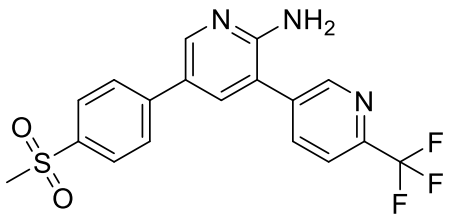
Product data sheet

MedKoo Cat#: 526661 Name: MMV390048 CAS#: 1314883-11-8 Chemical Formula: $C_{18}H_{14}F_3N_3O_2S$ Exact Mass: 393.0759 Molecular Weight: 393.3842	
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:
MMV390048, also known as MMV-048, is a novel antimalarial compound belonging to the aminopyridine class. MMV390048 competitively inhibited the binding of only a single protein, P. falciparum PI4 kinase, to the beads. In combination with a partner drug, MMV390048 has the potential to become a new child-friendly treatment for uncomplicated malaria that could be given as one single dose, completing the treatment in just one day instead of the current three days.

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	TBD	TBD

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.54 mL	12.71 mL	25.42 mL
5 mM	0.51 mL	2.54 mL	5.08 mL
10 mM	0.25 mL	1.27 mL	2.54 mL
50 mM	0.05 mL	0.25 mL	0.51 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. Paquet T, Le Manach C, Cabrera DG, Younis Y, Henrich PP, Abraham TS, Lee MCS, Basak R, Ghidelli-Disse S, Lafuente-Monasterio MJ, Bantscheff M, Ruecker A, Blagborough AM, Zakutansky SE, Zeeman AM, White KL, Shackleford DM, Mannila J, Morizzi J, Scheurer C, Angulo-Barturen I, Martínez MS, Ferrer S, Sanz LM, Gamo FJ, Reader J, Botha M, Dechering KJ, Sauerwein RW, Tungtaeng A, Vanachayangkul P, Lim CS, Burrows J, Witty MJ, Marsh KC, Bodenreider C, Rochford R, Solapure SM, Jiménez-Díaz MB, Wittlin S, Charman SA, Donini C, Campo B, Birkholtz LM, Hanson KK, Drewes G, Kocken CHM, Delves MJ, Leroy D, Fidock DA, Waterson D, Street LJ, Chibale K. Antimalarial efficacy of MMV390048, an inhibitor of Plasmodium phosphatidylinositol 4-kinase. Sci Transl Med. 2017 Apr 26;9(387):eaad9735. doi: 10.1126/scitranslmed.aad9735. PMID: 28446690; PMCID: PMC5731459.

In vivo study

1. Paquet T, Le Manach C, Cabrera DG, Younis Y, Henrich PP, Abraham TS, Lee MCS, Basak R, Ghidelli-Disse S, Lafuente-Monasterio MJ, Bantscheff M, Ruecker A, Blagborough AM, Zakutansky SE, Zeeman AM, White KL, Shackleford DM, Mannila J, Morizzi J, Scheurer C, Angulo-Barturen I, Martínez MS, Ferrer S, Sanz LM, Gamo FJ, Reader J, Botha M, Dechering KJ, Sauerwein RW, Tungtaeng A, Vanachayangkul P, Lim CS, Burrows J, Witty MJ, Marsh KC, Bodenreider C, Rochford R, Solapure SM, Jiménez-Díaz MB, Wittlin S, Charman SA, Donini C, Campo B, Birkholtz LM, Hanson KK, Drewes G, Kocken CHM, Delves MJ,

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Leroy D, Fidock DA, Waterson D, Street LJ, Chibale K. Antimalarial efficacy of MMV390048, an inhibitor of Plasmodium phosphatidylinositol 4-kinase. Sci Transl Med. 2017 Apr 26;9(387):eaad9735. doi: 10.1126/scitranslmed.aad9735. PMID: 28446690; PMCID: PMC5731459.

7. Bioactivity

Biological target:

MMV390048 is a representative of a new chemical class of Plasmodium PI4K inhibitors (Kdapp=0.3 µM) that binds to the ATP binding site of Plasmodium PI4K

In vitro activity

The in vitro activity of MMV390048 against intraerythrocytic life cycle stages of P. falciparum (NF54 drug-sensitive strain) showed a steep inhibition curve with 50 and 90% inhibitory concentration (IC50 and IC90, respectively) values of 28 and 40 nM, respectively (fig. S1). Against a panel of multidrug-resistant clinical isolates of P. falciparum, the ratio of the maximum/minimum IC50 values for MMV390048 was 1.5-fold, suggesting that MMV390048 has a low risk for cross-resistance (table S1) (10). The prophylactic activity of MMV390048 against the liver stages of Plasmodium that precede symptomatic blood-stage infection was determined in vitro using Plasmodium cynomolgi, a simian parasite species closely related to P. vivax. In a cell-based assay, MMV390048, administered to a primary rhesus hepatocyte cell culture 2 hours after inoculum (allowing sporozoites to invade the hepatocytes), showed potent inhibition of liver-stage development of both schizonts and hypnozoites (fig. S7). The IC50 values were 64 nM for schizonts and 61 nM for hypnozoites (fig. S7). The ability of MMV390048 to block all life cycle stages of the malaria parasite suggests that this compound should be further developed and may contribute to malaria control and eradication as part of a single-dose combination treatment.

Reference: Sci Transl Med. 2017 Apr 26; 9(387): eaad9735. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5731459/

In vivo activity

The prophylactic effect of MMV390048 was also evaluated in vivo in P. cynomolgi–infected macaques (Macaca mulatta). Two cohorts of malaria-naïve monkeys were used during this experiment. In cohort 1, MMV390048 (20 mg/kg) was administered orally to three study animals on day 1 before sporozoite inoculation; in cohort 2, two control monkeys were administered orally with the same volume of vehicle. Detectable parasite infection occurred on day 8 after inoculation in the two control monkeys (Fig. 3A). In contrast to the control group, animals from cohort 1 did not present any parasitemia when observed for up to 100 days after inoculation, revealing prophylactic efficacy and full protection by MMV390048 (Fig. 3A, monkeys 3, 4, and 5). To test the host-to-vector-to-host transmission-blocking efficacy of MMV390048 in vivo, a model comprising mouse-to-mosquito-to-mouse transmission of P. berghei infection was used. Within the course of this study, MMV390048 (administered orally at 2 mg/kg) inhibited parasite transmission to the mosquito vector, with a 69.3 and a 30.3% reduction in oocyst intensity (mean number of parasites per midgut) and prevalence (% infected mosquitoes), respectively, observed over two replicate experiments (Table 1 and Fig. 2G). This resulted in a 37.2 and 46.5% reduction in sporozoite intensity and prevalence (Table 1). By fitting data from the mouse-to-mouse assay to a chain binomial model, the effect size of the intervention was estimated, assessing the ability of MMV390048 to reduce the basic reproductive number R0 (assuming 100% coverage). An effect size of 28.5% was estimated [95% confidence interval (CI), 22.8 to 33.7%], suggesting that MMV390048 is capable of acting as a transmission-blocking agent in lower transmission settings.

Reference: Sci Transl Med. 2017 Apr 26; 9(387): eaad9735. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5731459/