Regulation of the terminal phase of the complement component pathway is a clinically validated approach for the therapeutic treatment of complement disorders. Inhibition of complement activation at the C5 level, with the monovalent complement peptide RA101495, demonstrates an inhibition of rare disorders such as PNH and aHUS. However, even in these settings there remains a continued unmet need primarily due to its insufficient bioavailability and lack of activity in patients with C5 mutations and lack of universal access.

Ra Pharmaceuticals has developed a macrophilic synthetic peptide, RA101495, which binds complement C5 with subnanomolar affinity and absolutely inhibits its cleavage into C5a and C5b upon activation of the classical, alternative or lectin pathways. In vitro studies also demonstrated that RA101495 is capable of preventing MAC assembly after thrombin mediated complement activation and is a potent disruptor of the interaction in between C5b and C6.

Inhibition of complement activity was evaluated in cynomolgus monkeys following single- and multi-dose subcutaneous (SC) administration. RA101495 inhibited high SC bioavailability and low, single dose fully inhibited complement-mediated hemolytic activity (>95%). Repeat dosing was well tolerated in monkeys and rats at high multiples of the projected human therapeutic dose and resulted in sustained and predictable inhibition of complement activity. RA101495 fully inhibited the hemolysis of erythrocytes from PNH patients after activation of the alternative pathway. The synthetic peptide offers a novel pharmacologic approach for targeting the human complement system by associated complement dysfunction. As a product designed for convenient self-administration, RA101495 offers a superior over monoclone antibody therapy for patients with PNH and aHUS, including those with C5 polymorphisms and other complement disorders, especially those associated with hypocomplementogenic states.

RA101495 binds human CS with high affinity

RA101495 binds human CS with high affinity as evaluated by Surface Plasmon Resonance (SPR).

RA101495 inhibits C5 cleavage

RA101495 binds to CS and absolutely inhibits its cleavage into C5a and C5b by the CS convertase as determined by using a BLA assay (C5b-9 was measured in picograms of C5a). This mechanism of complement inhibition is similar to the one displayed by the monoclonal antibody Eculizumab.

RA101495 inhibits C5 cleavage

RA101495 exhibits excellent PK/PD correlation in single and repeat dose studies in NHPs

RA101495 exhibits excellent PK/PD correlation in single and repeat dose studies in NHPs. RA101495 inhibits complement activation in human and non-human primates. Single and repeat dose in cynomolgus monkeys demonstrated a clear correlation between circulating drug levels and inhibition of complement mediated hemolysis (assessed by using an in vivo old hemolysis assay).

RA101495 provides sustained inhibition of complement activity in a dose dependent manner

Repeat dosing studies in cynomolgus monkeys resulted in first suppression of complement mediated hemolytic activity (>95%). Sustained inhibition was observed at all dose levels evaluated in the study.

RA101495 inhibits hemolysis of PNH erythrocytes upon activation of the complement alternative pathway

The ability of RA101495 to prevent the hemolysis of PNH erythrocytes was evaluated using a modified hemolysis assay. RA101495 inhibited hemolysis in single and multiple dose studies in cynomolgus monkeys. RA101495 exhibited PK/PD correlation and resulted in dose dependent inhibition of hemolysis.

Preclinical safety data supports the use of RA101495 in human clinical studies

The safety of RA101495 has been evaluated in repeat dose GMP toxicity studies. RA101495 is safe and well-tolerated in non-human primates and rhesus at high multiples of anticipated human therapeutic doses.

RA101495 is a small synthetic macrophilic peptide designed for self-administration and to be used in the treatment of rare complement-mediated disorders, including aHUS and PNH. RA101495 is active in preclinical studies and is poised to be developed as an oral, non-invasive therapeutic for the treatment of complement-mediated disorders.