产品名称：Ponatinib(AP24534)
产品别名：Ponatinib；帕纳替尼

生物活性：

Description	Ponatinib (AP24534) is an orally active multi-targeted kinase inhibitor with IC50s of 0.37 nM, 1.1 nM, 1.5 nM, 2.2 nM, and 5.4 nM for Abl, PDGFRα, VEGFR2, FGFR1, and Src, respectively.			
IC_{50} & Target	VEGFR2	PDGFRα	FGFR1	c-Kit
	1.5 nM (IC_{50})	1.1 nM (IC_{50})	2.2 nM (IC_{50})	12.5 nM (IC_{50})
In Vitro	Ponatinib (AP24534) potently inhibits native ABL (IC_{50}: 0.37 nM), ABL^{T315I} (IC_{50}: 2.0 nM), and other clinically important ABL kinase domain mutants (IC_{50}: 0.30-0.44 nM). Ponatinib also inhibits SRC (IC_{50}: 5.4 nM) and members of the VEGFR, FGFR, and PDGFR families of receptor tyrosine kinases. Ponatinib potently inhibits proliferation of Ba/F3 cells expressing native BCR-ABL (IC_{50}: 0.5 nM). All BCR-ABL mutants tested remained sensitive to Ponatinib (IC_{50}: 0.5-36 nM) including BCR-ABL^{T315I} (IC_{50}: 11 nM) [1]. Ponatinib inhibits the in vitro kinase activity of FLT3, KIT, FGFR1, and PDGFRα with IC_{50} values of 13, 13, 2, and 1 nM, respectively. Ponatinib inhibits phosphorylation of all 4 RTKs in a dose-dependent manner, with IC_{50} values between 0.3 to 20 nM. Consistent with these activated receptors being important in driving leukemogenesis Ponatinib also potently inhibits the viability of all 4 cell lines with IC_{50} values of 0.5 to 17 nM. In contrast, the IC_{50} for inhibition of RS4;11 cells which express native (unmutated) FLT3, is more than 100 nM[2].			
In Vivo	In a survival model in which mice are instead injected with Ba/F3 BCR-ABL^{T315I} cells, administration of Dasatinib at doses as high as 300 mg/kg has no effect on survival time. By contrast, treatment with Ponatinib (AP24534) prolongs survival in a dose-dependent manner. Ponatinib dosed orally for 19 days at 5, 15, and 25 mg/kg prolongs median survival to 19.5, 26, and 30 days, respectively compare to 16 days for vehicle-treated mice ($p<0.01$ for all three dose levels). The anti-tumor activity of Ponatinib (AP24534) is further assessed in a xenograft model in which Ba/F3 BCR-ABL^{T315I} cells are injected subcutaneously into mice. Tumor growth is inhibited by Ponatinib in a dose-dependent manner compare to vehicle-treated mice, with significant suppression of tumor growth upon daily oral dosing at 10 and 30 mg/kg (%T/C = 68% and 20%, respectively; $p<0.01$ for both dose levels). Daily oral dosing of 50 mg/kg Ponatinib causes significant tumor regression (%T/C = 0.9%, $p<0.01$), with a 96% reduction in mean tumor volume at the final measurement compared to the start of treatment. Ponatinib is well tolerated at all efficacious dose levels for the duration of the study; maximal decreases in body weight are <5%, <5%, and <12% for the 10, 30, and 50 mg/kg dose groups, respectively, with no signs of overt toxicity[1]. Ponatinib (1-25 mg/kg) is administered orally, once daily for 28 days, to mice bearing MV4-11 xenografts. Ponatinib potently inhibits tumor growth in a dose-dependent manner. Administration of 1 mg/kg, the lowest dose tested, leads to significant inhibition of tumor growth (TGI=46%, $P<0.01$) and doses of 2.5 mg/kg or greater results in tumor regression[2].			

In Vitro:

DMSO : ≥ 50 mg/mL (93.89 mM)

* "≥" means soluble, but saturation unknown.

	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	1.8777 mL	9.3886 mL	18.7772 mL
	5 mM	0.3755 mL	1.8777 mL	3.7554 mL
	10 mM	0.1878 mL	0.9389 mL	1.8777 mL

Solvent&Solubility	*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: ≥ 10 mg/mL (18.78 mM); Clear solution 此方案可获得 ≥ 10 mg/mL (18.78 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 100.0 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: ≥ 10 mg/mL (18.78 mM); Clear solution 此方案可获得 ≥ 10 mg/mL (18.78 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 100.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. O'Hare T, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell, 2009, 16(5), 401-412. [2]. Gozgit JM, et al. Potent activity of ponatinib (AP24534) in models of FLT3-driven acute myeloid leukemia and other hematologic malignancies. Mol Cancer Ther, 2011, 10(6), 1028-1035. [3]. Uchida T, et al. Hes1 upregulation contributes to the development of FIP1L1-PDGRA-positive leukemia in blast crisis. Exp Hematol. 2014 May;42(5):369-379.e3.

实验参考：

Cell Assay	Ba/F3 cell lines are distributed in 96-well plates (4×10^3 cells/well) and incubated with escalating concentrations of Ponatinib for 72 hr. The inhibitor ranges used are: 0-625 nM for cells expressing BCR-ABL and 0-10,000 nM for BCR-ABL negative cells. Proliferation is measured using a methanethiosulfonate (MTS)-based viability assay. IC_{50}values are reported as the mean of three independent experiments performed in quadruplicate. For cell proliferation experiments with CML or normal primary cells, mononuclear cells are plated in 96-well plates (5×10^4 cells/well) over graded concentrations of Ponatinib (0-1000 nM) in RPMI supplemented with 10% FBS, L-glutamine, penicillin/streptomycin, and 100 μM β-mercaptoethanol. Following a 72 hr incubation, cell viability is assessed by subjecting cells to an MTS assay[1].
	Mice[1]. For Ba/F3 survival model, Ba/F3 cells expressing native BCR-ABL or BCR-ABL^{T315I} are injected into the tail vein of female SCID mice (100 μL of a 1×10^7 cells/mL suspension in serum-free medium). Beginning 72 hr later mice are treated once daily by oral gavage with vehicle (25 mM citrate buffer, pH 2.75), Ponatinib, or Dasatinib for up to 19 consecutive days. Moribund animals are sacrificed as per IACUC guidelines. On necropsy, mice have marked splenomegaly due to tumor cell infiltration.

Animal Administration	Survival data are analyzed using Kaplan-Meier method, and statistical significance is evaluated with a Log-rank test comparing the survival time of each treatment group with the vehicle group. For Ba/F3 Tumor Model, Ba/F3 BCR-ABL^{T315I} cells are implanted subcutaneously into the right flank of female nude mice (100 μL of a 1×10^7 cells/mL cell suspension in serum-free medium). Mice are randomized to treatment groups when the average tumor volume reaches approximately 500 mm^3. Mice are treated once daily by oral gavage with vehicle (25 mM citrate buffer, pH 2.75) or Ponatinib for up to 19 consecutive days. Tumor volume (mm^3) is calculated. To determine tumor growth inhibition when the treatment period is finished, mean tumor volume for treatment group/mean tumor volume for control group (%T/C) is calculated at the final measurement.
References	[1]. O'Hare T, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell, 2009, 16(5), 401-412. [2]. Gozgit JM, et al. Potent activity of ponatinib (AP24534) in models of FLT3-driven acute myeloid leukemia and other hematologic malignancies. Mol Cancer Ther, 2011, 10(6), 1028-1035. [3]. Uchida T, et al. Hes1 upregulation contributes to the development of FIP1L1-PDGRA-positive leukemia in blast crisis. Exp Hematol. 2014 May;42(5):369-379.e3.