产品名称：Ganetespib (STA-9090)
产品别名：Ganetespib

生物活性：

Description	Ganetespib is a heat shock protein 90 (HSP90) inhibitor which exhibits potent cytotoxicity in a wide variety of hematological and solid tumor cell lines.
IC_{50} & Target	HSP90
In Vitro	Ganetespib causes depletion of receptor tyrosine kinases, extinguishing of downstream signaling, inhibition of proliferation and induction of apoptosis with IC_{50} values ranging 2-30 nM in genomically-defined NSCLC cell lines. Ganetespib is also approximately 20-fold more potent in isogenic Ba/F3 pro-B cells rendered IL-3 independent by expression of EGFR and ERBB2 mutants[1]. Ganetespib exhibits potent in vitro cytotoxicity in a range of solid and hematologic tumor cell lines, induces the degradation of known Hsp90 client proteins, displays superior potency to the ansamycin inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG)[2]. Ganetespib is a potent HSP90 inhibitor, and shown to kill canine tumor cell lines in vitro[3]. Ganetespib possesses superior JAK/STAT inhibitory activity to both P6 and 17-AAG in terms of potency or duration of response in the HEL92.1.7 cells[4].
In Vivo	Ganetespib (125 mg/kg, i.v.) accumulates in tumors relative to normal tissues and displays greater in vivo efficacy than 17-AAG without increased toxicity and inhibits proliferation and induces apoptosis in parallel with EGFR depletion in NCI-H1975 xenografts[1]. Ganetespib (100, 125, 150 mg/kg, i.v.) shows potent antitumor efficacy in solid and hematologic xenograft models of oncogene addiction, as evidenced by significant growth inhibition and/or regressions[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 32 mg/mL (87.82 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7442 mL	13.7212 mL	27.4424 mL
	5 mM	0.5488 mL	2.7442 mL	5.4885 mL
	10 mM	0.2744 mL	1.3721 mL	2.7442 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 (6.86 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.86 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 (6.86 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.86 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 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 (6.86 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.86 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 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]. Shimamura T, et al. Ganetespib (STA-9090), a Non-Geldanamycin HSP90 Inhibitor, has Potent Antitumor Activity in In Vitro and In Vivo Models of Non-Small Cell Lung Cancer. Clin Cancer Res. 2012 Jul 17. [2]. Ying W, et al. Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy. Mol Cancer Ther. 2012 Feb;11(2):475-84. [3]. London CA, et al. Phase I evaluation of STA-1474, a prodrug of the novel HSP90 inhibitor ganetespib, in dogs with spontaneous cancer. PLoS One. 2011;6(11):e27018. [4]. Proia DA, et al. Multifaceted intervention by the Hsp90 inhibitor ganetespib (STA-9090) in cancer cells with activated JAK/STAT signaling. PLoS One. 2011 Apr 14;6(4):e18552. [5]. Stewart E, et al. Identification of Therapeutic Targets in Rhabdomyosarcoma through Integrated Genomic, Epigenomic, and Proteomic Analyses. Cancer Cell. 2018 Sep 10;34(3):411-426.e19.

实验参考：

Cell Assay	Cells are grown in 96-well plates based on optimal growth rates determined empirically for each line. Twenty-four hours after plating, cells are treated with the indicated compounds or controls for 72 hours. AlamarBlue is added (10% v/v) to the cells, and the plates are incubated for 3 hours and, then, subjected to fluorescence detection. For the comparative viability/apoptosis assay, NCI-H1975 cells are treated with escalating concentrations of ganetespib for the indicated time periods and subjected to viability analysis via CellTiter Fluor and apoptosis via Caspase Glo 3/7. [2]
Animal Administration	Mice: NCI-H1975 or HCC827 cells are cultured as above and 0.5-1×10^7 cells are mixed with 50% RPMI 1640/50% Matrigel and subcutaneously injected into the flanks of SCID mice. For efficacy studies, animals with 100-200 mm^3 tumors are then randomized into treatments groups of eight. Tumor volumes (V) are calculated by the equation V=0.5236×L×W×T (Length, width, and thickness). Animals are treated by intravenous bolus tail vein injection at 10 mL/kg with ganetespib formulated in 10/18 DRD (10% DMSO, 18% Cremophor RH 40, 3.6% dextrose and 68.4% water). As a measurement of in vivo efficacy, the relative size of treated and control tumors [(%T/C) value] is determined from the change in average tumor volumes of each drug-treated group relative to the vehicle-treated group, or itself in the case of tumor regression. Body weights are monitored daily. For biomarker studies, mice bearing NCI-H1975 xenografts are treated with either a single dose of vehicle or ganetespib, or with 5 daily doses of vehicle or ganetespib, in groups of 3 or 8, and harvested at various time points. Tumors are excised and flash frozen in liquid nitrogen for

	preparation of protein lysates or fixed in 10% neutral buffered formalin for immunohistochemistry. [1]
Kinase Assay	Exponentially growing cells are processed in lysis buffer (20 mM HEPES, pH 7.4, 1 mM EDTA, 5 mM $MgCl_2$, 100 mM KCl) and incubated with increasing concentrations of 17-AAG or ganetespib for 30 min at 4°C, and incubated with biotin-GM linked to Dynabeads MyOne Streptavidin T1 magnetic beads for 1 h at 4°C. Beads are washed three times in lysis buffer and heated for 5 min at 95°C in SDS-PAGE sample buffer. Samples are resolved on 4-12% Bis-Tris gradient gel and Western blots are performed using an anti-HSP90 antibody. [1]
References	[1]. Shimamura T, et al. Ganetespib (STA-9090), a Non-Geldanamycin HSP90 Inhibitor, has Potent Antitumor Activity in In Vitro and In Vivo Models of Non-Small Cell Lung Cancer. Clin Cancer Res. 2012 Jul 17. [2]. Ying W, et al. Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy. Mol Cancer Ther. 2012 Feb;11(2):475-84. [3]. London CA, et al. Phase I evaluation of STA-1474, a prodrug of the novel HSP90 inhibitor ganetespib, in dogs with spontaneous cancer. PLoS One. 2011;6(11):e27018. [4]. Proia DA, et al. Multifaceted intervention by the Hsp90 inhibitor ganetespib (STA-9090) in cancer cells with activated JAK/STAT signaling. PLoS One. 2011 Apr 14;6(4):e18552. [5]. Stewart E, et al. Identification of Therapeutic Targets in Rhabdomyosarcoma through Integrated Genomic, Epigenomic, and Proteomic Analyses. Cancer Cell. 2018 Sep 10;34(3):411-426.e19.