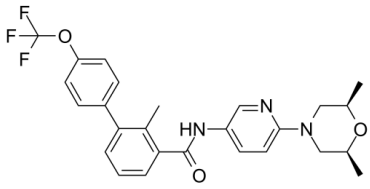
Data Sheet

Product Name:	Erismodegib
Cat. No.:	CS-0904
CAS No.:	956697-53-3
Molecular Formula:	C26H26F3N3O3
Molecular Weight:	485.50
Target:	Smo
Pathway:	Stem Cell/Wnt
Solubility:	H2O : < 0.1 mg/mL (insoluble); DMSO : 50 mg/mL (102.99 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Erismodegib (Sonidegib) is a potent and selective **Smoothened (Smo)** antagonist with **IC_{50}**s of 1.3 nM and 2.5 nM for mouse and human Smo, respectively. IC50 & Target: IC50: 1.3 nM (mSmo), 2.5 nM (hSmo)[1] **In Vitro:** The IC_{50} values for Erismodegib (Sonidegib) for the major human CYP450 drug metabolizing enzymes is greater than 10 μM[1]. Erismodegib (Sonidegib), a small molecule, clinically investigated SMO inhibitor, used alone and in combination with Nilotinib, inhibits the Hh pathway in $CD34^+$ chronic phase (CP)-chronic myeloid leukaemia (CML) cells, reducing the number and self-renewal capacity of CML leukaemia stem cell (LSC). Erismodegib interacts directly with SMO, in a similar fashion to cyclopamine, to reduce expression of downstream Hh signaling targets. Primary $CD34^+$ CP-CML cells are cultured in serum free media (SFM)±Erismodegib for 6, 24 and 72 hours (h). At 72 h, while there is variability between the biological samples, GLI1 is significantly downregulated following exposure to Erismodegib (10 nM; 0.78-fold and 100 nM; 0.73-fold, respectively ($p<0.01$)[2]. **In Vivo:** Erismodegib (Sonidegib) is a weak base with a measured pK_a of 4.2 and exhibits relatively poor aqueous solubility. In the subcutaneous $Ptch^{+/-}p53^{-/-}$ medulloblastoma allograft mouse model, Erismodegib demonstrates dose-related antitumor activity after 10 days of oral administration of a suspension of the diphosphate salt. At a dose of 5 mg/kg/day qd, Erismodegib significantly inhibits tumor growth, corresponding to a T/C value of 33% ($p<0.05$ as compared to vehicle controls). When dosed at 10 and 20 mg/kg/day qd, Erismodegib affords 51 and 83% regression, respectively[1]. Bone marrow cells and spleen cells from a subset of treated mice are transplanted into secondary recipient mice. Transplantation of either bone marrow (BM) or spleen cells from mice treated with Erismodegib+Nilotinib results in reduced white cell count (WCC) and reduces leukaemia development in secondary recipients compared to Erismodegib or Nilotinib alone[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [2]$CD34^+$ CP-CML cells are seeded in SFM alone ±Erismodegib± Nilotinib and cultured for 24-72 h prior to assessment. Proliferation is measured using colorimetric assessment of BrDU incorporation. Proportion of viable cells versus those in early and late apoptosis is assessed by flow cytometry using annexin V-FITC and 7-amino-actinomycin D (7-AAD, Via-Probe solution). Cell cycle status is assessed using Ki67 (FITC) expression and 7-AAD incorporation[2]. **Animal Administration:** LDE225 is dissolved in DMSO and then diluted with PBS or saline[2].[2]Mice[2]

The transgenic $EGFP^+$/SCLtTA/TRE-BCR-ABL mouse model is used to investigate the effect of Erismodegib treatment on CML LSC in vivo. Scl-tTa-BCR-ABL mice in the FVB/N background are crossed with transgenic GFP-expressing mice. Bone marrow cells are obtained 4 weeks post induction, GFP^+ cells are selected by flow cytometry and transplanted by tail vein injection (10^6 cells/mouse) into wild-type FVB/N recipient mice, irradiated at 900 cGy, generating a large cohort of mice with similar time of onset of leukemia. Blood samples obtained 4 weeks post transplantation confirmed a neutrophilic leukocytosis in recipient mice. Mice are treated with Nilotinib (50 mg/kg by gavage, daily), Erismodegib (80 mg/kg by gavage, daily), Erismodegib+ Nilotinib, or with vehicle alone (control). After 3 weeks of treatment, animals are euthanised and marrow content of femurs and tibiae, spleen cells and blood obtained. Total white cell count (WCC), GFP-expressing WCC, myeloid cells, and GFP+ progenitors and stem cells are measured by

flow cytometry. Survival is assessed in a subset of mice for 120d post discontinuation of treatment. Spleen and BM cells from a subset of mice in each arm are pooled and 5×10^6 cells/mouse (8 mice/condition) are transplanted into wild-type FVB/N recipient mice irradiated at 900 cGy. Engraftment is monitored by drawing peripheral blood (PB) every 4 weeks. The percentage of GFP^+ cells in PB is analyzed by flow cytometry.

References:

[1]. Pan S, et al. Discovery of NVP-LDE225, a Potent and Selective Smoothened Antagonist. ACS Med Chem Lett. 2010 Mar 16;1(3):130-4.

[2]. Irvine DA, et al. Deregulated hedgehog pathway signaling is inhibited by the smoothened antagonist LDE225 (Sonidegib) in chronic phase chronic myeloid leukaemia. Sci Rep. 2016 May 9;6:25476.

CAIndexNames:

[1,1'-Biphenyl]-3-carboxamide, N-[6-[(2R,6S)-2,6-dimethyl-4-morpholinyl]-3-pyridinyl]-2-methyl-4'-(trifluoromethoxy)-, rel-

SMILES:

O=C(C1=C(C)C(C(C=C2)=CC=C2OC(F)(F)F)=CC=C1)NC3=CC=C(N=C3)N4C[C@@H](C)O[C@@H](C)C4

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA