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产品名称：ARQ-092
产品别名：Miransertib

生物活性：

Description	Miransertib (ARQ-092) is an orally bioavailable, selective, and potent allosteric Akt inhibitor with IC50s of 2.7 nM, 14 nM and 8.1 nM for Akt1, Akt2, Akt3, respectively.		
IC_{50} & Target	Akt1	Akt3	Akt2
	2.7 nM (IC_{50})	8.1 nM (IC_{50})	14 nM (IC_{50})
In Vitro	Miransertib (ARQ-092; Compound 21a) demonstrates high enzymatic potency against Akt1, Akt2 and Akt3, as well as potent cellular inhibition of Akt activation and the phosphorylation of the downstream target PRAS40. Miransertib shows strong affinity for un-phosphorylated fulllength Akt1 and potently inhibited the phosphorylated form of full-length Akt isoforms. In a large panel of cell lines derived from various tumor types, Miransertib shows potent anti-proliferative activity in cell lines containing PIK3CA/PIK3R1 mutations compared to those with wild-type (wt) PIK3CA/PIK3R1 or PTEN loss. Miransertib shows excellent inhibition of p-Akt (S473) and p-Akt (T308) in both AN3CA and A2780 cells. The inhibition of the downstream protein p-PRAS40 (T246) is observed with Miransertib (IC_{50}=0.31 μM)[1].		
In Vivo	In a mouse pharmacokinetic study, (po at 100 mg/kg, iv at 5 mg/kg), Miransertib (ARQ-092; Compound 21a) shows an oral bioavailability of 23%. Miransertib results in 99%, 95% and 58% reductions in p-Akt (S473), p-Akt (T306) and p-PRAS40 (T246), respectively, after tumor-bearing mice are treated with 100 mg/kg po. The inhibition of phosphorylation is sustained at eight hours. The plasma concentration of Miransertib at one hour is 2.1 μM and decreased to 0.26 μM at 8 hours, while in the tumor, the concentration is 21.0 μM at one hour and 9.6 μM at 8 hours[1]. To determine the effects of Miransertib (ARQ-092) on cardiac function, echocardiographic analysis of $SHP2^{+/+}$and $SHP2^{Y279C/+}$ littermates is conducted, either in the presence of orally administered vehicle or Miransertib (100 mg/kg/day), at 12, 14, and 16 weeks of age. By 12 weeks of age, $SHP2^{Y279C/+}$ mice show significant left ventricular hypertrophy, as indicated by decreased chamber dimension and increased posterior wall thickness compared with those of littermate controls; hypertrophy in these mice continued to progress over the 4 week time period. Treatment of the $SHP2^{Y279C/+}$ mice with Miransertib normalizes the hypertrophic cardiomyopathy (HCM) phenotype as early as 2 weeks following treatment, with levels comparable to those in $SHP2^{+/+}$ at this time point[2].		

In Vitro:

DMSO： 12.5 mg/mL (28.90 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.3120 mL	11.5602 mL	23.1203 mL
	5 mM	0.4624 mL	2.3120 mL	4.6241 mL
	10 mM	0.2312 mL	1.1560 mL	2.3120 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。

Solvent&Solubility	***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: ≥ 1.25 mg/mL (2.89 mM); Clear solution 此方案可获得 ≥ 1.25 mg/mL (2.89 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 12.5 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。
References	[1]. Lapierre JM, et al. Discovery of 3-(3-(4-(1-Aminocyclobutyl)phenyl)-5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-amine (ARQ 092): An Orally Bioavailable, Selective, and Potent Allosteric AKT Inhibitor. J Med Chem. 2016 Jul 14;59(13):6455-69. [2]. Wang J, et al. In vivo efficacy of the AKT inhibitor ARQ 092 in Noonan Syndrome with multiple lentigines-associated hypertrophic cardiomyopathy. PLoS One. 2017 Jun 5;12(6):e0178905.

实验参考：

Cell Assay	Anti-proliferative cellular assays are conducted using the CellTiter Non-Radioactive Cell Proliferation Assay, which utilizes the production of formazan from a tetrazolium compound by live cells. AN3CA and A2780 cells are obtained from the ATCC. AN3CA cells are cultured in DMEM, and A2780 cells are cultured in RPMI. Cells are plated in 96-well plates at 2,000-10,000 cells/well, cultured for 24 h, and treated with the test compound for 72 h at a final DMSO concentration no greater than 0.5% v/v. PMS stock reagent (0.92 mg/mL in DPBS) is diluted 20-fold in MTS stock reagent (2 mg/mL in DPBS), and this MTS/PMS mixture is diluted 5-fold into each well of the 96-well plate. The plates are incubated for 3-4 h, and the absorbance of formazan is measured at 490 nm. The data are normalized to the untreated controls, the dose-response curves are fit to a four-parameter logistic equation, and the IC50 values are determined. All IC50 values reported are the geometric mean of at least two independent determinations[1].
Animal Administration	Mice[2] $SHP2^{Y279C/+}$ mice are used. Only male progeny are used for the experiments herein and all mice are maintained on outbred C57BL6/J backgrounds, backcrossed for more than 10 generations. Either vehicle or Miransertib (100 mg/kg body weight) is then daily administered by oral gavage for 4 weeks. Administration began at 12 weeks of age (after established hypertrophy is indicated), and continued for 4 weeks, until the mice reach 16 weeks of age. As controls, $SHP2^{+/+}$ and $SHP2^{Y279C/+}$ mice are treated with vehicle alone.
	[1]. Lapierre JM, et al. Discovery of 3-(3-(4-(1-Aminocyclobutyl)phenyl)-5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-amine (ARQ 092): An Orally Bioavailable, Selective, and Potent Allosteric AKT Inhibitor. J Med Chem. 2016 Jul

References	14;59(13):6455-69. [2]. Wang J, et al. In vivo efficacy of the AKT inhibitor ARQ 092 in Noonan Syndrome with multiple lentigines-associated hypertrophic cardiomyopathy. PLoS One. 2017 Jun 5;12(6):e0178905.