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产品名称：Trametinib (DMSO solvate)
产品别名：曲美替尼二甲亚砜；GSK-1120212 (DMSO solvate); JTP-74057 (DMSO solvate)

生物活性：

Description	Trametinib DMSO solvate (GSK-1120212 (DMSO solvate);JTP-74057 (DMSO solvate)) is a potent MEK inhibitor that specifically inhibits MEK1/2, with an IC50 value of about 2 nM.	
IC_{50} & Target	MEK1	MEK2
	2 nM (IC_{50})	2 nM (IC_{50})
In Vitro	In BRAF mutant SK-MEL-28 cells and KRAS mutant HCT116 cells, Trametinib (GSK1120212;JTP-74057) DMSO solvate causes dose-dependent inhibition of ERK1/2 phosphorylation as well as dose-dependent growth inhibition. In both SK-MEL-28 and HCT116 cells, Trametinib DMSO solvate inhibits 50% p-ERK1/2 at nearly equivalent concentrations (0.8 and 1.8 nM, respectively). However, as the slopes of the curves reflect, in SK-MEL-28 cells, Trametinib DMSO solvate inhibits 90% p-ERK1/2 at a lower concentration (3.4 nM) than in HCT116 (33.3 nM). Furthermore, in both cell lines, 50% growth inhibition is only achieved at concentrations Trametinib DMSO solvate that produces near complete ERK1/2 inhibition (85 and 90%, respectively)[2].	
In Vivo	Trametinib (GSK1120212;JTP-74057) DMSO solvate is evaluated in vivo in an A549 (KRAS mutant cell line) xenograft model, orally dosing daily for 21 days (qd×21). In this study, near complete tumor growth inhibition is observed at 5.0 and 2.5 mg/kg [92 and 87% tumor growth inhibition (TGI), respectively] and to a lesser degree at 0.5 and 0.1 mg/kg (62 and 58% TGI). Although 5 mg/kg is the maximally tolerated dose (MTD) in this study, 3 mg/kg is the typically observed MTD. Dose-dependent antitumor activity with Trametinib DMSO solvate treatment has been similarly reported for several other KRAS and BRAF mutant tumor models[2].	
Solvent&Solubility	***In Vitro:***	
	DMSO : 69 mg/mL (99.49 mM; Need ultrasonic)	
	H_2O : < 0.1 mg/mL (insoluble)	

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4419 mL	7.2095 mL	14.4190 mL
	5 mM	0.2884 mL	1.4419 mL	2.8838 mL
	10 mM	0.1442 mL	0.7209 mL	1.4419 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 (3.60 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.60 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% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (3.60 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (3.60 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 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: ≥ 2.5 mg/mL (3.60 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.60 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]. Yamaguchi T, et al. Suppressive effect of an orally active MEK1/2 inhibitor in two different animal models for rheumatoid arthritis: a comparison with leflunomide. Inflamm Res, 2012, 61(5), 445-454. [2]. Abe H, et al. Discovery of a Highly Potent and Selective MEK Inhibitor: GSK1120212 (JTP-74057 DMSO Solvate). ACS Med Chem Lett. 2011 Feb 28;2(4):320-4.

实验参考：

Cell Assay	SK-MEL-28, and HCT116 cell lines are plated in triplicate 96 well microtitre plates at 5000 cells per well in culture media. Trametinib dissolved in DMSO or negative control (0.1% DMSO) are added the following day and one plate is harvested with 50 μL of CellTiter-Glo for a time 0 (T=0) measurement. Remaining duplicate cell plates are typically incubated for 72 h. Cells are then lysed with 50 μL CellTiter-Glo, and chemiluminescent signal is read on the Wallac EnVision 2100 plate reader. For measurement of cellular ERK1/2 phosphorylation, cells are seeded and treated with Trametinib, and lysed after 72 h in Tris lysis buffer supplemented with phosphatase and protease inhibitors. All samples are analyzed with a phospho-ERK1/2 ELISA. Plates are read on MSD.SI6000 and curves are analyzed using the XLfit curve-fitting tool. For comparison of the growth assay curve and pERK1/2 assay curve, data are background subtracted and normalized to the vehicle treatment control[2].
Animal Administration	Mice[2] A549 (human non-small cell lung carcinoma) model is established from cells grown in tissue culture and harvested aseptically using a trypsin digest. Female athymic mice (strain *nu/nu*) are injected subcutaneously with between 5×10^6 and 10^7 cells in 50% martigel. Tumors are allowed to establish for one to four weeks before use. Trametinib is administered orally at the indicated doses in 0.2 mL/20 g by weight. Tumors are measured twice weekly using Vernier calipers. Antitumor activity is

	defined as tumor growth inhibition representing the % volume differential in tumor growth between the treated and control tumors at the time vehicle tumors exceeded a volume of 1000 mm^3.
References	[1]. Yamaguchi T, et al. Suppressive effect of an orally active MEK1/2 inhibitor in two different animal models for rheumatoid arthritis: a comparison with leflunomide. Inflamm Res, 2012, 61(5), 445-454. [2]. Abe H, et al. Discovery of a Highly Potent and Selective MEK Inhibitor: GSK1120212 (JTP-74057 DMSO Solvate). ACS Med Chem Lett. 2011 Feb 28;2(4):320-4.