A Selective RET Inhibitor for the Treatment of Solid Tumors

Overview

Drug Name	FHND71
Description	FHND71 is a novel kinase inhibitor which specifically targets activated forms of rearranged during transfection (RET). It has the characteristics of excellent selectivity, long-term efficacy in vivo, low effective dose, and the ability to cross the blood-brain barrier. The unique pharmacokinetic profile of FHND71 supports the frequency of once-a-day dosing and strong efficacy in target organ and brain tumor. FHND71 has granted IND approval from NMPA and FDA. It is currently in the dose-escalation segment of the phase 1 trial for patients with RET-driven solid tumors.
Target	RET
Drug Modality	Small molecule
Indication	Solid tumors
Product Category	Kinase inhibitor
Mechanism of Action	Inhibition of RET kinase
Status	Phase I
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for FHND71. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

Rearranged During Transfection (RET)

E-mail: inquiry@protheragen.com

www.protheragen.com

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

Introduction	RET is a receptor tyrosine kinase (RTK) that contains an intracellular tyrosine kinase domain, a transmembrane domain, and a large extracellular domain. Activation of RET proteins requires the constitution of a heterogeneous ternary complex, which usually includes the glial cell line-derived neurotrophic factor (GDNF) family ligands and GDNF family co-receptors. Once assembled, newly formed ternary complexes lead to the auto-phosphorylation of the RET intracellular tyrosine kinase domains, which activates downstream signalling pathways involved in cell proliferation, growth, differentiation, and survival.
Approved Name	Ret proto-oncogene
Official Symbol	RET
Gene Type	Protein coding
Synonyms	Cadherin-related family member 16; RET receptor tyrosine kinase; Rearranged during transfection
Ensembl	ENSG00000165731
Gene ID	5979
mRNA Refseq	NM_020975
Protein Refseq	NP_066124
OMIM	164761
UniProt ID	P07949
Chromosome Location	10q11.21

Clinical Resources

Gene Function	This proto-oncogene can undergo oncogenic activation through both cytogenetic rearrangement and activating point mutations. RET alterations have been found primarily in thyroid cancers and non-small cell lung cancer (NSCLC). Point mutations represent the main RET alteration in medullary thyroid cancer and may occur in extracellular or intracellular domains, resulting in a ligand-independent RET activation. RET fusions are common in NSCLC as well as in papillary thyroid cancer and could result in either ligand-independent activation or aberrant RET expression.
Pathway	PI3K/AKT, RAS/RAF, MAPK, and PLCγ pathways
Major Conditions	Cancer

E-mail: inquiry@protheragen.com

www.protheragen.com

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

Drug Modality

Small Molecule

FHND71 is a selective RET inhibitor with unique pharmacokinetic profile that developed by computer-aided drug design, chemical structure-activity analysis, structure optimization, and in vitro and in vivo biological activity screening.
In PK/PD studies, FHND71 had longer mean retention time in plasma and tumor tissue compared to selpercatinib. In addition, compared with selpercatinib, FHND71 inhibited the phosphorylation of RET and the downstream signaling proteins in tumor tissues for a longer time.

Indication

Advanced Solid Malignancies with RET Genomic Alterations

Variations in RET expression have been discovered in many solid tumor types. Adenocarcinomas are the most frequent histology to carry RET rearrangements, followed by adenosquamous, squamous cell, and neuroendocrine cancers. Non-small cell lung cancer (NSCLC) and thyroid cancer are the most common cancer types harboring RET alterations. RET fusions have been identified in approximately 2% of NSCLC; and 10-20% of papillary, Hurthle cell, anaplastic, and poorly differentiated thyroid cancers. RET point mutations are common in medullary thyroid carcinoma.
According to the International Agency for Research on Cancer (IARC), lung cancer is the malignancy of highest impact among men and women globally, both in terms of the total number of individuals it affects (2.2 million new cases in 2020) and the total number of resulting deaths (1.8 million in 2020). NSCLC and small cell lung cancer (SCLC) are the two most common forms of lung cancer, of which NSCLC is the more common form, accounting for about 85% of all cases.
Thyroid cancer is a malignancy that originates in the thyroid, a ductless gland composed of spheroidal follicles located over and on either side of the trachea. According to the IARC, the global incidence of thyroid cancer in 2020 was approximately 586,200 and the five-year global revalence was nearly two million. The main types of thyroid cancer are papillary carcinoma, follicular carcinoma, Hurthle cell carcinoma, medullary thyroid carcinoma, and anaplastic thyroid carcinoma. Among them, papillary carcinoma accounts for 80% of all thyroid

cancers.

Mechanism of Action

Selective Inhibition of RET Kinase

RET kinase has been identified as an important driver of certain solid tumors, including NSCLC and thyroid cancer. Genomic alterations in the RET kinase, including gene fusions and point mutations, lead to overactive RET signaling and uncontrolled cell growth. FHND71 is a novel kinase inhibitor that specifically targets the activated form of RET and has a unique pharmacokinetic profile.

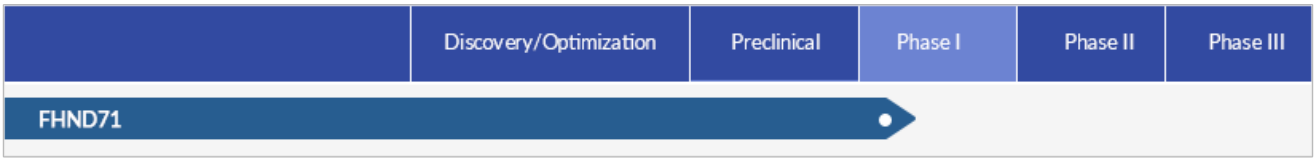
In PK/PD studies, FHND71 had longer T_{max} and MRT in plasma and tumor tissue compared with selpercatinib. FHND71 is optimally distributed into tissues. The exposure of FHND71 in tumor tissue (AUC_{0-t}) was approximately 28 times higher than that of selpercatinib at 4 h after dosing, and the concentration of FHND71 in brain tissue was approximately 33 times higher than that of selpercatinib. Thus, the indication for FHND71 may be extended to primary or metastatic brain cancers associated with RET mutations.

In the Ba/F3 KIF5B-RET tumor model, FHND71 showed significant anti-tumor efficacy at oral dose levels ≥3 mg/kg once daily (QD) without significant toxicity. FHND71 QD showed anti-tumor activity similar to that of selpercatinib administered at 30 mg/kg twice daily (BID). Upon the treatment of 30 mg/kg FHND71 QD, significant tumor regression (100% TGI) was observed in patient-derived xenograft models.

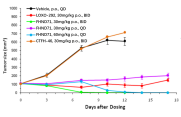
Status

The Status of FHND71

Patents for compounds have been applied in the United States, Europe, Japan, Korea, Australia, Canada, Russia, and India.

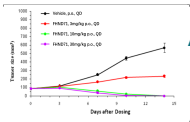


Data



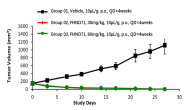
Anti-tumor Activity of FHND71 in Ba/F3 KIF5B-RET V804M Allograft Model

The anti-tumor activity of FHND71 QD was similar to that of LOXO-292 at the dose of 30 mg/kg BID. FHND71 was more effective than LOXO-292.



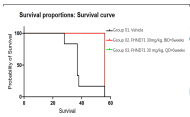
Anti-tumor Activity of FHND71 in Ba/F3 KIF5B-RET Allograft Model

At dose levels ≥3 mg/kg QD, FHND71 exhibited strong anti-tumor activity with TGI > 60%.



Therapeutic Efficacy of FHND71 in Subcutaneous OV9421 (NCOA4-RET Alteration) Xenograft Model

FHND71 showed significant anti-tumor efficacy at doses of 30 mg/kg and 60 mg/kg with TGI of 99.62% and 99.66% ($p<0.001$), respectively.



Survival Curves of FHND71 in the Treatment of Intracranial CR2518 (CCDC6-RET Alteration) Xenograft Model

FHND71 significantly prolonged life time with MST of 56 days (ILS=51%, $p<0.005$).

E-mail: inquiry@protheragen.com

www.protheragen.com

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