 Discovery and Characterization of Potent and Selective AXL Receptor Tyrosine Kinase Inhibitor AB801

Dillon H. Miles, Susan L. Papcak, Corinne N. Foley, Shiewei Qu, Manjunath Lami, Sinivas Paladugu, Hsin-Ting Huang, Nidhi Tibrewal, Ada Chen, Joseph Kulisch, Stefan Garrido-Shaqfeh, Patricia Fabia, Subhasree Sridhar, Sun Liu, Debbie Swinarski, Xiaoning Zhao, Ester Fernandez-Salas, David Green, Lixia Jin, Manmohan R. Leleti

Arctus Biosciences, Inc., 3920 Point East Drive, Hayward, CA 94545, USA

ABSTRACT

AB801 exhibits a favorable in vitro pharmacokinetic profile with low toxicity, exquisite in human hepatocyte (hMERTK) selectivity, and predicted to exhibit moderate clearance, long half-life, and good oral bioavailability in humans (Table 2).

AB801 is known to be a potent inhibitor of AXL receptor tyrosine kinase and has shown selectivity against MERTK and TYRO3. However, its pharmacokinetic profile and selectivity in human hepatocytes have not been extensively studied.

INITIAL DESIGN, OPTIMIZATION, AND CHARACTERIZATION OF AB801

The initial design and optimization of AB801 involved the use of a structure-based drug design approach, where the compound was designed to inhibit the tyrosine kinase activity of AXL. The optimization process involved the enhancement of the inhibitory activity and selectivity against AXL while maintaining good oral bioavailability.

Characterization and Comparison of AB801 and Benchmark AXL Inhibitors

The characterization of AB801 involved the comparison with benchmark AXL inhibitors to evaluate its potency, selectivity, and pharmacokinetic properties. The results showed that AB801 had high selectivity, low plasma levels, and good oral bioavailability.

Pan-Kinase Selectivity of AB801

In addition to being selective against MERTK and TYRO3, AB801 was tested against a broad non-redundant kinase panel to determine any potential off-target liabilities. Using a SOCI-based competition binding assay, AB801 showed <3% of selectivity against other kinases, indicating an excellent pharmacological profile.

Preclinical Pharmacokinetic Characterization

AB801 was found to have low to moderate clearance and a suitable half-life in all preclinical species tested. AB801 has high oral bioavailability in rats and exposure in species-dependent.

PROJECTED HUMAN PHARMACOGENOMICS

Projected Human Pharmacokinetics

Table 1: Projected human pharmacokinetic profile of AB801. The model includes human hepatic microsomal metabolism, intrinsic CYP3A4/2D6 activity, and efflux transporters.

Safety of AB801

AB801 displays a good safety profile with limited direct and time-dependent CYP inhibition; additional studies showed limited CYP inhibition. Taken together, there is a low potential for CDD. HEG inhibition of 1 and 10 µM was 8% and 48%, respectively, supportive of a large therapeutic window.

REFERENCES AND NOTES