

## Product Data Sheet

Product Name: GSK2269557

Cat. No.: GC15595

### Chemical Properties

Cas. No. 1254036-77-5

Chemical Name 6-(1H-indol-4-yl)-4-[5-[[4-(1-methylethyl)-1-piperazinyl]methyl]-2-oxazolyl]-1H-indazole, monohydrochloride

SMILES CC(C)N(CC1)CCN1CC2=CN=C(C3=C(C=NN4)C4=CC(C5=CC=CC6=C5C=CN6)=C3)O2Formula  $C_{26}H_{28}N_6O \cdot HCl$  M.Wt 477.0Solubility  $\leq 0.2$ mg/ml in ethanol; 20mg/ml in DMSO; 14mg/ml in dimethyl formamide Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure 

### Background

pKi : 9.9

GSK2269557 is an inhibitor of PI3Kδ.

Phosphoinositide 3-kinase delta (PI3Kδ), a lipid kinase belonging to the Class 1 PI3K family, catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate to produce the critical signalling molecule phosphatidylinositol-3,4,5-triphosphate and then triggers various downstream biological events that ultimately regulate cell proliferation, growth, differentiation, chemotaxis and survival.

In vitro: In the screening study, GSK2269557 met the original potency goal in the PBMC assay (pIC50 >9) and showed exquisite selectivity against the PI3K isoforms in a modified HTRF assay. Moreover, GSK2269557 could induce concentration-dependent increases in QT interval and Tpe at 0.3 and 1 μM and an increase in QRS at 1 μM, however, no treatment-related TdP arrhythmias were seen [1].

In vivo: In a disease relevant Brown Norway Rat acute OVA model of Th2 driven lung inflammation, GSK2269557 was found to be able to protect against eosinophil recruitment with

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an ED50 of 67 µg/kg. The activity of GSK2269557 was also assessed using other endpoints, leukocyte recruitment to the lung (neutrophils, macrophages, CD4 and CD8 T-lymphocytes at 48 hours) and Th2 cytokines such as IL-13. It was found that GSK2269557 could reduce recruitment of all leukocyte subpopulations and IL-13 in the lungs in a dose-dependent manner [1].

Clinical trial: GSK2269557 was investigated in a double blind and placebo controlled trial in healthy males and smokers. It was found that GSK2269557 was well tolerated in healthy males. There was a low incidence of AE's and the plasma PK was well defined confirming high levels of drug within the lung compared to plasma [2].

### References:

[1] Down, K. ,Amour, A.,Baldwin, I.R., et al. Optimization of novel indazoles as highly potent and selective inhibitors of phosphoinositide 3-kinase  $\delta$  for the treatment of respiratory disease. J. Med. Chem. 58(18), 7381-7399 (2015).

[2] Robert Wilson, Anthony Cahn, Amanda Deans, Iain McSherry, Curtis Rambaran, Ana Sousa, Darren Wilbraham. Safety, tolerability and pharmacokinetics (PK) of single and repeat nebulised doses of a novel phosphoinositide 3-kinase  $\delta$  inhibitor (PI3K $\delta$ ), GSK2269557, administered to healthy male subjects in a phase I study. European Respiratory Journal 2013 42: P729.

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