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产品名称：LOXO-101
产品别名：Larotrectinib

生物活性：

Description	Larotrectinib (LOXO-101) is an ATP-competitive oral, selective inhibitor of the tropomyosin-related kinase (TRK) family receptors, with low nanomolar 50% inhibitory concentrations against all three isoforms (TRKA, B, and C).		
IC_{50} & Target	TrkA	TrkB	TrkC
In Vitro	Larotrectinib (LOXO-101) is an ATP-competitive oral inhibitor of the tropomyosin-related kinase (TRK) family of receptor kinases (TRKA, B, and C), with low nanomolar 50% inhibitory concentrations against all three isoforms, and 1,000-fold or greater selectivity relative to other kinases[1][2]. Measurement of proliferation following treatment with Larotrectinib (LOXO-101) demonstrates a dose-dependent inhibition of cell proliferation in all three cell lines. The IC50 is less than 100 nM for CUTO-3.29 and less than 10 nM for KM12 and MO-91 consistent with the known potency of this drug for the TRK kinase family[3].		
In Vivo	In rat and monkey studies, Larotrectinib (LOXO-101) demonstrates 33-100% oral bioavailability and 60-65% plasma protein binding. It has low brain penetration, and is well tolerated in 28 day (d) GLP toxicology studies. A single dose (30 mg/kg) of Larotrectinib (LOXO-101) reduces tyrosine phosphorylation of TRKA and downstream signal transduction (pERK) in the tumor >80%[1]. Athymic nude mice injected with KM12 cells are treated with Larotrectinib (LOXO-101) orally daily for 2 weeks. Dose-dependent tumor inhibition is observed demonstrating the ability of this selective compound to inhibit tumor growth in vivo[4]. Larotrectinib (LOXO-101) (200mg/kg/day p.o for six weeks) reduces leukemic infiltration to undetectable levels in the bone marrow and spleen compared to vehicle-treated mice. Mice treated with Larotrectinib (LOXO-101) are still alive and leukemia-free four weeks after the cessation of treatment, as determined by Xenogen imaging[5].		
Solvent&Solubility	***In Vitro:*** **DMSO： ≥ 4.6 mg/mL (10.74 mM)** * "≥" means soluble, but saturation unknown.		

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3340 mL	11.6702 mL	23.3405 mL
	5 mM	0.4668 mL	2.3340 mL	4.6681 mL
	10 mM	0.2334 mL	1.1670 mL	2.3340 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。

[1]. Karyn Bouhana, et al. LOXO-101, a pan TRK inhibitor, For The Treatment Of TRK-driven Cancers.

[2]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049-57.

[3]. Nagasubramanian R, et al. Infantile Fibrosarcoma With NTRK3-ETV6 Fusion Successfully Treated

References	With the Tropomyosin-Related Kinase Inhibitor LOXO-101. Pediatr Blood Cancer. 2016 Aug;63(8):1468-70. [4]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101in Acute Lymphoblastic Leukemia. Blood 2016 128:278. [5]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049-57.

实验参考：

Animal Administration	Mice[4] Athymic nude mice are used throughout the study. 5×10^5 KM12 cells are injected subcutaneously into the dorsal flank area of the mice. Tumor volume is monitored by direct measurement with calipers and calculated by the formula: length × ($width^2$)/2. Following the establishment of tumor and when the tumor size is between 150-200 mm^2, mice are randomly selected to receive diluent, 60 mg/kg/dose or 200 mg/kg/dose of Larotrectinib (LOXO-101). Larotrectinib (LOXO-101) is administered by oral gavage once daily for 14 days. After the last dose, tissue and blood are collected at 3, 6 and 24 hours post-treatment[4].
References	[1]. Karyn Bouhana, et al. LOXO-101, a pan TRK inhibitor, For The Treatment Of TRK-driven Cancers. [2]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049-57. [3]. Nagasubramanian R, et al. Infantile Fibrosarcoma With NTRK3-ETV6 Fusion Successfully Treated With the Tropomyosin-Related Kinase Inhibitor LOXO-101. Pediatr Blood Cancer. 2016 Aug;63(8):1468-70. [4]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101in Acute Lymphoblastic Leukemia. Blood 2016 128:278. [5]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049-57.