR-positive advanced NSCLC and second-line treatment of EGFR T790M mutation-positive NSCLC.
Target	EGFR
Drug Modality	Small molecule
Indication	NSCLC
Product Category	Tyrosine kinase inhibitor
Mechanism of Action	Irreversibly binding to EGFR and selectively inhibiting EGFR mutations
Status	Phase III (NMPA)
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for FHND41. Potential collaboration can be strategic alliance, licensing, or marketing agreement.

E-mail: inquiry@protheragen.com

www.protheragen.com

101-4 Colin Dr, Holbrook, NY 11741, USA

Target

Epidermal Growth Factor Receptor

Introduction	The epidermal growth factor receptor (EGFR) is a commonly expressed transmembrane glycoprotein of the growth factor receptor tyrosine kinase family. EGFR is expressed in many normal human tissues, and activation of the proto-oncogene results in elevated EGFR expression in many types of human tumors. The extracellular domain of the EGFR binds several ligands, including EGF and transforming growth factor alpha (TGF-α). Ligand binding activates the tyrosine kinase activity of the intracellular domain of the EGFR, triggering cell division and proliferation, and tumor cell dissemination and escape from apoptosis.
Approved Name	Epidermal growth factor receptor
Official Symbol	EGFR
Gene Type	Protein coding
Synonyms	ERBB; ERBB1; ERRP
Ensembl	ENSG00000146648
Gene ID	1956
mRNA Refseq	NM_005228.5
Protein Refseq	NP_005219.2
OMIM	131550
UniProt ID	P00533
Chromosome Location	7p11.2

Clinical Resources

Gene Function	EGFR is a cell surface protein that binds to epidermal growth factor, thus inducing receptor dimerization and tyrosine autophosphorylation leading to cell proliferation. Mutations in this gene are associated with lung cancer.
Major Conditions	Cancer

Drug Modality

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Small Molecule

FHND41 is a third-generation EGFR inhibitor that irreversibly binds to EGFR protein, and demonstrates strong inhibitory effect on EGFR T790M mutations as well as EGFR sensitive mutations.

Indication

Non-small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for about 85% of all cases. According to the International Agency for Research on Cancer (IARC), lung cancer is the most influential malignancy globally, with 2.2 million new cases in 2020, accounting for 11.4% of all new cancers, and causing a total of 1.8 million deaths in 2020, equivalent to 18% of all cancer deaths.
NSCLC is further subdivided into squamous cell carcinoma, adenocarcinoma, lung adenocarcinoma, and large cell carcinoma based on the cell type that occurs, as well as more poorly differentiated variants. Treatment for NSCLC is determined by many factors, including the type and stage of cancer, the presence and extent of metastasis, the size, location and extent of the tumor, and the patient's general health. Treatment may include surgery, radiotherapy, chemotherapy, immunotherapy, or any combination thereof. The market for NSCLC totaled $24.1 billion in 2021 in the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan. The total market for NSCLC drugs in the seven major markets is predicted to nearly double to $48 billion by 2031.

Mechanism of Action

Irreversibly Binding to EGFR and Selectively Inhibiting EGFR Mutations

Tyrosine kinase inhibitors (TKIs) that target human epidermal growth factor receptor (EGFR) are now the standard treatment for patients with advanced EGFR mutant non-small cell lung cancer (NSCLC). First-generation EGFR TKIs that competitively and reversibly bind to ATP-binding sites at the intracellular tyrosine kinase domain of EGFR have significantly improved outcomes in NSCLC patients with activated EGFR

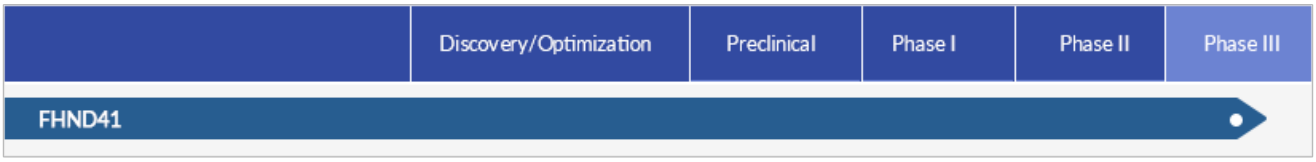
mutations. Because of the limited effectiveness of second-generation TKIs in circumventing the resistance of T790M to first-generation TKIs, third-generation TKIs are developed to more effectively target the T790M mutation. Because of the increased specificity of third-generation TKIs for T790M and thus mutant EGFR compared to wild-type EGFR, these TKIs are well tolerated and result in few wild-type EGFR adverse effects. FHND41 is a third-generation TKI that selectively inhibits EGFR mutations, especially T790M mutation. The pharmacological properties of FHND41 are:

- High selectivity and potent in vitro and in vivo anti-tumor activity
- Blood-brain barrier (BBB)-crossing ability
- Only one active metabolite, leading to reduced toxicity and side effects
- Safety for cardiovascular system
- Long half-life

Status

The Status of FHND41

Compound patents have been granted in the United States, Europe, Japan, Australia, Canada and South Korea. Crystal patents have been granted in the United States and Australia.



Data

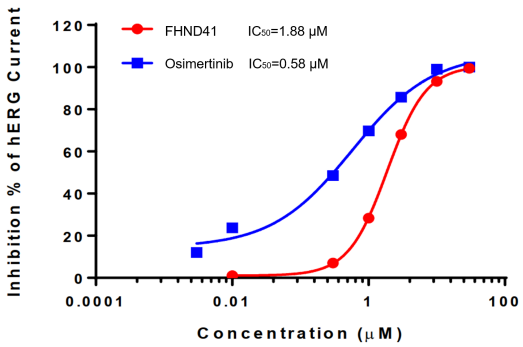
Inhibition of FHND41 and Osimertinib on the hERG Currents

The Exposure of FHND41, Osimertinib, and Their Active Metabolites

E-mail: inquiry@protheragen.com

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80 mg	C_{max}	AUC_{0-t}
FHND41	**168.1**	**9120**
M10 (% of FHND41)	-	1~2%
Osimertinib	**195.9**	**10260**
AZ5104 (% of osimertinib)	-	~10%
AZ7550 (% of osimertinib)	-	~10%

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