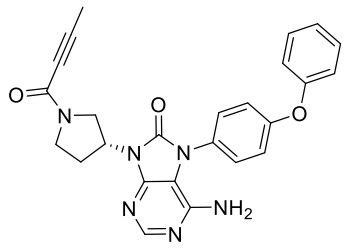
Product data sheet

MedKoo Cat#: 206611 Name: Tirabrutinib free base CAS#: 1351636-18-4 (free base) Chemical Formula: $C_{25}H_{22}N_6O_3$ Exact Mass: 454.1753 Molecular Weight: 454.49	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

Tirabrutinib, also known as ONO-4059 and GS-4059, is a potent and orally active Bruton agammaglobulinemia tyrosine kinase (BTK) in hibitor. Upon administration, ONO-4059 covalently binds to BTK within B cells, thereby preventing B-cell receptor signaling and impeding B-cell development. As a result, this agent may inhibit the proliferation of B-cell malignancies. BTK, a cytoplasmic tyrosine kinase and member of the Tec family of kinases, plays an important role in B lymphocyte development, activation, signaling, proliferation and survival.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	65.0	143.02
DMSO:PBS (pH 7.2) (1:2)	0.3	0.66
DMF	30.0	66.01
Ethanol	1.0	2.20

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.20 mL	11.00 mL	22.00 mL
5 mM	0.44 mL	2.20 mL	4.40 mL
10 mM	0.22 mL	1.10 mL	2.20 mL
50 mM	0.04 mL	0.22 mL	0.44 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Kozaki R, Vogler M, Walter HS, Jayne S, Dinsdale D, Siebert R, Dyer MJS, Yoshizawa T. Responses to the Selective Bruton's Tyrosine Kinase (BTK) Inhibitor Tirabrutinib (ONO/GS-4059) in Diffuse Large B-cell Lymphoma Cell Lines. Cancers (Basel). 2018 Apr 23;10(4):127. doi: 10.3390/cancers10040127. PMID: 29690649; PMCID: PMC5923382.
2. Hofland T, de Weerdt I, Ter Burg H, de Boer R, Tannheimer S, Tonino SH, Kater AP, Eldering E. Dissection of the Effects of JAK and BTK Inhibitors on the Functionality of Healthy and Malignant Lymphocytes. J Immunol. 2019 Oct 15;203(8):2100-2109. doi: 10.4049/jimmunol.1900321. Epub 2019 Sep 11. PMID: 31511358.

In vivo study

1. Ariza Y, Murata M, Ueda Y, Yoshizawa T. Bruton's tyrosine kinase (Btk) inhibitor tirabrutinib suppresses osteoclastic bone resorption. Bone Rep. 2019 Mar 15;10:100201. doi: 10.1016/j.bonr.2019.100201. PMID: 30956999; PMCID: PMC6431727.

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2. Das S, Bar-Sagi D. BTK signaling drives CD1dhiCD5+ regulatory B-cell differentiation to promote pancreatic carcinogenesis. Oncogene. 2019 Apr;38(17):3316-3324. doi: 10.1038/s41388-018-0668-3. Epub 2019 Jan 11. PMID: 30635655; PMCID: PMC6486434.

7. Bioactivity

Biological target:

Tirabrutinib (ONO-4059) is a BTK inhibitor with an IC50 of 2.2 nM.

In vitro activity

To assess the susceptibility of B-cell malignancies to tirabrutinib, a panel of 64 hematopoietic cell lines, including 10 GCB-DLBCL and 11 ABC-DLBCL lines, was screened (Table 1). Six showed a response to tirabrutinib when concentrations up to 10,000 nM were used; four of these were derived from ABC-type DLBCL (TMD8 with EC50 of 4.5 nM; OCI-LY10, U2932, and HBL1 each with an EC50 of approximately 3000 nM). The other responding cell lines were Pfeiffer, a GCB-DLBCL with an EC50 of around 3000 nM, and REC1, an MCL line with an EC50 of 33 nM. The cell line most sensitive to tirabrutinib was the CD79B mutant cell line TMD8.

Reference: Cancers (Basel). 2018 Apr; 10(4): 127. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5923382/

In vivo activity

As illustrated in Fig 1a, b and Supplementary Figure S1a, inflammatory stimulation of splenic B cells from naïve mice upregulated BTK activation as measured by pBTK (Y223) expression. Cytokine treatment of B cells did not alter total BTK protein levels (Supplementary Fig. S1a). This increase was accompanied by an expansion of the $CD1d^{hi}CD5^{+}$ B_{reg} population (Fig. 1c, 1d). Significantly, inhibition of BTK activation by tirabrutinib (Fig. 1a, 1b, Supplementary Fig. S1a) attenuated cytokine-induced $CD1d^{hi}CD5^{+}$ B_{reg} differentiation (Fig. 1c, 1d). Furthermore, tirabrutinib markedly downregulated expression of both $CD1d^{hi}CD5^{+}$ B_{reg} functional markers, IL-10 (Fig. 1e, Supplementary Fig. S1b) and IL-35 (heterodimer of Ebi3 and p35, encoded by the *Ebi3* and *IL12A* genes, respectively) (Fig. 1f, 1g), which are critical mediators of $CD1d^{hi}CD5^{+}$ B_{reg} immunosuppressive function. Collectively, these results directly implicate the BTK signaling pathway in promoting $CD1d^{hi}CD5^{+}$ B_{reg} differentiation and production of the immunomodulatory cytokines IL-10 and IL-35.

Reference: Oncogene. 2019 Apr;38(17):3316-3324. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6486434/

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.