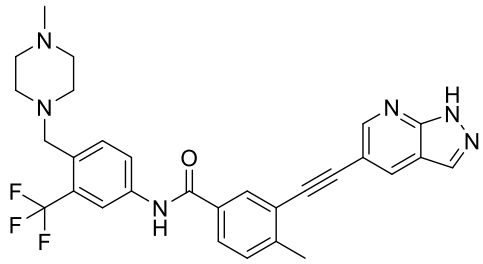
Product data sheet

MedKoo Cat#: 407111 Name: Olverembatinib (GZD824) CAS#: 1257628-77-5 Chemical Formula: $C_{29}H_{27}F_3N_6O$ Exact Mass: 532.21984 Molecular Weight: 532.22	
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:

Olverembatinib, also known as GZD824, is a novel orally bioavailable inhibitor against a broad spectrum of Bcr-Abl mutants including T315I. GZD824 tightly bound to Bcr-Abl(WT) and Bcr-Abl(T315I) with K(d) values of 0.32 and 0.71 nM, respectively, and strongly inhibited the kinase functions with nanomolar IC(50) values. GZD824 potently suppressed proliferation of Bcr-Abl-positive K562 and Ku812 human CML cells with IC(50) values of 0.2 and 0.13 nM, respectively. GZD824 also displayed good oral bioavailability (48.7%), a reasonable half-life (10.6 h), and promising in vivo antitumor efficacy. It induced tumor regression in mouse xenograft tumor models driven by Bcr-Abl(WT) or the mutants and significantly improved the survival of mice bearing an allograft leukemia model with Ba/F3 cells harboring Bcr-Abl(T315I). GZD824 represents a promising lead candidate for development of Bcr-Abl inhibitors to overcome acquired imatinib resistance.

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	80.0	150.3

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.88 mL	9.39 mL	18.79 mL
5 mM	0.38 mL	1.88 mL	3.76 mL
10 mM	0.19 mL	0.94 mL	1.88 mL
50 mM	0.04 mL	0.19 mL	0.38 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. Wang Y, Zhang L, Tang X, Luo J, Tu Z, Jiang K, Ren X, Xu F, Chan S, Li Y, Zhang Z, Ding K. GZD824 as a FLT3, FGFR1 and PDGFRα Inhibitor Against Leukemia In Vitro and In Vivo. Transl Oncol. 2020 Apr;13(4):100766. doi: 10.1016/j.tranon.2020.100766. Epub 2020 Apr 1. PMID: 32247263; PMCID: PMC7125355.

2. Ren X, Pan X, Zhang Z, Wang D, Lu X, Li Y, Wen D, Long H, Luo J, Feng Y, Zhuang X, Zhang F, Liu J, Leng F, Lang X, Bai Y, She M, Tu Z, Pan J, Ding K. Identification of GZD824 as an orally bioavailable inhibitor that targets phosphorylated and nonphosphorylated breakpoint cluster region-Abelson (Bcr-Abl) kinase and overcomes clinically acquired mutation-induced resistance against imatinib. J Med Chem. 2013 Feb 14;56(3):879-94. doi: 10.1021/jm301581y. Epub 2013 Jan 28. PMID: 23301703.

In vivo study

Product data sheet

1. Wang Y, Zhang L, Tang X, Luo J, Tu Z, Jiang K, Ren X, Xu F, Chan S, Li Y, Zhang Z, Ding K. GZD824 as a FLT3, FGFR1 and PDGFRα Inhibitor Against Leukemia In Vitro and In Vivo. Transl Oncol. 2020 Apr;13(4):100766. doi: 10.1016/j.tranon.2020.100766. Epub 2020 Apr 1. PMID: 32247263; PMCID: PMC7125355.

2. Ren X, Pan X, Zhang Z, Wang D, Lu X, Li Y, Wen D, Long H, Luo J, Feng Y, Zhuang X, Zhang F, Liu J, Leng F, Lang X, Bai Y, She M, Tu Z, Pan J, Ding K. Identification of GZD824 as an orally bioavailable inhibitor that targets phosphorylated and nonphosphorylated breakpoint cluster region-Abelson (Bcr-Abl) kinase and overcomes clinically acquired mutation-induced resistance against imatinib. J Med Chem. 2013 Feb 14;56(3):879-94. doi: 10.1021/jm301581y. Epub 2013 Jan 28. PMID: 23301703.

7. Bioactivity

Biological target:

Olverembatinib (GZD824, HQP1351) is a potent and orally active pan-Bcr-Abl inhibitor that strongly inhibits native Bcr-Abl and Bcr-AblT315I with IC50s of 0.34 nM and 0.68 nM, respectively.

In vitro activity

To validate the anti-proliferation effect of GZD824 in leukemia cells, different single-gene-driven proliferation cells were selected including MV4–11Flt3-ITD, MOLM-13Flt3-ITD, KG-1 FGFR1OP2-FGFR1 and EOL-1FIP1L1-PDGFRa as models. It was shown that GZD824 inhibits the viability of all 4 cell lines with IC50 values of 2.00 ± 1.10, 6.01 ± 6.10, 3.66 ± 1.93 and 7.56 ± 2.73 nM, respectively, but was more than 50-fold less potent against other leukemia cells such as NB4 and HL60, independent of FLT3-ITD, FGFR1OP2-FGFR1 or FIP1L1-PDGFRa mutations (Table 1). The anti-proliferation activities of GZD824 were also investigated in Ba/F3 stable cells, and used three marketed FLT3 inhibitors, midostaurin, gilteritinib and quizartinib as controls. It was shown that these three FLT3 inhibitors were insensitive to FLT3-ITD-F691I and FLT3-ITD-F691R mutants, but GZD824 clearly inhibited cell growth with IC50 values of 1.4 and 9.4 nM, respectively (Table 2). GZD824 was also found to be sensitive to most cells harboring different FLT3 kinase domain mutants such as D835N//G/A and D842H/R but less sensitive to D835H/V/Y/I. Even for R834Q mutation, which is resistant to all marketed second generation FLT3 inhibitors, GZD824 possesses inhibitory activity with an IC50 value of 76.2 nM. Western blotting (WB) results showed that GZD824 clearly inhibits the activation of FLT3-ITD-F691I and its downstream signal proteins such as STAT5 (Figure 2B).

Reference: Transl Oncol. 2020 Apr;13(4):100766. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32247263/

In vivo activity

The antitumor efficacy in vivo of GZD824 was also evaluated in MV4–11Flt3-ITD, Ba/F3- FLT3-ITDF691I and KG-1 FGFR1OP2-FGFR1 cells using CB17-SCID mouse xenograft models. The animals were repeatedly administrated vehicle or GZD824 once every 2 days via oral gavage (10 and 20 mg/kg, q2d) for 16 consecutive days. GZD824 was well tolerated in all of the tested groups with no mortality or significant side effects observed during treatment (Tables S2, S3). It was shown that the GZD824 almost completely eradicates xenograft tumors of MV4–11 and KG-1 at a dose of 10 or 20 mg/kg respectively (Figure 5, A, C, E). WB assays in the tumor tissue showed that GZD824 suppresses the FLT3 and FGFR1 activation and induces apoptosis in MV4–11Flt3-ITD, Ba/F3-FLT3-ITDF691I and KG-1 FGFR1OP2-FGFR1 xenograft model (Figure 5, E and F).

Reference: Transl Oncol. 2020 Apr;13(4):100766. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32247263/

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.