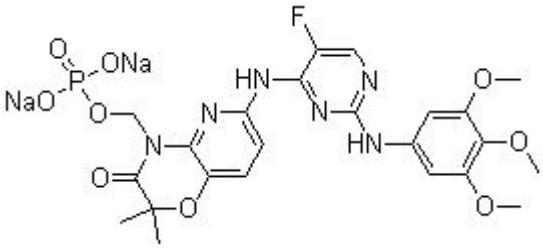
Product Introduction

R788 (Fostamatinib) Disodium

R788 (Fostamatinib) disodium, a prodrug of the active metabolite R406, is a **Syk** inhibitor with **IC50** of 41 nM, strongly inhibits Syk but not Lyn, 5-fold less potent to Flt3. Phase 2.

Technical Data:

Molecular Weight (MW):	624.42	
Formula:	$C_{23}H_{24}FN_6O_9P.2Na$	
Solubility (25°C) * **<1 mg/ml means slightly soluble or insoluble:**	DMSO 0.4 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1025687-58-4	

Biological Activity

R935788 is a methylene phosphate prodrug of R406, which can be rapidly converted to R406 in vivo. R406 (in vitro active form of R935788) selectively inhibits Syk-dependent signaling with EC50 values ranging from 33 nM to 171 nM, more potently than Syk-independent pathways in different cells. [1] R406 inhibits cellular proliferation of a variety of diffuse large B-cell lymphoma (DLBCL) cell lines with EC50 values ranging from 0.8 μM to 8.1 μM. [2] R406 treatment reduces basal phosphorylation of BLNK, Akt, glycogen synthase kinase-3 (GSK-3), forkhead box O (FOXO) and ERK not only in cells with high (TCL-002) but also

in cells with low levels of phosphorylated Syk (TCL1-551). In addition, R406 completely inhibits the anti-IgM induced Bcr signal in TCL1 leukemias. Despite the higher levels of constitutively active Syk in TCL1 leukemias, R406 is not selectively cytotoxic to the leukemic cells. [3]

Given that plasma half-life of R406 in mice is less than 2 hours, R935788 is administered in 3 divided doses at 3-hour intervals to provide continuous Syk inhibition during each day of treatment, mimicking the longer plasma half-life in humans (15 hours). Despite the relatively modest cytotoxic effect in vitro, R935788 significantly inhibits the proliferation and survival of leukemic cell in vivo, which is associated with the blocking of antigen-dependent B-cell receptor (Bcr) signaling rather than inhibition of constitutive Syk activity. R935788 treatment at 80 mg/kg/day for 18-21 days potently inhibits tumor growth of TCL1-002, TCL1-551 and TCL1-870 in mice with undetectable leukemic $CD5^+/B220^+$ cells at the last day of treatment, significantly prolongs the survival of the treated mice with median survival increased from 45/46 days to 170/172 days, and completely eradicates the malignant cells in a substantial proportion of mice after a 6-month follow-up period without affecting the production of normal B lymphocytes. R935788 treatment also induces an early and transient migration of both normal and malignant B cells from spleen and lymph nodes to peripheral blood, which is subsequently followed by selective growth inhibition of the malignant B-cell population. In addition, R935788 is also effective against spontaneously developing TCL1 leukemias in Eμ-TCL1 transgenic mice. [3]

Clinically used oral formulation of R406.

References

[1] Braselmann S, et al. J Pharmacol Exp Ther, 2006, 319(3), 998-1008.

[2] Chen L, et al. Blood, 2008, 111(4), 2230-2237.

[3] Suljagic M, et al. Blood, 2010, 116(23), 4894-4905.

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