

产品名称: **EPZ015666**
 产品别名: **GSK3235025**

生物活性:					
Description	EPZ015666 (GSK3235025) is an orally available inhibitor of PRMT5 with an IC ₅₀ of 22 nM.				
IC ₅₀ & Target	IC50: 22 nM (PRMT5)[1]				
In Vitro	Treatment of MCL cell lines with EPZ015666 (GSK3235025) leads to inhibition of SmD3 methylation and cell death, with IC50 values in the nanomolar range[1]. EPZ015666 (GSK3235025), a potent peptide-competitive and SAM-cooperative inhibitor with >10,000-fold specificity against PRMT5 relative to other methyltransferases[2].				
In Vivo	EPZ015666 (GSK3235025) is orally bioavailable and amenable to in vivo studies. We performed 21-d efficacy studies in severe combined immunodeficiency (SCID) mice bearing subcutaneous Z-138 and Maver-1 xenografts, with twice-daily (BID) oral dosing on four dose groups: 25, 50, 100 and 200 mg per kilogram of body weight (mg/kg). After 21 d of continuous dosing, animals are euthanized, and blood and tissues are analyzed to determine the relationship between methyl-mark pharmacodynamics and tumor-growth inhibition (TGI). EPZ015666 (GSK3235025) showed dose-dependent exposure and TGI after 21 d in both MCL models. Tumors in all EPZ015666 (GSK3235025) dose groups measured on day 21 showed statistically significant differences in weight, volume and tumor growth compared to vehicle-treated tumors. Dosing at 200 mg/kg BID induced tumor stasis in Z-138 cells, with >93% TGI after 21 d, whereas Maver-1 cells showed >70% TGI. Additionally, a third MCL xenograft is tested using the Granta-519 cell line, a fast-growing model that reached endpoint on day 18 and showed dose-dependent efficacy with 45% TGI in the 200 mg/kg group. EPZ015666 (GSK3235025) is well tolerated in all three models, with minimal bodyweight loss in the 200 mg/kg dose group and no other clinical observations[1].				
Solvent&Solubility	In Vitro: DMSO : 100 mg/mL (260.80 mM; Need ultrasonic)				
	<div>Preparing Stock Solutions</div>	<div>Solvent / Mass / Concentration</div>	1 mg	5 mg	10 mg
		1 mM	2.6080 mL	13.0399 mL	26.0797 mL
		5 mM	0.5216 mL	2.6080 mL	5.2159 mL
		10 mM	0.2608 mL	1.3040 mL	2.6080 mL
	<p>*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。</p> <p>储备液的保存方式和期限：-80℃，6 months；-20℃，1 month。-80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。</p> <p>In Vivo:</p> <p>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：</p> <p>——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</p>				
	1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline				
	Solubility: ≥ 2.5 mg/mL (6.52 mM); Clear solution				
	此方案可获得 ≥ 2.5 mg/mL (6.52 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。				

	<p>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。</p> <p>2. 请依序添加每种溶剂：10% DMSO \rightarrow 90% (20% SBE-β-CD in saline) Solubility: \geq 2.5 mg/mL (6.52 mM); Clear solution 此方案可获得 \geq 2.5 mg/mL (6.52 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 生理盐水溶液中，混合均匀。</p> <p>3. 请依序添加每种溶剂：10% DMSO \rightarrow 90% corn oil Solubility: \geq 2.5 mg/mL (6.52 mM); Clear solution 此方案可获得 \geq 2.5 mg/mL (6.52 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。</p>
References	<p>[1]. Chan-Penebre E, et al. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. <u>Nat Chem Biol.</u> 2015 Jun;11(6):432-7.</p> <p>[2]. Kryukov GV, et al. MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. <u>Science.</u> 2016 Mar 11;351(6278):1214-8.</p>
实验参考：	
Cell Assay	<p>Cultured cells in linear/log-phase growth are split to a seeding density of 2×10^5 cells/mL in 2-20 mL of media, depending on the yield required at the end of the growth period. Compound is diluted in DMSO and added to each culture vessel with a final DMSO concentration of 0.2%. Cells are allowed to grow for 96 h undisturbed. At the conclusion of each treatment period, cells are harvested by centrifugation (5 min, 1,200 rpm), and cell pellets are rinsed once with PBS before being frozen on dry ice pending further processing. Long-term proliferation assays are performed on all MCL lines, with slight adjustments to initial seeding densities, depending on growth characteristics for each cell line. All assays are carried out for 12 d[1].</p>
Animal Administration	<p>Mice[1] Male CD-1 mice (25-40 g; n=6, with 3 per time point) are treated with a single dose of EPZ015666 (GSK3235025) at 2 mg/kg by intravenous tail-vein injection and 10 mg/kg by oral gavage administration, with both doses formulated in 20% N-N-dimethylacetamide in water. Animals are fasted overnight and weighed before dose administration on the day of dosing. Approximately 30 μL of blood are taken from animals by submandibular or retro-orbital bleeding at pre-specified time intervals (seven time points). For the last time point (24 h), samples are collected via cardiac puncture while the animals are under anesthesia (70% CO₂:30% O₂). Blood samples are transferred into K₂-EDTA tubes and placed on wet ice before centrifugation at 4°C (3,000g, 15 min) to obtain plasma within 30 min after sample collection. Plasma samples are stored at $-70 \pm 10^\circ\text{C}$ before protein precipitation and LC-MS/MS analysis. We constructed standard calibration curves by analyzing a series of control plasma aliquots containing 100 ng/mL labetalol as an internal standard and 1-3,000 ng/mL EPZ015666 (GSK3235025). Four levels of quality control are also included in the analysis (3-2,400 ng/mL EPZ015666 (GSK3235025)). Data are analyzed using Phoenix WinNonlin 6.2.1.</p>
	<p>[1]. Chan-Penebre E, et al. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. <u>Nat Chem Biol.</u> 2015 Jun;11(6):432-7.</p>

References

[2]. Kryukov GV, et al. MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. *Science*. 2016 Mar 11;351(6278):1214-8.



源叶生物