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产品名称: **Gilteritinib**  
产品别名: **ASP2215**

| 生物活性:                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                       |             |             |              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------|-------------|--------------|
| Description                                                                                                                                                      | Gilteritinib is a potent FLT3/AXL inhibitor with IC <sub>50</sub> s of 0.29 nM/0.73 nM, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |             |             |              |
| IC <sub>50</sub> & Target                                                                                                                                        | IC50: 0.29 nM (FLT3)[1]<br>IC50: 0.35 nM (LTK), 0.73 nM (AXL), 1.2 nM (EML4-ALK), 230 nM (c-KIT)[2]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |             |             |              |
| In Vitro                                                                                                                                                         | <p>Of the 78 tyrosine kinases tested, Gilteritinib (ASP2215) inhibits FLT3, leukocyte tyrosine kinase (LTK), anaplastic lymphoma kinase (ALK), and AXL kinases by over 50% at 1 nM with an IC50 value of 0.29 nM for FLT3, approximately 800-fold more potent than for c-KIT[1]. Gilteritinib inhibits the activity of eight of the 78 tested kinases by over 50% at concentrations of either 1 nM (FLT3, LTK, ALK, and AXL) or 5 nM (TRKA, ROS, RET, and MER). The IC50s are 0.29 nM for FLT3 and 0.73 nM for AXL. Gilteritinib inhibits FLT3 at an IC50 that is approximately 800-fold more potent than the concentration required to inhibit c-KIT (230 nM). The antiproliferative activity of Gilteritinib is evaluated against MV4-11 and MOLM-13 cells, which endogenously express FLT3-ITD. After 5 days of treatment, Gilteritinib inhibits the growth of MV4-11 and MOLM-13 cells with mean IC50s of 0.92 nM (95% CI: 0.23-3.6 nM) and 2.9 nM (95% CI: 1.4-5.8 nM), respectively. Growth suppression of MV4-11 cells is accompanied by inhibition of FLT3 phosphorylation. Relative to vehicle control cells, phosphorylated FLT3 levels are 57%, 8%, and 1% after 2 h of treatment with 0.1 nM, 1 nM, and 10 nM Gilteritinib, respectively. In addition, doses as low as 0.1 nM or 1 nM result in the suppression of phosphorylated ERK, STAT5, and AKT, all of which are downstream targets of FLT3 activation. To investigate the effects of Gilteritinib on AXL inhibition, MV4-11 cells that expressed exogenous AXL are treated with Gilteritinib. At concentrations of 1 nM, 10 nM, and 100 nM for 4 h, Gilteritinib treatment decreases phosphorylated AXL levels by 38%, 29%, and 22%, respectively[2].</p> |                                       |             |             |              |
| In Vivo                                                                                                                                                          | <p>In MV4-11 xenografted-mice, the concentration of Gilteritinib (ASP2215) in tumors is more than 20-fold higher than that in plasma with oral administration of Gilteritinib at 10 mg/kg for 4 days. Treatment of Gilteritinib for 28 days results in dose-dependent inhibition of MV4-11 tumor growth and induces complete tumor regression at more than 6 mg/kg. Further, Gilteritinib decreases tumor burden in bone marrow and prolonged the survival of mice intravenously transplanted with MV4-11 cells[1].</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                       |             |             |              |
| Solvent&Solubility                                                                                                                                               | <b>In Vitro:</b><br>DMSO : 2 mg/mL (3.62 mM; Need ultrasonic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                       |             |             |              |
|                                                                                                                                                                  | <b>Preparing Stock Solutions</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Solvent / Mass / Concentration</b> | <b>1 mg</b> | <b>5 mg</b> | <b>10 mg</b> |
|                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1 mM                                  | 1.8093 mL   | 9.0463 mL   | 18.0927 mL   |
|                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 5 mM                                  | ---         | ---         | ---          |
|                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 10 mM                                 | ---         | ---         | ---          |
| <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>[1]. ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in acute myeloid leukemia (AML). 2014</p>                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                       |             |             |              |



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|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>References</b>            | ASCO Annual Meeting.<br><br>[2]. Mori M, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Invest New Drugs. 2017 Oct;35(5):556-565.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>实验参考:</b>                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Cell Assay</b>            | The effect of Gilteritinib on MV4-11 and MOLM-13 cells is assessed using the CellTiter-Glo Luminescent Cell Viability Assay. Subsequent studies are conducted to examine the effect of Gilteritinib and Quizartinib on Ba/F3 cells expressing either FLT3-ITD, FLT3-D835Y, FLT3-ITD-D835Y, FLT3-ITD-F691 L, or FLT3-ITD-F691I. MV4-11 and MOLM-13 cells are treated with DMSO or increasing concentrations of Gilteritinib (0.01, 0.1, 1, 10, and 100 nM) for 5 days, and cell viability is measured using CellTiter-Glo <sup>®</sup> 2].                                                                                                                                                                                                                                                                                             |
| <b>Animal Administration</b> | Mice <sup>[1]</sup><br>Antitumor activity is evaluated in nude mice transplanted with MV4-11 AML cells. The pharmacokinetics in xenografted mice is also investigated. MV4-11 xenografted-mice are treated with oral administration of Gilteritinib at 10 mg/kg for 4 days. Treatment of Gilteritinib for 28 days results in dose-dependent inhibition of MV4-11 tumor growth and induces complete tumor regression at more than 6 mg/kg <sup>[1]</sup> .                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Kinase Assay</b>          | The kinase inhibitory activity of Gilteritinib is tested against a panel of 78 tested kinases using ATP concentrations that are approximately equal to the $K_m$ value for each kinase in a TK-ELISA or off-chip mobility shift assay. Initially, two concentrations of Gilteritinib (1 nM and 5 nM) are tested to assess each compound's inhibitory effect on TK activity. Further studies are then conducted using a dose range of Gilteritinib to determine $IC_{50}$ values for kinases in which activity is inhibited by >50% with 1 nM Gilteritinib as well as for c-KIT. TK-ELISA and MSA assays are used to conduct $IC_{50}$ studies for FLT3, LTK, AXL, and c-KIT; the HTRF KinEASE-TK assay is performed to assess the $IC_{50}$ value of echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK) <sup>[2]</sup> . |
| <b>References</b>            | [1]. ASP2215, a novel FLT3/AXL inhibitor: Preclinical evaluation in acute myeloid leukemia (AML). 2014 ASCO Annual Meeting.<br>[2]. Mori M, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Invest New Drugs. 2017 Oct;35(5):556-565.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |