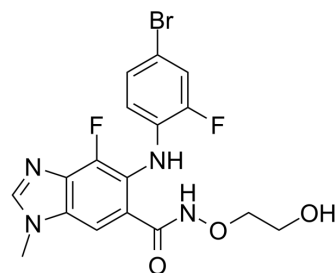


Binimetinib

Cat. No.:	HY-15202		
CAS No.:	606143-89-9		
Molecular Formula:	C ₁₇ H ₁₅ BrF ₂ N ₄ O ₃		
Molecular Weight:	441.23		
Target:	MEK; Autophagy		
Pathway:	MAPK/ERK Pathway; Autophagy		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

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

Concentration	Mass		
	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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 1% CMC >> 0.5% Tween-80
Solubility: 10 mg/mL (22.66 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
- Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution
- Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
Solubility: ≥ 2.5 mg/mL (5.67 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Binimetinib (MEK162) is an oral and selective MEK1/2 inhibitor. Binimetinib (MEK162) inhibits MEK with an IC₅₀ of 12 nM.

IC₅₀ & Target	MEK 12 nM (IC ₅₀)	Autophagy
In Vitro	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>	
In Vivo	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>	

PROTOCOL

Cell Assay ^[2]	<p>MCF7 cells infected as indicated are seeded in 12-well plates (2×10⁴). 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 H₂O, 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-G₁ cells is carried out in a FACScalibur cytometer using Cell Quest software^[2].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^{[1][2]}	<p>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 administered 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×width²)×(π/6). At the end of the experiment, the animals are anesthetized with 1.5% isoflurane-air mixture and killed by cervical dislocation. Tumors are removed 2 hours following the last administration.</p> <p>Rats^[1] Rat collagen-induced arthritis (CIA) and rat adjuvant-induced arthritis (AIA) models are used to determine efficacy in the</p>

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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2020 Mar 16;37(3):387-402.e7.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Neuro Oncol. 2019 Mar 18;21(4):486-497.
- Cell Syst. 2020 Nov 18;11(5):478-494.e9.
- Oncogene. 2016 Jun 9;35(23):2961-70.

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- [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.

Caution: Product has not been fully validated for medical applications. For research use only.

India Contact:

Life Technologies (India) Pvt. Ltd.

306, Aggarwal City Mall, Opposite M2K Pitampura, Delhi – 110034 (INDIA). Ph: +91-11-42208000, 42208111, 42208222, Mobile: +91-9810521400, Fax: +91-11-42208444

Email: customerservice@lifetechindia.com Website: www.lifetechindia.com