产品名称：Brigatinib
产品别名：Brigatinib AP-26113；布格替尼

生物活性：

Description	Brigatinib is a highly potent and selective **ALK** inhibitor, with an **IC_{50}** of 0.6 nM.
IC_{50} & Target	IC50: 0.6 nM (ALK)[1]
In Vitro	Brigatinib potently inhibits the in vitro kinase activity of ALK (IC50, 0.6 nM) and all five mutant variants tested, including G1202R (IC50, 0.6-6.6 nM). Brigatinib demonstrates a high degree of selectivity, only inhibiting 11 additional native or mutant kinases with IC50 <10 nM. These include ROS1, FLT3, and mutant variants of FLT3 (D835Y) and EGFR (L858R; IC50, 1.5-2.1 nM). Brigatinib exhibits more modest activity against EGFR with a T790M resistance mutation (L858R/T790M), native EGFR, IGF1R, and INSR (IC50, 29-160 nM) and does not inhibit MET (IC50 >1000 nM). In cellular assays, brigatinib inhibits ALK and ROS1 with IC50s of 14 and 18 nM, respectively. Brigatinib inhibits FLT3 and IGF-1R with about 11-fold lower potency (IC50, 148-158 nM) and inhibits mutant variants of FLT3 and EGFR with 15- to 35-fold lower potency (IC50, 211-489 nM). Brigatinib inhibits cell growth with GI50 values ranging from 503 to 2,387 nM in three ALK-negative ALCL and NSCLC cell lines[1]. Brigatinib inhibits ALK activity and abrogates proliferation of ALK addicted neuroblastoma cell lines, with IC50 of 75.27 ± 8.89 nM. Brigatinib inhibits both the ALK-I1171N and the ALK-G1269A mutant receptors at 10 and 4 nM levels, respectively[3].
In Vivo	Brigatinib (10, 25, or 50 mg/kg once daily, p.o.) leads to a dose-dependent inhibition of tumor growth in ALK+ Karpas-299 (ALCL) and H2228 (NSCLC) xenograft mouse models. Brigatinib markedly enhances survival of mice bearing ALK+ brain tumors compared with PF-02341066[1]. Brigatinib (10, 25, 50 mg/kg, p.o.) results in dose-dependent antitumor activity, with tumor regressions in a mouse model of NSCLC[2].
Solvent&Solubility	***In Vitro:*** **Ethanol : 10 mg/mL** (**17.12 mM;** Need ultrasonic and warming) **DMSO : 2 mg/mL** (**3.42 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7121 mL	8.5603 mL	17.1206 mL
	5 mM	0.3424 mL	1.7121 mL	3.4241 mL
	10 mM	0.1712 mL	0.8560 mL	1.7121 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: ≥ 0.5 mg/mL (0.86 mM); Clear solution

	此方案可获得 ≥ 0.5 mg/mL (0.86 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 5.0 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% (20% SBE-β-CD in saline) Solubility: ≥ 0.5 mg/mL (0.86 mM); Clear solution 此方案可获得 ≥ 0.5 mg/mL (0.86 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 5.0 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: ≥ 0.5 mg/mL (0.86 mM); Clear solution 此方案可获得 ≥ 0.5 mg/mL (0.86 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 5.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。 4.请依序添加每种溶剂： 10% EtOH→40% PEG300 →5% Tween-80→45% saline Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (1.71 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 EtOH 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。 5.请依序添加每种溶剂： 10% EtOH →90% (20% SBE-β-CD in saline) Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (1.71 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 10.0 mg/mL 的澄清 EtOH 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 6.请依序添加每种溶剂： 10% EtOH →90% corn oil Solubility: ≥ 1 mg/mL (1.71 mM); Clear solution 此方案可获得 ≥ 1 mg/mL (1.71 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 10.0 mg/mL 的澄清 EtOH 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Zhang S, et al. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538 [2]. Huang WS, et al. Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. J Med Chem. 2016 May 26;59(10):4948-64. [3]. Siaw JT, et al. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22

实验参考：

Cell Assay	Cells are seeded at 15,000 per well with serial dilutions of the indicated inhibitors. After 72 hours cell viability is assessed by resazurin. IC_{50}values are calculated with GraphPad Prism 6.0 by fitting data

	to a log (inhibitor concentration) vs. normalized response (variable slope) equation. Each experiment is performed in duplicate and repeated at least three times. [3]
Animal Administration	Mice: (1) Eight- to 10-week-old female SCID/beige mice are injected intravenously with 5×10^6 H3122 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reaches appr 300 mm^3 (day zero). Treatments are administered orally for up to 21 consecutive days at a 10 mL/kg dose volume. Subcutaneous tumors are measured two or three times weekly. Tumor volume (in mm^3) is calculated using the formula $(L\times W^2)/2$. When a tumor reaches 10% of the body weight of the host, the animal is euthanized via CO_2 asphyxiation. (2) Eight- to 10-week old female SCID/beige mice are injected subcutaneously with 2.5×10^6 Karpas-299 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reached appr 180 mm^3 (day zero). Treatments are administered orally for 14 consecutive days at a 10 mL/kg dose volume. Tumor volume is measured and calculated as described for the H3122 model. [2]
Kinase Assay	In vitro HotSpot^{SM} kinase profiling of 289 kinases is performed. The assay is conducted in the presence of 10 μM [^{33}P]-ATP, using brigatinib concentrations ranging from 0.05 nM to 1 μM. [1]
References	[1]. Zhang S, et al. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538 [2]. Huang WS, et al. Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. J Med Chem. 2016 May 26;59(10):4948-64. [3]. Siaw JT, et al. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22