产品名称：Entrectinib
产品别名：恩曲替尼；NMS-E628; RXDX-101

生物活性：

Description	Entrectinib (NMS-E628) is a potent, orally available, and CNS-active **pan-Trk**, **ROS1**, and **ALK** inhibitor. Entrectinib inhibits TrkA, TrkB, TrkC, ROS1 and ALK with **IC_{50}** values of 1, 3, 5, 12 and 7 nM, respectively. Antitumor activity.
IC_{50} & Target	IC50: 1 nM (TrkA), 1 nM (TrkB), 1 nM (TrkC), 1 nM (ROS1),1 nM (ALK)[1]
In Vitro	Entrectinib (NMS-E628) is found to be exquisitely active in inhibiting the proliferation of a limited number of cell lines: the TRKA-driven colorectal carcinoma cell line KM12 (IC50 of 17 nM), the ALK-dependent ALCL cell lines SU-DHL-1, Karpas-299, SUP-M2 and SR-786 (IC50 of 20, 31, 41, and 81 nM, respectively), the ALK-dependent NSCLC cell line NCI-H2228 (IC50 of 68 nM) and the FLT3-dependent AML cell line MV-4-11 (IC50 of 81 nM). Entrectinib potently blocks proliferation of Ba/F3-TEL-TRKB (IC50 of 2.9 nM), Ba/F3-TEL-TRKC (IC50 of 3.3 nM), and Ba/F3-TEL-ROS1 (IC50 of 5.3 nM) cells, with a high degree of selectivity versus parental Ba/F3 cells or those transformed by nontargeted kinases such as ABL and RET, which are inhibited with IC50s in the range of 2 to 3 μM[1]. Entrectinib significantly inhibits the growth of TrkB-expressing NB cells in vitro, and it significantly enhances the growth inhibition of Irino-TMZ when used in combination[2].
In Vivo	Oral administration of entrectinib to tumor-bearing mice induces regression in relevant human xenograft tumors, including the TRKA-dependent colorectal carcinoma KM12, ROS1-driven tumors, and several ALK-dependent models of different tissue origins, including a model of brain-localized lung cancer metastasis[1]. Single agent therapy results in significant tumor growth inhibition in animals treated with entrectinib compared to control animals[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 31 mg/mL (55.29 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7837 mL	8.9184 mL	17.8368 mL
	5 mM	0.3567 mL	1.7837 mL	3.5674 mL
	10 mM	0.1784 mL	0.8918 mL	1.7837 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (4.46 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (4.46 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.46 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.46 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Ardini E, et al. Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor with Activity in Multiple Molecularly Defined Cancer Indications. Mol Cancer Ther. 2016 Apr;15(4):628-39. [2]. Iyer R, et al. Entrectinib is a potent inhibitor of Trk-driven neuroblastomas in a xenograft mouse model. Cancer Lett. 2016 Mar 28;372(2):179-86.

实验参考：

Cell Assay	NLF, NLF-TrkB, SY5Y or SY5Y-TrkB cells are plated in 96 well plates, and they are exposed to drug at different concentrations (1, 5, 10, 20, 30, 50 and 100 nM of entrectinib, 1.5 μM Irino and 50 μM TMZ, respectively) for one hr followed by addition of 100 ng/mL of BDNF. Plates are harvested at 24, 48, and 72 hr following addition of drug. The plates are processed and cell viability is analyzed using a standard SRB assay protocol[2].
Animal Administration	Mice: Entrectinib is reconstituted in 0.5% methylcellulose containing 1% Tween 80 at a final dosing volume of 10 mL/kg (e.g., 0.2 mL for a 20 gm mouse). Treatment with entrectinib, Irino and TMZ started about 15–17 days after tumor inoculation when the average tumor size is 0.2 cm^3. Mice are sacrificed when tumor volume reached 3 cm^3. Tumors are harvested and flash frozen on dry ice for analysis of protein expression[2].
References	[1]. Ardini E, et al. Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor with Activity in Multiple Molecularly Defined Cancer Indications. Mol Cancer Ther. 2016 Apr;15(4):628-39. [2]. Iyer R, et al. Entrectinib is a potent inhibitor of Trk-driven neuroblastomas in a xenograft mouse model. Cancer Lett. 2016 Mar 28;372(2):179-86.