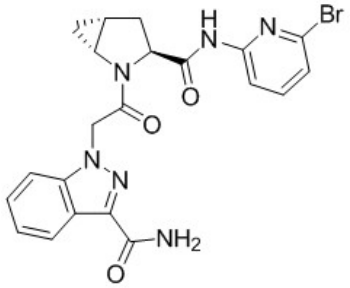
Discovery of Highly Potent, Selective and Orally Bioavailable Complement Alternative Pathway Inhibitors for Treatment of PNH

S. Flohr[1], J. Maibaum[1], E. L. Lorthiois[1], F. Cumin[1], A. Vulpetti[1], A. Schubart[1], A. Risitano[2], N. Ostermann[1], K. Anderson[1], J. Eder[1]*

[1]Novartis, [2]University of Naples

The complement system is one of the major defense mechanisms of the innate immune system composed of the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). There is strong scientific evidence for AP involvement in Paroxysmal Nocturnal Hemoglobinuria (PNH) and other immune disorders. The serine proteases Factor B (FB) and Factor D (FD) are part of the central amplification loop of the AP.

We report on the discovery and preclinical evaluation of highly potent and selective low-molecular weight FD inhibitors which were identified using structure guided optimization. Oral administration of these inhibitors blocked systemic and ocular lipopolysaccharide (LPS)-induced activation of the AP in mice. In vitro inhibition of FD is shown to prevent both hemolysis and erythrocyte C3 deposition on human PNH erythrocytes ex vivo differentiating it from the standard of care, eculizumab.



[1] Jürgen Maibaum, Sha-Mei Liao, Anna Vulpetti, Nils Ostermann, Stefan Randl, Simon Rüdisser, Edwige Lorthiois, Paul Erbel, Bernd Kinzel, Fabrice A Kolb, Samuel Barbieri, Julia Wagner, Corinne Durand, Kamal Fettis, Solene Dussauge, Nicola Hughes, Omar Delgado, Ulrich Hommel,Ty Gould, Aengus Mac Sweeney, Bernd Gerhartz, Frederic Cumin, Stefanie Flohr, Anna Schubart, Bruce Jaffee, Richard Harrison, Antonio Maria Risitano, Jörg Eder and Karen Anderson, *Nature Chemical Biology*, **2016**, 12, 1105–1110.

[2] Edwige Lorthiois, Karen Anderson, Anna Vulpetti, Olivier Rogel, Frederic Cumin, Nils Ostermann, Stefan Steinbacher, Aengus Mac Sweeney, Omar Delgado, Sha-Mei Liao, Stefan Randl, Simon Rüdisser, Solene Dussauge, Kamal Fettis, Laurence Kieffer, Andrea de Ekernez, Louis Yang, Constanze Hartwieg, Upendra A Argikar, Laura R. LaBonte, Ronald Newton, Viral Kansara, Stefanie Flohr, Ulrich Hommel, Bruce Jaffee, and Jürgen Maibaum, *J. Med.Chem.*, **2017**, in press.