Therapeutic Development of Complement C5 inhibitor Coversin™ with Extended Half-life via PASylation®

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The complement C5 inhibitor Coversin is in clinical development for treatment of paroxysmal nocturnal hemoglobinuria (PNH) and has been shown to be safe and effective in phase 1 single dose and multiple dose trials in healthy volunteers. A single phase 2 PNH patient, resistant to the standard of care eculizumab, has been treated with Coversin for a period of more than 7 months and responded well to treatment.

In contrast to eculizumab, which is intravenously administered twice monthly by a health care professional, Coversin will be self-administered as a once daily subcutaneous injection. While this may provide patient convenience compared to intravenous administration, even longer intervals between subcutaneous dosing would enhance that convenience.

To extend Coversin’s half-life and explore the potential for subcutaneous administration at longer dosing intervals Coversin has been modified by the addition of a 600 amino acid proline/alanine-serine (PAS) N-terminal fusion tag to generate PAS-Coversin (68kDa). The unstructured and uncharged PAS polypeptide gives Coversin an apparent molecular size of approximately 720kDa, thus retarding kidney filtration and extending the half-life of PAS-Coversin by 52-fold in mice compared to unmodified Coversin. Furthermore, in vitro complement lytic and C5 binding assays indicate PAS-Coversin inhibits complement C5 as potently as unmodified Coversin.

Recent work has shown that PAS-Coversin can be administered to mice by subcutaneous injection and has very high bioavailability when administered via this route. The bioactive protein can be produced in both (commercially scaleable) bacterial and yeast expression systems. The further development of PAS-Coversin for therapeutic purposes with the potential for weekly dosing will be presented.

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Declaration of Interests:
Miles Nunn is employed by and holds share options in Akari Therapeutics plc, which is developing Coversin and PAS-Coversin for treatment of human disease

Arne Skerra is Chairman and shareholder of XL-protein GmbH, which develops and commercializes PASylation® technology for human therapy