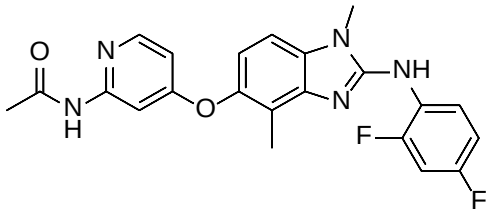
Product data sheet

MedKoo Cat#: 407137 Name: CHZ868 CAS#: 1895895-38-1 Chemical Formula: $C_{22}H_{19}F_2N_5O_2$ Exact Mass: 423.1507 Molecular Weight: 423.42	
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:

CHZ868 or CHZ-868 is a potent and selective type II JAK inhibitor which demonstrates activity in JAK inhibitor persistent cells, murine MPN models, and MPN patient samples. CHZ868 showed significant activity in murine MPN models and induced reductions in mutant allele burden not observed with type I JAK inhibitors. CHZ868 stabilizes JAK2 in an inactive conformation. CHZ868 potently suppressed the growth of CRLF2-rearranged human B-ALL cells, abrogated JAK2 signaling, and improved survival in mice with human or murine B-ALL. CHZ868 and dexamethasone synergistically induced apoptosis in JAK2-dependent B-ALLs and further improved in vivo survival compared to CHZ868 alone. CHZ868 may be useful for patients with JAK2-dependent leukemias and other disorders.

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	100.0	236.17

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. Wu SC, Li LS, Kopp N, Montero J, Chapuy B, Yoda A, Christie AL, Liu H, Christodoulou A, van Bodegom D, van der Zwet J, Layer JV, Tivey T, Lane AA, Ryan JA, Ng SY, DeAngelo DJ, Stone RM, Steensma D, Wadleigh M, Harris M, Mandon E, Ebel N, Andraos R, Romanet V, Dölemeyer A, Sterker D, Zender M, Rodig SJ, Murakami M, Hofmann F, Kuo F, Eck MJ, Silverman LB, Sallan SE, Letai A, Baffert F, Vangrevelinghe E, Radimerski T, Gaul C, Weinstock DM. Activity of the Type II JAK2 Inhibitor CHZ868 in B Cell Acute Lymphoblastic Leukemia. Cancer Cell. 2015 Jul 13;28(1):29-41. doi: 10.1016/j.ccell.2015.06.005. PMID: 26175414; PMCID: PMC4505625.

In vivo study

1. Wu SC, Li LS, Kopp N, Montero J, Chapuy B, Yoda A, Christie AL, Liu H, Christodoulou A, van Bodegom D, van der Zwet J, Layer JV, Tivey T, Lane AA, Ryan JA, Ng SY, DeAngelo DJ, Stone RM, Steensma D, Wadleigh M, Harris M, Mandon E, Ebel N, Andraos R, Romanet V, Dölemeyer A, Sterker D, Zender M, Rodig SJ, Murakami M, Hofmann F, Kuo F, Eck MJ, Silverman LB, Sallan SE, Letai A, Baffert F, Vangrevelinghe E, Radimerski T, Gaul C, Weinstock DM. Activity of the Type II JAK2 Inhibitor

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CHZ868 in B Cell Acute Lymphoblastic Leukemia. Cancer Cell. 2015 Jul 13;28(1):29-41. doi: 10.1016/j.ccell.2015.06.005. PMID: 26175414; PMCID: PMC4505625.

7. Bioactivity

Biological target: CHZ868 is a type II JAK2 inhibitor with an IC50 of 0.17 μM in EPOR JAK2 WT Ba/F3 cell.

In vitro activity

The activity of CHZ868 to MPL mutant cells was assessed in vitro. CHZ868 potently inhibited the proliferation of 32D cells expressing MPLW515L (Figures 1F-G). CHZ868 treatment abrogated phosphorylation of Y1007/Y1008 in the JAK2 activation loop, consistent with a type II mechanism of action (Figure 1H, Figure S1O). Inhibitor washout studies confirmed that phosphorylation of JAK2 and STAT5 was gradually restored within 4-24 hr after removing CHZ868 (Figure S1U). CHZ868 potently induced apoptosis in JAK2 and MPL mutant cells as reflected by caspase 3 activation (Figure 1I) and by annexin V staining (Figure S1V), and exhibited enhanced killing of JAK2V617F SET2 cells. These findings demonstrate that type II JAK2 inhibition with CHZ868 shows significant activity in JAK2V617F and MPLW515L mutant cells, including potent inhibition of JAK2 and STAT phosphorylation and induction of cell death.

Reference: Cancer Cell. 2015 Jul 13;28(1):29-41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4503933/

In vivo activity

The efficacy of CHZ868 at inhibiting myeloproliferation was assessed in vivo. CHZ868 dosed at 30-40 mg/kg orally once daily inhibited JAK-STAT signaling in vivo consistent with potent target inhibition (Figure 4A). CHZ868 therapy resulted in significant reduction in the proportion of mutant cells in the bone marrow (Figure 4B). A significant decrease of mutant allele burden in the CD71+Ter119+ erythroid progenitor compartment with CHZ868 was observed as compared to vehicle-treated mice (Figure 4C), consistent with a mutant-biased reduction in erythroid output. These data demonstrate that type II JAK2 inhibition with CHZ868 reduces mutant allele burden in vivo.

Reference: Cancer Cell. 2015 Jul 13;28(1):29-41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4503933/