产品名称：LOXO-101 (sulfate)
产品别名：Larotrectinib sulfate； LOXO-101 sulfate; ARRY-470 sulfate

生物活性：

Description	Larotrectinib sulfate (LOXO-101 sulfate; ARRY-470 sulfate) 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 sulfate 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 sulfate are still alive and leukemia-free four weeks after the cessation of treatment, as determined by Xenogen imaging[5].		

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (**94.96 mM**; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8993 mL	9.4965 mL	18.9930 mL
	5 mM	0.3799 mL	1.8993 mL	3.7986 mL
	10 mM	0.1899 mL	0.9496 mL	1.8993 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: ≥ 3.25 mg/mL (6.17 mM); Clear solution

此方案可获得 ≥ 3.25 mg/mL (6.17 mM，饱和度未知) 的澄清溶液。

	以 1 mL 工作液为例，取 100 μL 32.5 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% (20% SBE-β-CD in saline) Solubility: ≥ 3.25 mg/mL (6.17 mM); Clear solution 此方案可获得 ≥ 3.25 mg/mL (6.17 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 32.5 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 3.25 mg/mL (6.17 mM); Clear solution 此方案可获得 ≥ 3.25 mg/mL (6.17 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 32.5 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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]. 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. [5]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101in Acute Lymphoblastic Leukemia. Blood 2016 128:278.

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]. Doebele RC, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with

源叶生物

	Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049-57. [5]. Kathryn G, et al. Genetic Modeling and Therapeutic Targeting of ETV6-NTRK3 with Loxo-101in Acute Lymphoblastic Leukemia. Blood 2016 128:278.

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