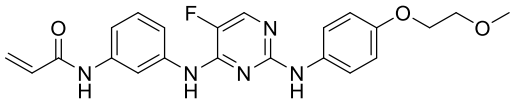
Product data sheet

MedKoo Cat#: 204480 Name: Spebrutinib CAS#: 1202757-89-8 Chemical Formula: $C_{22}H_{22}FN_5O_3$ Exact Mass: 423.17067 Molecular Weight: 423.44	
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:
Spebrutinib, also known as AVL-292 or CC-292, is an orally bioavailable, selective inhibitor of BrutonÂ's agammaglobulinemia tyrosine kinase (BTK), with potential antineoplastic activity. Upon administration, AVL-292 targets and covalently binds to BTK, thereby preventing its activity. By irreversibly inhibiting BTK, administration of this agent may lead to an inhibition of B cell receptor (BCR) signaling and may inhibit cell proliferation of B-cell malignancies.

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	50.0	118.08
DMSO:PBS (pH 7.2) (1:30)	0.03	0.07
DMF	20.0	47.23
Ethanol	0.5	1.18

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.36 mL	11.81 mL	23.62 mL
5 mM	0.47 mL	2.36 mL	4.72 mL
10 mM	0.24 mL	1.18 mL	2.36 mL
50 mM	0.05 mL	0.24 mL	0.47 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. Vidal-Crespo A, Rodriguez V, Matas-Cespedes A, Lee E, Rivas-Delgado A, Giné E, Navarro A, Beà S, Campo E, López-Guillermo A, Lopez-Guerra M, Roué G, Colomer D, Pérez-Galán P. The Bruton tyrosine kinase inhibitor CC-292 shows activity in mantle cell lymphoma and synergizes with lenalidomide and NIK inhibitors depending on nuclear factor-κB mutational status. Haematologica. 2017 Nov;102(11):e447-e451. doi: 10.3324/haematol.2017.168930. Epub 2017 Aug 24. PMID: 28838994; PMCID: PMC5664406.
2. Arnason JE, Brown JR. B cell receptor pathway in chronic lymphocytic leukemia: specific role of CC-292. Immunotargets Ther. 2014 Jan 24;3:29-38. doi: 10.2147/ITT.S37419. PMID: 27471698; PMCID: PMC4918232.

In vivo study

1. Lee-Vergés E, Hanna BS, Yazdanparast H, Rodríguez V, Rodríguez ML, Giró A, Vidal-Crespo A, Rosich L, Amador V, Aymerich M, Villamor N, Delgado J, Lichter P, Pérez-Galán P, López-Guerra M, Campo E, Seiffert M, Colomer D. Selective BTK inhibition

improves bendamustine therapy response and normalizes immune effector functions in chronic lymphocytic leukemia. Int J Cancer. 2019 Jun 1;144(11):2762-2773. doi: 10.1002/ijc.32010. Epub 2019 Jan 16. PMID: 30468254.
2. Daryaee F, Zhang Z, Gogarty KR, Li Y, Merino J, Fisher SL, Tonge PJ. A quantitative mechanistic PK/PD model directly connects Btk target engagement and in vivo efficacy. Chem Sci. 2017 May 1;8(5):3434-3443. doi: 10.1039/c6sc03306g. Epub 2017 Mar 14. PMID: 28507715; PMCID: PMC5417014.

7. Bioactivity

Biological target:

Spebrutinib (CC-292) is a covalent inhibitor of Btk with IC50 value of 0.5 nM.

In vitro activity

CC-292 (10–1000 nM) had a cytostatic effect in a subset of cell lines, with REC-1, MINO and UPN-1 appearing to be the most sensitive, while MAVER-1 and Z138 were the most resistant to CC-292, following a trend similar to that for ibrutinib (Figure 1A,B). CC-292 induced marginal apoptosis (10–15%) in the most sensitive cell lines (UPN-1 and REC-1) (Online Supplementary Figure S1). Identification of Tyr223 pBTK is considered a surrogate marker for kinase activity.6 MCL cell lines pre-incubated with CC-292 were IgM-stimulated to mimic BCR activation. As displayed in Figure 1C, CC-292 significantly reduced both constitutive and IgM-induced BTK phosphorylation at the Y223 residue in MCL cell lines and primary cells, independently of their sensitivity to the inhibitor.

Reference: Haematologica. 2017 Nov; 102(11): e447–e451. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664406/

In vivo activity

Mice treated with CC-292 experienced a substantial decrease in the number of both $Ly6C^{hi}$ and $Ly6C^{low}$ monocytes ($p = 0.0016$ and $p < 0.0002$, respectively; Fig. **5***b*), with no major alteration of the patrolling-to-inflammatory ratio (Fig. **5***a*). Moreover, this study analyzed the effect of the treatment on T-cell populations in PB, which are known to increase along with disease course. This study detected a decrease in $CD4^+$ and $CD8^+$ T-cell numbers after single-agent treatment ($CD8^+$: $p = 0.0128$ and $CD4^+$: $p = 0.1020$). While CLL development is associated with a drop in the $CD4^+/CD8^+$ cell ratio due to $CD8^+$ T-cell expansion, CC-292 treatment resulted in a significant increase in the $CD4^+/CD8^+$ cell ratio in PB ($p = 0.0079$; Supporting Information Fig. S6*e*). Collectively, these data show that CC-292 treatment results in a normalization of CLL-induced changes in monocyte and T-cell numbers.

Reference: Int J Cancer. 2019 Jun 1;144(11):2762-2773. https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.32010

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.