上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：TMC353121
产品别名：TMC353121

生物活性：

Description	TMC353121 is a potent respiratory syncytial virus (RSV) fusion inhibitor with pEC50 of 9.9.
IC_{50} & Target	pEC50: 9.9 (RSV)[1]
In Vitro	TMC353121 shows activity against groups A and B RSV and against a panel of clinical isolates with equal potency[1]. TMC353121 is a potent RSV fusion inhibitor in vitro. TMC353121 is active against wild-type RSV (strain LO), with a 50% effective concentration (EC50) of 0.07 ng/mL in HeLaM cells[2].
In Vivo	After i.v. bolus administration of a single dose of 10 mg/kg to Sprague-Dawley rats, the plasma drug concentration-time profile of TMC353121 exhibits multicompartmental pharmacokinetics. Mean plasma drug concentrations decrease rapidly during the first hours after dosing and then more slowly, with a half-life of about 12 h, as determined for the last part of the curve between 8 and 24 h postdose. TMC353121 is rapidly eliminated from plasma (CL=8.6 liters/h/kg) and extensively distributed (V_{ss}=55 liters/kg)[2]. TMC353121 is administered once, i.v. at 2.5 mg/kg or at 0.25 mg/kg. Drug levels are determined in lung tissue, serum, and BAL fluid at different time points. TMC353121 followed multicompartment pharmacokinetics, with a fast decay in serum within the first hour after i.v. injection, followed by a slower decay. The drug is eliminated quickly from the blood resulting in very low blood levels after 24 h. Lung concentrations are much higher than serum concentrations and in BAL fluid the drug is just above the limit of detection at 8 h after injection. Very low drug levels can still be detected in the lung 5 days after treatment[3].
Solvent&Solubility	***In Vitro:*** **DMSO : 50 mg/mL** (**89.49 mM;** Need ultrasonic) **H_2O : < 0.1 mg/mL** (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	1.7898 mL	8.9492 mL	17.8984 mL
	5 mM	0.3580 mL	1.7898 mL	3.5797 mL
	10 mM	0.1790 mL	0.8949 mL	1.7898 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 (4.47 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (4.47 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 (4.47 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (4.47 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 (4.47 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.47 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]. Bonfanti JF, et al. Selection of a respiratory syncytial virus fusion inhibitor clinical candidate. 2. Discovery of a morpholinopropylaminobenzimidazole derivative (TMC353121). J Med Chem. 2008 Feb 28;51(4):875-96. [2]. Rouan MC, et al. Pharmacokinetics-pharmacodynamics of a respiratory syncytial virus fusion inhibitor in the cotton rat model. Antimicrob Agents Chemother. 2010 Nov;54(11):4534-9. [3]. Olszewska W, et al. Antiviral and lung protective activity of a novel respiratory syncytial virus fusion inhibitor in a mouse model. Eur Respir J. 2011 Aug;38(2):401-8.

实验参考：

Animal Administration	Rats[2] Sprague-Dawley and cotton rats are given a single-bolus dose of 10 mg/kg TMC353121 intravenously (i.v.). Blood samples are taken from the orbital venous plexus of three Sprague-Dawley rats at 15 min and 1, 8, and 24 h postdose and from six Sprague-Dawley rats and six cotton rats at 3 h postdose. Blood samples are centrifuged at 1,500× g for 10 min, and plasma is separated and frozen until bioanalysis. After blood sampling, the rats are exsanguinated from the vena femoralis under isoflurane-oxygen anesthesia. Then they are euthanized by CO_2asphyxiation, and the lungs are subjected to lavage once via a tracheal cannula with phosphate-buffered saline (PBS) containing 2% bovine serum albumin (BSA) at room temperature at a volume of 5 mL per Sprague-Dawley rat or 2.5 mL per cotton rat. After gentle injection of the lavage fluid into the lungs, the fluid is withdrawn for collection of the bronchoalveolar lavage fluid (BALF) and the lungs are dissected. BALF is collected in order to assess TMC353121 concentrations in the lung epithelial lining fluid (ELF) after correction for the dilution with lavage fluid. A single lavage with a short dwelling time is applied as previously recommended for better accuracy of the determination of ELF dilution. BSA is added to the lavage fluid in order to prevent the adsorption of TMC353121 to syringes or other containers. The BALF is centrifuged at 300× g for 10 min, and the supernatant is separated. BALF supernatant and lung tissue samples are then frozen until bioanalysis. BALF

	supernatant is referred as BALF throughout this paper. Mice[3] Inbred 8- to 12-week-old female BALB/c mice are used. TMC353121 is administered intravenously in saline at doses of 0.25-10 mg/kg, and at various times in relation to the RSV infection. Mice are infected with 2×10^6 plaque-forming unit (PFU) of plaque-purified human strain RSV A2 (100 μL intranasally). Individual body weight is used to monitor animal health and response to infection, and is recorded daily.
References	[1]. Bonfanti JF, et al. Selection of a respiratory syncytial virus fusion inhibitor clinical candidate. 2. Discovery of a morpholinopropylaminobenzimidazole derivative (TMC353121). J Med Chem. 2008 Feb 28;51(4):875-96. [2]. Rouan MC, et al. Pharmacokinetics-pharmacodynamics of a respiratory syncytial virus fusion inhibitor in the cotton rat model. Antimicrob Agents Chemother. 2010 Nov;54(11):4534-9. [3]. Olszewska W, et al. Antiviral and lung protective activity of a novel respiratory syncytial virus fusion inhibitor in a mouse model. Eur Respir J. 2011 Aug;38(2):401-8.