产品名称：MEK162 (ARRY-162, ARRY-438162)
产品别名：Binimetinib

生物活性：

Description	Binimetinib (MEK162) is an oral and selective MEK1/2 inhibitor. Binimetinib (MEK162) inhibits MEK with an IC50 of 12 nM.	
IC_{50} & Target [1]	MEK	Autophagy
	12 nM (IC_{50})	
In Vitro	In MCF7 cells, RSK3 or RSK4 expression decreases response to treatment with any of the PI3K inhibitors alone. However, the combination of PI3K inhibition with Binimetinib (MEK162) or BI-D1870 completely reverses the resistance of RSK-expressing cells[2]. Binimetinib (MEK162) blocks basal ERK phosphorylation in all HRAS mutant cell lines. The combination of RAD001 and AZD6244/MEK162 causes a stronger inhibition of S6 kinase than single use of RAD001 on Western blot. The combination of RAD001 and AZD6244/MEK162 also translated in a stronger blockade of cell growth in HRAS mutant cells than single use. Binimetinib (MEK162) shows stronger synergism with RAD001 than AZD6244[3].	
In Vivo	Treatment with Binimetinib (ARRY-438162) reduces disease severity in a dose-related manner in both animal models. ARRY-438162 in the CIA model inhibits increases in ankle diameter by 27% and 50% at 1 and 3 mg/kg, while Ibuprofen has 46% inhibition. When combined with Ibuprofen, these same two doses result in 74% and 72% inhibition, respectively. Microscopic examination of the ankle joints show Binimetinib (ARRY-438162) significantly inhibits lesions (inflammation, cartilage damage, pannus formation and bone resorption) by 32% and 60% at 1 and 3 mg/kg, while treatment with Ibuprofen alone results in 17% inhibition, which is not significantly different from the controls. When these two doses of Binimetinib (ARRY-438162) are combined with ibuprofen, the result is 54% and 77% inhibition of joint destruction. In AIA, 3 and 10 mg/kg of Binimetinib (ARRY-438162) inhibit AIA ankle diameter 11% and 34%, while MTX has 33% inhibition. When combined with MTX, 3 and 10 mg/kg of Binimetinib (ARRY-438162) result in 55% and 71% inhibition. Microscopic examination of ankle joints for inflammation and bone resorption also shows improved efficacy versus either compound alone[1]. When Binimetinib (MEK162) is combined with BEZ235, a significant reduction of tumor growth is observed (P=0.01). This increase in antitumor activity is accompanied by a decrease in phospho-ERK and phospho-S6 staining. No significant changes are observed in phospho-4EBP1 staining, a direct target of mTOR activity[2].	

In Vitro:

DMSO : 50 mg/mL (**113.32 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.2664 mL	11.3320 mL	22.6639 mL
	5 mM	0.4533 mL	2.2664 mL	4.5328 mL
	10 mM	0.2266 mL	1.1332 mL	2.2664 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

Solvent&Solubility	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 (5.67 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.67 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 (5.67 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.67 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 (5.67 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.67 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]. J Pheneger, et al. 2006, ACR Annual Scientific Meeting. Abst 794. [2]. Serra V, et al. RSK3/4 mediate resistance to PI3K pathway inhibitors in breast cancer. J Clin Invest, 2013, 123(6), 2551-2563. [3]. Kiessling MK, et al. Mutant HRAS as novel target for MEK and mTOR inhibitors. Oncotarget. 2015 Dec 8;6(39):42183-96. [4]. Cheng H, et al. PIK3CA(H1047R)- and Her2-initiated mammary tumors escape PI3K dependency by compensatory activation of MEK-ERK signaling. Oncogene. 2016 Jun 9;35(23):2961-70. [5]. Seip K, et al. Fibroblast-induced switching to the mesenchymal-like phenotype and PI3K/mTOR signaling protects melanoma cells from BRAF inhibitors. Oncotarget. 2016 Apr 12;7(15):19997-20015.

实验参考：

Cell Assay	MCF7 cells infected as indicated are seeded in 12-well plates (2×10^4). After 24 hours, cells are treated with BEZ235 (100 or 200 nM), BKM120 (0.75 or 1 μM), GDC-0941 (1 μM), or MK2206 (2 μM) alone or in combination with Binimetinib (MEK162) (1 μM), BI-D1870 (10 μM), or AZD6244 (1 μM), as indicated in text. Cell numbers are quantified by fixing cells with 4% glutaraldehyde or methanol, washing the cells twice in H_2O, and staining the cells with 0.1% crystal violet. The dye is subsequently extracted with 10% acetic acid, and its absorbance is determined (570 nm). Growth curves are performed in triplicate. Viability assays with CellTiter-Glo are performed by plating 2,000 cells in 96-well plates, adding the drug at 24 hours, and assaying 4 to 5 days after drug addition. Cell-cycle and hypodiploid apoptotic cells are quantified by flow cytometry. Briefly, cells are washed with PBS, fixed in cold 70% ethanol, and then stained with propidium iodide while being treated with RNase. Quantitative analysis of sub-G_1 cells is carried out in a FACScalibur cytometer using Cell

	Quest software [2].
Animal Administration	Mice[2] Six-week-old female athymic nude *Foxn1^{nu}* mice are used. Mice are treated once daily with placebo, BEZ235, BKM120, MK-2206, or Binimetinib (MEK162) by oral gavage. BEZ235 (25-30 mg/kg, 6IW [6 days on 1 day off]) and BKM120 (30 mg/kg, 6IW) are dissolved in 10% NMP-90% PEG, freshly formulated, and administrated within 30 minutes. MK-2206 (100 mg/kg, 3IW) is formulated in 30% Captisol and Binimetinib (MEK162) (6 mg/kg, BID) in 0.5% Tween-80, 1% carboxymethyl cellulose. For tumor growth studies, mice are treated for 7-24 days, depending on the xenograft model and treatment regime. Tumor xenografts are measured with calipers 3 times a week, and tumor volume is determined using the following formula: (length×width^2)×(π/6). At the end of the experiment, the animals are anesthetized with 1.5% isofluorane-air mixture and killed by cervical dislocation. Tumors are removed 2 hours following the last administration. Rats[1] Rat collagen-induced arthritis (CIA) and rat adjuvant-induced arthritis (AIA) models are used to determine efficacy in the subacute inflammation setting. In the CIA studies, rats with established disease, induced by injections of Type II collagen, are treated with 0.3, 1 or 3 mg/kg ARRY-438162 (PO, BID) with or without 30 mg/kg ibuprofen (PO, QD) for six days. Body weight and ankle diameter are used to monitor disease progression on days 0-7. The AIA model is induced by an injection of a lipoidal amine in FCA on day 0. The AIA rats are treated with 1, 3 or 10 mg/kg Binimetinib (ARRY-438162) (PO, QD) beginning on day 8 and continuing for 6 days, with or without the addition of 0.05 mg/kg CL14377 (PO, QD) which is dosed days 0-13. Disease progression is monitored on days 7-14 measuring both paw diameter and body weight.
References	[1]. J Pheneger, et al. 2006, ACR Annual Scientific Meeting. Abst 794. [2]. Serra V, et al. RSK3/4 mediate resistance to PI3K pathway inhibitors in breast cancer. J Clin Invest, 2013, 123(6), 2551-2563. [3]. Kiessling MK, et al. Mutant HRAS as novel target for MEK and mTOR inhibitors. Oncotarget. 2015 Dec 8;6(39):42183-96. [4]. Cheng H, et al. PIK3CA(H1047R)- and Her2-initiated mammary tumors escape PI3K dependency by compensatory activation of MEK-ERK signaling. Oncogene. 2016 Jun 9;35(23):2961-70. [5]. Seip K, et al. Fibroblast-induced switching to the mesenchymal-like phenotype and PI3K/mTOR signaling protects melanoma cells from BRAF inhibitors. Oncotarget. 2016 Apr 12;7(15):19997-20015.