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# Complement in human disease: approved and up-and-coming therapeutics

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## SUMMARY

The complement system is recognised as a protector against bloodborne pathogens and controller of normal immune and tissue homeostasis. However, dysregulated complement activity is associated with unwanted, or non-resolving, immune responses and inflammation which induce or exacerbate the pathogenesis of a broad range of inflammatory and autoimmune diseases. Although the merit of targeting complement clinically has long been acknowledged, the overall complement drug approval rate has been modest. However, the success of the humanised-anti C5 antibody eculizumab in effectively treating paroxysmal nocturnal haemoglobinuria and atypical haemolytic syndrome has revitalised the field. Further, increased understanding of complement biology has led to the identification of novel targets for drug development and this, in combination with advances in drug discovery and development technologies, has resulted in a surge of interest in bringing new complement therapeutics into the clinic. At present, the rising number of approved drugs still almost exclusively target rare diseases, but the substantial pipeline of up-and-coming treatment options will likely provide opportunities to also expand the clinical targeting of complement to common diseases.

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CONTRIBUTORS

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## INTRODUCTION

The complement system represents one of the oldest components of the immune system and is central to the detection and destruction of invasive, bloodborne pathogens.[1] Although initially assigned to the innate arm of immunity, the complement system also partakes in the control of adaptive immunity[2] by directing the activation and function of B and T cell responses through control of key signalling pathways and cell metabolism.[2] Further, complement emerged as an important contributor to the secession of immune responses, general immune homeostasis, and the regenerative pathways that underly tissue repair.[2,3]

Because of the broad functional reach of complement, dysregulation of complement contributes to a wide range of human diseases. Particularly, inappropriate, uncontrolled, and/or chronic complement activation can either induce inflammatory or autoimmune conditions or exacerbate the pathological impact of non-complement, tissue destructive, triggers.[3] Thus, merit in targeting complement has been recognised for more than half a century, however, progress in providing successful treatment options has been comparatively modest until recently.[4] Reasons include (1) the complexity of the system with several positive and negative feedback loops and a high degree of functional redundancy; (2) a lack of reliable biomarkers to measure complement activity in patients; (3) an incomplete understanding of the exact molecular mechanisms that underly complement contributions to disease pathology; (4) limited availability of preclinical animal models that accurately replicate human complement-driven disease states; and (5) the concern that complement inhibition may expose treated patients to opportunistic infections.

The finding that eculizumab, a humanised anti-C5 antibody that was approved by the Food and Drug Administration (FDA) in 2007, can prevent complement-mediated lysis of erythrocytes and efficiently treat paroxysmal nocturnal haemoglobinuria (PNH) validated complement as a successful clinical target. It also alleviated safety concerns surrounding long-term therapeutic complement blockage as the overall incidence of serious infections was 5.9% in the eculizumab treatment group and 4.1% in the placebo group.[5] In parallel, there have been important new insights into our understanding of complement functions and control,[6] which provide new pharmacological targets. Recent advances in drug discovery and development technologies also have allowed for the generation of more specific and effective complement inhibitors, with improved target engagement and fewer side effects. Overall, this contributed to increased industry investment into the development of complement treatment options, and a recent surge in complement drugs that have progressed into the clinic. This review will provide an overview of the complement therapeutics that are currently FDA or European Medicines Agency (EMA) approved and several up-and-coming new treatment options with Orphan Drug, Emergency Use, or Breakthrough Therapy designation.

## THE COMPLEMENT SYSTEM

### Activation and function

The human complement system is considered a pathogen- or danger-associated molecular pattern (PAMP or DAMP) recognition system and consists of over 50 members, which

are either circulating in the blood or lymph (and are mostly secreted by the liver) or are expressed on cell-surfaces and, in some cases, on/in subcellular compartments.[1,2] The molecular pathways underlying complement activation and regulation are complex and we will thus recapitulate critical key concepts only. For an in-depth mechanistic overview of complement activation, regulation, and its classic inflammation-driving activties geared towards clinicians, we suggest reference[7]. In the absence of pathogenic or altered self-derived threats, the complement core components C3 and C5 circulate mostly in inactive forms. C3 and C5 processing into biologically active fragments can be initiated via three distinct activation pathways, the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). The three pathways are triggered by distinct PAMPs and DAMPs but share several common components and lead to the assembly of C3 activating CP/LP and AP C3 convertases, C5 activating CP/LP and AP C5 convertases, and the induction of the pathogen-killing terminal pathway (TP) (figure 1). C3 and the AP, particularly, garner attention as complement targeting options because a small proportion of C3 is activated tonically via hydrolysis of the C3 internal thioester bond and can seed complement activation on injured tissue, and the AP strongly amplifies complement activation originally initiated via the CP and/or LP (figure 1).[8]

The C3 convertases cleave C3 into bioactive C3a and C3b, and the C5 convertases process C5 into C5a and C5b.[1,2] The anaphylatoxins C3a and C5a induce endothelial cell stimulation and subsequent immune cell transmigration and activation via engagement and signal induction of their respective seven-transmembrane domain receptors, C3a receptor (C3aR) and C5aR1 and/or C5aR2.[2] The opsonin C3b opsonises pathogens and dangerously altered self-structures for detection and removal by scavenger cells that express receptors for C3b and particularly for the major C3b breakdown product, inactivated C3b (iC3b) (CR3, CD11b-CD18 complex; and CR4, CD11c-Cd18 complex), while C5b, together with the complement components C6 – C9 form the lytic membrane attack complex (MAC) in susecptible target pathogens and cell membranes.[9] Overall, complement activation protects against infections via inducing the general inflammatory reaction, enhancing and/or modulating immune responses, and direct killing of select pathogens. Complement also opsonises noxius self-derived threats, such as immune complexes (ICs) and apoptotic cells,[10] and is, thus, considered an important physiological housekeeper (figure 1).

## Regulation

Once activated, complement latches onto targets indiscriminately, including healthy host cells in the vicinity of the complement triggering PAMPs or DAMPs. To avoid detrimental tissue pathology, complement is tightly controlled by fluid-phase and cell surface-bound regulators[1] that engage four staggered, regulative strategies. Firstly, complement is controlled at the early level of PAMP or DAMP recognition via the plasma serpin C1 inhibitor (C1-INH), which irreversibly binds to the protease components of the C1 and MBL/ficolin/collectin–MASP complexes and inhibits their ability to cleavage activate C4 and trigger CP or LP activation.[1,2] The second level of regulation aims at preventing unwanted C3b/C4b deposition on host cells via the regulatory protease Factor I (FI) that initiates the breakdown of deposited C3b (and C4b) together with fluid-phase or cell-bound co-factors (FH, C4b binding protein (C4BP), CD46 (membrane cofactor protein, MCP),

and complement receptor 1 (CR1)). The third level of regulation involves increasing the dissociation of C3 and C5 convertases that still succeeded in forming on host cells via regulators with decay accelerating activities (FH, C4BP, CD46, CR1, and CD55 (decay accelerating factor, DAF)). Finally, in case the first three mechanisms fail to be fully effective, the fourth level of complement control engages regulators that stall MAC insertion into cell surfaces (CD59, clusterin, and vitronectin) (figure 1).[1]

## COMPLEMENT-DRIVEN DISEASES

Complement perturbation-associated pathologies contribute directly to rare diseases such as PNH and atypical haemolytic uremic syndrome (aHUS)[11,12] as well as to common conditions including rheumatic diseases, ischemia-reperfusion injuries, and atherosclerosis.[3,13-15] Further, the numbers of diseases in which complement dysregulation has conclusively been identified as a pathology driver is increasing.[14] A topical example is the finding that heightened complement activation observed in patients with Coronavirus Disease 2019 (COVID-19) contributes to detrimental endothelial cell dysfunction and thrombotic events that accompany severe cases of COVID-19.[16] This prompted the FDA to provide Emergency Use Authorization for the anti-C5a antibody vilobelimab for hospitalised patients with severe COVID-19 in April 2023.[17] Table 1 summarises the diseases for which approved complement therapeutics exist at the time of writing and provides key information on the known pathology-driving complement components and/or effector functions that are currently successful drug targets.

## DRUG CLASSES FOR COMPLEMENT-TARGETED THERAPEUTICS

From a mechanistic point of view there is ample opportunity to block unwanted complement activation pharmacologically (figure 1). For example, complement inhibitors can be targeted to the DAMP or PAMP recognition component of complement, the specific activation pathways (LP, CL, and AP), the C3/C5convertases, C3 or C5 itself, and their activation effector molecules or complexes (for example, C3a, C5a and their respective receptors, CR3, and the MAC etc.). Further, there is opportunity to co-opt the functions of complement regulators as therapeutic approaches (for example, C1-INH, CR1, and FH). In addition to distinct interception points for treatment, complement-targeted drugs cover different drug modalities ranging from purified or recombinant proteins that are not antibodies, antibodies and nanobodies, modified peptides and small molecule inhibitors, to genetic therapies.[18]

Below, we have broadly categorised the currently approved complement treatment options (and some of those that are further progressed through the drug development pipeline) into 4 classes, although each class is not necessarily mutually exclusive. These include: 1) complement regulator therapies; 2) complement activation pathway inhibitors; 3) C3 or C5 inhibitors; and 4) complement effector/receptor inhibitors.

### Complement regulator therapies

Historically, the first approved therapy that can be classified as a complement inhibitor, is **CI-INH**, which is approved for treatment of hereditary angiooedema (HAE). HAE is caused by the inherited deficiency of the gene *SERPING1* which encodes C1-INH.[19] Hallmark

symptoms are recurrent episodes of non-pruritic, localised, oedema in subcutaneous and submucosal tissues involving the face, extremities, skin, gastrointestinal tract, or genitals.[20] Episodes can have various triggers (medications, stress or trauma, etc.) and vary in frequency, duration, and severity. HAE can involve the upper respiratory tract, leading to potentially life-threatening swelling of the throat and larynx and abdominal attacks which can cause severe bowel obstruction.[20] Although initially, uncontrolled complement-mediated anaphylaxis with subsequent oedema was considered a disease driver, today HAE is recognised as a bradykinin-triggered disease. This is because the inhibitory activity of C1-INH extends from the serine proteases C1s/r (part of the C1 complex) and MASP1/2 (figure 1) to other key plasma proteases including kallikrein and it is the kallikrein-mediated excessive bradykinin production that underlies vascular permeability and angiooedema in HAE.[15] For therapeutic purposes, C1-INH was and is isolated from large pools of human plasma from healthy donors and supplied as a pasteurised formulation for intravenous or subcutaneous administration (eg. **Cinryze, Berinert, Haegarda**).[3] Recently, recombinant forms of C1-INH have become available (**Ruconest**).

The concept of increasing complement regulation via boosting endogenous regulatory mechanisms, ideally at the site of inflammation, is of considerable interest. For example, other complement regulators such as modified/soluble forms of CR1 can be directed to sites of inflammation as they detect deposited C3d, a C3b breakdown product.[21] Further, fusion proteins between regulatory domains of the AP regulator FH and the LP regulator small mannose-binding lectin (MBL)-associated protein (sMAP) can control complement activation broadly while cyclic peptide ‘recruiters’ can direct endogenous FH to the site of inflammation.[22,23] These approaches could provide targeted inhibition to sites of injury or inflammatory hot-spots while leaving infection-protective systemic complement activity largely intact.[24]

## Complement activation pathway inhibitors

Targeting systemic chronic complement activation, on the other hand, can be efficiently achieved by blocking the activation pathways either alone or in combination (figure 1). **sutimlimab** (Sanofi), is an approved humanised monoclonal antibody that blocks the critical C1 complex serine protease C1s, and thus prevents CP activation.[25] Other approaches currently at early stages in clinical development for targeting the CP include inhibition of C1q with an anti-C1q antibody fragment that prevents the PAMP and DAMP recognition activity of C1q[26] and a humanised monoclonal antibody against C2 ablating further CP induction.[27] Targeting C1q (eg. **ANX005**; Annexon) could be of particular interest for neurodegenerative disease given the role of C1q and microglial activation in pathogenesis.[28,29]

LP activation is currently targeted through inhibition of MASP1 and/or 2 via development of the humanised monoclonal anti-MASP-2 antibody **narsoplimab** (Omeros) which is undergoing Phase 3 trials[30] and Omeros’ human monoclonal anti-MASP3 antibody **OMS906.** MASP3 is a FD activator and as such a key driver in AP C3 and C5 convertase formation.[31]

AP inhibition is most notably targeted through inhibition of serine proteases FB and FD, because both are required for successful AP activation and propagation: FD is the critical rate-limiting enzyme for the cleavage of FB into its active form Ba, which enables C3 and C5 AP convertase formation (figure 1).[32] In consequence, direct targeting of FB is also pursued as a viable approach,[33] generally through orally active small molecules. Oral pathway inhibitors (as opposed to infusions) could represent notable improvements to patient convenience and compliance, if approved. Several companies with FB and FD inhibitors are currently in the last phases of clinical trials. These include **iptacopan** (Novartis) which is a FB inhibitor and the two FD inhibitors **danicopan** and **vemircopan** (Alexion and AstraZeneca) for PNH and aHUS as well as other complement-mediated kidney diseases.[34-36] Of note, only about 1-2 % of active FD is required to cleavage-activate FB. Thus, although FD is, in principle, an excellent drug target, its potency in triggering the AP may pose a hurdle to inhibiting FD efficiently therapeutically.

## C3 and C5 inhibitors

Cleavage of C3 and C5 leads to generation of anaphylatoxins and allows for MAC formation, both major drivers of disease (table 1). Thus, targeting C3 and C5 were among the earliest therapeutic approaches considered, and an anti-C5 antibody became the second complement targeted drug and the first complement inhibitor brought into the clinic: the humanised anti-C5 monoclonal antibody **eculizumab** developed by Alexion and administered via intravenous infusion was FDA approved for PNH in 2007 (see below).[37] The enormous success of Alexion's C5 antibody has increased efforts in approaches to reign in uncontrolled C5 activity. These include, for example, **crovalimab**, an anti-C5 antibody tested for self-administered subcutaneous dosing in PNH (Roche),[38] the PEGylated aptamer **avacincaptad pegol** (Iveric Bio),[39] which inhibits C5 processing into C5a/C5b and is under Priority Review with the FDA for eye injection treatment of geographic atrophy (GA), as well as novel modalities such as the cyclic peptide C5 inhibitor **zilucoplan** (RA Pharma),[40] and the recombinant tick-derived small protein **nomacopan** (Akari Therapeutics),[41] which blocks both C5 activation by the C5 convertase and leukotriene B4 activity.[41] Many of these C5-targeting drugs are expected to be approved in coming years as Phase 3 trials are completed.

C3 inhibitors to date have been solely advanced by a family of cyclic peptide inhibitors termed 'compstatins'[42] and are currently being commercialised as **pegcetacoplan** (Appellis) and **AMY-101** (Amyndas Pharmaceuticals).[43] p**egcetacoplan** was recently approved as infusion for PNH,[44] and as an intravitreal administered version for GA.[45] Both companies are pursuing multiple disease indications.[3] Subcutaneously administered investigational RNAi targeting C3 or C5 (for example, **ARO-C3** (Arrowhead Pharmaceuticals) or **cemdisiran** (Alnylam Pharmaceuticals)) are also in clinical development (for example, in IgA nephropathy).[46,47] Targeting complement activation at the C3 level has the advantage that it leads to broad inhibition of most inflammatory complement effector functions and also prevents pathological extravascular haemolysis which is driven by exuberant deposition of C3 activation fragments onto red blood cells (RBCs) and their MAC-mediated lysis (mostly in the liver).[48] Inhibition at the C5 level achieves specific ablation of C5a generation and TP activation (MAC formation) but preserves the C3 activation fragment-

driven protective phagocytosis of pathogens and noxious antigens, the IC clearance capacity of complement, and the C3aR-driven pathways controlling tissue repair and immune homeostasis[2,3] – thus, C5 targeted drugs allow C3-driven beneficial functions to still occur. Overall, the choice of targeting C3 or C5 depends on the individual disease and disease progression stage being treated.

### Complement effector/receptor inhibitors

The final class of complement inhibitory drugs that we discuss here are designed to target the effector molecules generated upon complement activation or their respective receptors. Selectively inhibiting one specific activation component would preserve most immune-protective functions of complement, which may be important for treating common long-term conditions such as cardiovascular and neurodegenerative diseases that require life-long dosing of drugs to the elderly population. A major complement effector target is C5a (figure 1) because of C5a's central role in endothelial and immune cell activation. Indeed, perturbed or unwanted acute and chronic C5aR1 signalling is suggested to underly a wide variety of pathologies, making the C5a–C5aR1 axis an attractive drug target.[49] Currently, there is one small molecule C5aR1 antagonist, **avacopan** (Amgen), clinically approved for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[50] Additional C5aR1 inhibitors in early clinical development include the small molecule inhibitors **ACT-1014-6470** (Idorsia Pharmaceuticals)[51] and **ALS-205** (Alsonex, administered subcutaneously)[52] and the monoclonal anti-C5aR1 antibody **avdoralimab** (Innate Pharma).[53] Alternative approaches include antibody-mediated targeting of C5a itself and in April 2023, the anti-C5a antibody **vilobelimab** (inflaRx) received FDA Emergency Use Authorization for treatment of COVID-19 in hospitalised adults based on successful trial outcomes.[17,54] Other effector/receptor targets in the complement cascade that are currently underdeveloped are C3a and C3aR1, and the second receptor for C5a, C5aR2 (both activators and inhibitors may have utility).[55,56] Drugs that selectively inhibit the formation of the MAC are also in their infancy.[57]

## APPROVED COMPLEMENT-TARGETING DRUGS

At the time of writing, and aside from the C1-INH approved for HAE, whose effects are mostly complement-independent (see above), five complement-targeting therapies have been approved for clinical use (panel 1). The published core primary report clinical data used for FDA approval of these drugs is outlined in tables 2 - 4 and is expanded upon below.

### Anti-C5 therapy

The humanised anti-C5 antibody eculizumab was FDA-approved for the treatment of PNH in 2007.[37] This was a major breakthrough in the field because it proved that PNH is a true complement-mediated disease (table 1) and that complement inhibitory therapies could be harnessed without causing overwhelming infections. Eculizumab was approved based on two Phase 3 studies (table 2), which demonstrated that eculizumab treatment reduced intravascular haemolysis, stabilized haemoglobin levels, lowered RBC transfusion requirements, improved quality of life, and reduced frequency of thromboembolic events, leading to an improvement in overall survival in over 50% of patients (detailed in table 2

and[5,58,59]). Subsequent registry-based national studies have replicated these results.[60,61] The current general eculizumab treatment regimen is based on 600 mg intravenous infusion weekly for the first four weeks in the initial phase and 900 mg infusions every two weeks during the maintenance phase (with adjustments to individual patients with residual haemolysis due to possible eculizumab underdosing and incomplete C5 blockade).[62] Additionally, anti-C5 therapy may be a valid option for treatment of pregnant patients with PNH, who had a mortality rate between 8 – 20%. A large retrospective study demonstrated that eculizumab treatment (in combination with low-molecular-weight heparin) during pregnancy led to absence of maternal deaths, a low rate of thrombotic events, and high rate of foetal survival.[63]

Eculizumab was subsequently trialled as a possible therapy for other complement mediated diseases. In aHUS (table 1,[12]), four prospective Phase 2 clinical trials were used to garner approval by the FDA in 2011 (detailed in table 2 and [64-67]). The rarity of aHUS in combination with the life-threatening nature of severe episodes and absence of an efficient treatment at the time of the clinical trials precluded randomised controlled trials. aHUS patients were treated with 900 mg of eculizumab iv. for 4 weeks, 1200 mg for the fifth dose 1 week later, and then treated with a maintenance dose of 1200 mg every 2 weeks. Collectively, these clinical trials demonstrated that eculizumab normalises platelet counts, limits thrombotic microangiopathy (TMA), and increases renal function. Although these studies included a broad spectrum of patients requiring various frequencies of plasma exchanges or infusions pre-enrolment, the overall outcome across studies demonstrated that a minimum 63% and up to 80% of patients had reduced TMA remission events and a 20% – 100% decrease in the need for plasma exchanges or infusions or dialysis. Additionally, in combination, these Phase 2 trials demonstrated benefits for paediatric, adolescent and adult patients.[64-67] Notably, eculizumab has a major impact on long term renal function, and the time between onset of aHUS and treatment initiation correlates with substantial improvement in renal function. Based on the published data, it is estimated that the risk of end-stage renal disease in patients with aHUS has decreased from 50-60% to around 10-15% at 1 year follow-up.[12]

In 2017 eculizumab was also FDA approved for patients with anti-acetylcholine receptor (AChR) antibody-positive generalised myasthenia gravis (gMG) (table 1) (eculizumab is currently only approved for refractory MG patients in the EU). The Phase 3 REGAIN trial, which administered 1200 mg eculizumab infusions every two weeks over a median 22-months period (table 2), did not meet its primary endpoint, however post-hoc analyses and secondary outcomes indicated efficacy of eculizumab therapy over placebo.[68,69] Additional interim results from the open-label extension trial of REGAIN also supported improved outcomes, with a 75% reduction in the exacerbation rate of gMG along with improvements in daily activities, muscle strength, functional ability and general quality of life measurements seen in patients in the long-term.[70] In 2019, eculizumab was also approved for treatment of neuromyelitis optica spectrum disorder (NMSOD, table 1) with a similar dosing regimen as currently approved for PNH. Eculizumab led to a 94% reduction of NMSOD relapse over the 48-week trial when compared to placebo throughout its main trial and open-label extension (table 2 and[71,72]).

Ravulizumab represents the next generation of engineered eculizumab-derived antibodies. Ravulizumab differs in four amino acids from eculizumab and has improved pharmacokinetics due to increased neonatal Fc receptor Ab recycling which prolongs plasma circulative capabilities and reduced dosing frequency. The efficacy of ravulizumab was assessed in two randomised open-label Phase 3 studies which assessed the non-inferiority of ravulizumab compared to eculizumab in PNH. One trial included patients that had not previously received complement therapy (CHAMPION-301) and the other included patients that were clinically stable on eculizumab (CHAMPION-302) (table 3 and[73-75]). These studies established that ravulizumab was non-inferior to eculizumab in both patient groups, despite ravulizumab being administered every 8 weeks, versus 2 weeks in the case of eculizumab. In the case of aHUS, two single-arm studies demonstrated that ravulizumab was safe and had similar efficacy compared to eculizumab in both adult and paediatric patients without previous complement inhibitor treatment (table 3 and[76,77]). Of note, there are no direct eculizumab vs. ravulizumab head-to-head comparative studies published in patients with aHUS. Ravulizumab has been approved for the treatment of patients with aHUS in several countries in the EU, USA and Japan and for treatment of adult patients with $AChR^+$ gMG in the USA and EU in 2022 based on the Phase 3 CHAMPION-MG study (table 3 and[78]).

Currently, anti-C5 therapy is the most successful and most applied complement-targeting drug, and established standard of care for both PNH and aHUS. However, there are limitations to this therapy. About 30% of PNH patients have persistent anaemia or require RBC transfusions while under anti-C5 therapy, which has been linked to extravascular haemolysis.[79] Of note, there is a rare intrinsic resistance to anti-C5 therapy in a subset of Japanese patients due to two polymorphisms in the *C5* gene (p.Arg885His and p.Arg885Cys) which disrupt the eculizumab/ravulizumab target epitope.[80] Further, the need for frequent intravenous drug infusions is a burden on the patient, may reduce compliance, and can preclude the use of eculizumab and ravulizumab for some patients.[3] Finally, recurrent eculizumab treatment is extremely costly (about $450,000 year/patient). With regards to cost-minimization when using ravulizumab, data are still sparse, but one study concluded that in US patients with aHUS, ravulizumab treatment reduced associated costs by about 32 – 35% compared to eculizumab treatment.[81] The high cost of the currently approved anti-C5 therapies greatly reduces their availability, which is exacerbated in some geographic areas.[3] In consequence, non-complement therapies are used as the first line of treatment in $AChR^+$ gMG (with the international consensus indicating anti-C5 therapy in relapsing patients) and NMSOD, and anti-C5 therapy is often used only when other therapies are not successful.[82] Of note, susceptibility to meningococcal infections remains the key risk in patients receiving eculizumab and patients obtaining these therapies must receive meningococcal vaccines (both the meningococcal conjugate and serogroup B vaccine).

Therefore, there is a clear need for additional, pathology-tailored, and cost-efficient complement therapeutics with alternate routes of administration. The recent approval of three additional, non-anti-C5, complement therapeutics indicates that we are moving towards this goal.

## Other approved complement-targeting therapies

Most of the complement-driven pathologies that are currently successfully targeted involve unwanted C5b-driven MAC formation on host cells (table 1). However, C5aR1 engagement on immune and non-immune cells by C5a is also an acknowledged driver of disease (table 1) and C5aR1 inhibition has thus been viewed as an additional promising avenue to suppress hyper complement-mediated inflammation. In AAV (table 1), avacopan, a small molecule C5aR1 antagonist was shown to be non-inferior at 26 weeks and superior at 52 weeks to prednisone taper with regards to remission in patients, who were also treated with either cyclophosphamide (followed by azathioprine) throughout or rituximab for 4 weeks (followed by cyclophosphamide and then azathioprine), in a Phase 3 trial (table 4 and[50]). In 2021, the FDA and the Pharmaceutical and Medical Devices Agency (PMDA, Japan's Healthy Authority), and in 2022, EMA approved avacopan (Tavneos) as an add-on treatment to standard therapy including glucocorticoids for adult patients with severe active AVV.

Also, therapies that target complement upstream of C5 and on the C3 level (which will prevent extravascular haemolysis) have been/are being developed. As of today, the only approved drug targeting C3, is the pegylated cyclic peptide C3-inhibitor pegcetacoplan that was developed from the backbone of the initial compstatin molecule. A Phase 3 trial in patients with PNH demonstrated superiority to eculizumab as assessed by changes in haemoglobin levels and reduction in transfusion requirements (table 4 and[44,83]). In May 2021, pegcetacoplan became the third US FDA-approved treatment for adults with PNH, and the first to target C3. Shortly after, pegcetacoplan was approved for adults with PNH who remain anaemic despite stable anti-C5 therapy for at least 3 months by the EMA in December 2021 (Aspaveli). Inhibiting proximal complement activity with pegcetacoplan results in control of both C5/MAC-mediated intravascular and C3-mediated extravascular haemolysis. Additionally, pegcetacoplan is given subcutaneously (as a single 1080 mg/20 ml injection twice weekly) and can therefore be self-administered. This is a major step towards broadly increasing drug availability for patients and perhaps also compliance.

In March 2023, The FDA approved pegcetacoplan for use in patients with GA secondary to age-related macular degeneration (AMD) based on the combinational data from two randomised, double-masked, sham-controlled Phase 3 trials (OAKS and DERBY). pegcetacoplan is currently under review by the EMA for approval for GA treatment (table 4 and [84]). In the published trials, intravitreal injection of pegcetacoplan (Syfovre) resulted in reductions in GA lesional areas compared to sham injection.[85,86] It should be noted that, based on a post hoc analysis of the Phase 2 FILLY trial data, pegcetacoplan treatment seems to carry a dose-dependent increased risk of new-onset exudative AMD (eAMD),[87] which was treated with on-label anti-VEGF therapy. Nonetheless, this is the first therapy approved for treatment of GA secondary to AMD, and thus represents a breakthrough for the increasing proportion of patients affected by this debilitating condition in our ageing society.

Because amplification of initial complement activation by the AP contributes to the majority of complement-driven pathologies (figure 1 and table 1), FB and FD remain attractive targets in diseases with strong complement hyper-activation.[4] However, to preserve the beneficial roles of C3 in tissue homeostasis and repair, another strategy pursued is to inhibit the specific activation pathways upstream of C3 that trigger unwanted complement

activation in the first place. For example, in cold agglutinins disease (CAD), gMG and NMOSD, complement activation is set off by self-antibody/self-antigen complexes that bind C1 and initiate CP activation. Indeed, the inhibitory anti-C1s antibody, sutimlimab, normalized haemoglobin levels, reduced fatigue, and reduced the need for transfusions in CAD patients, with or without recent transfusion history in two independent Phase 3 trials (table 4 and[25,88]). Sutimlimab is approved by the FDA for treatment of CAD since 2022 as an infusion-based drug with body weight-dependent dosage (in conjunction with meningococcal pre-vaccination).

### Emerging new complement therapies:

The increasing number of complement-targeting drugs that have made it into the clinic is encouraging and starts to benefit a growing number of patients. This trend has a clear upward trajectory because there are currently substantial numbers of ongoing clinical trials focusing on complement targeting drugs (with over 40 in Phase 3 clinical trials (clinicaltrial.gov)). In this final section, we introduce several up-and-coming therapeutics that are not yet approved for any indication (and are, thus, not included in tables 2 - 4) but that, at the time of writing, have Orphan Drug or Breakthrough Therapy status (table 5).[31,89-95] There are several emerging focus areas in the most immediate up-and-coming drugs that are nearing clinical approval. One is the successful development of biosimilars based on existing anti-C5 therapies, or next generation engineered derivatives of anti-C5 antibodies, or C5-targeted peptides, with further improved pharmacokinetics and/or efficacy and administration routes to bring down costs and increase availability. Additionally, the trial success of oral medication add-ons to existing C5-therapy, such as FD inhibitor danicopan[90] to treat PNH, aHUS, gMG and GA, as well as stand-alone oral therapy FB inhibitor iptacopan[89] for PNH, C3 glomerulopathy and IgA nephropathy are likely to dramatically change the treatment landscape for patients with these diseases (table 5 and[96]). The second is the targeting of activation pathways, such as the LP, via the development of anti-MASP antibodies (narsoplimab/OMS721[91] and OMS906,[31] also see above) for treatment of TMA events associated with aHUS and stem cell transplantation and of PNH, respectively. Thirdly, the up-and-coming lines of complement therapeutics now focus on a commonly affected organ across different complement-associated pathologies, the kidney: several of the current Phase 3 trials involve patients with vascular kidney diseases, such as C3 glomerulopathy, IgA nephropathy, immunoglobulin-mediated membranoproliferative glomerulonephritis, lupus nephritis, membranous nephropathy, and acute kidney injury (table 5 and[96]). Lastly, complement-targeting therapies aim at expanding the age-range of patients eligible for treatment. Except for anti-C5 therapy in aHUS, all complement drugs in the clinic are approved for use in adults only. Some current Phase 3 trials elucidate the safety and efficacy of anti-complement drugs in adolescents and the paediatric patient population.

## FUTURE DIRECTIONS

Although increased knowledge about complement biology has helped in many aspects with drug development, it has also identified additional hurdles for successful pharmacological interventions. For example, complement receptors often function in a cell-specific and temporal fashion during inflammatory responses[2] and complement has emerged as a central

mediator of tissue homeostasis, repair, and regeneration, as well as certain developmental processes.[2] Further, increasing mechanistic insights into the heavy crosstalk of complement with other serum effector systems, such as the coagulation, renin-angiotensin, and kallikrein-kinin systems[97] also raised awareness that (long-term) complement targeting may inadvertently impact on these (and other) homeostatic pathways.

The location of detrimental complement activation is also becoming an increasing focus: the success of eculizumab and ravulizumab is in large parts based on their accessibility to the key location of complement dysregulation, the vasculature. However, complement is also produced in tissues and supports normal tissue/organ biology, and some key components function within cells where they control normal cell physiology. Both perturbations of tissue-active and intracellular complement are associated with a substantial range of pathologies, although it should be noted that the nature and functions of intracellular complement components are a matter of controversy in the field.[6] The poor tissue/cell penetrance of current complement inhibitors limits their effectiveness in re-setting tissue/cell-specific mechanisms of complement dysregulation. This poses currently a major hurdle in targeting complement in the central nervous system (CNS) – a tissue of acknowledged increasing importance of specific complement control[98] and pathological complement dysregulation which contributes to degenerative brain diseases.[2,29] Also, the finding that local and/or intracellular complement activation can have detrimental or beneficial effects during lung infections,[6] or in tumour development,[99] indicates that it will be important to also understand better where, when, and how to target complement across diseases. There are also substantial ongoing efforts to target complement in combinational drug treatments,[100] which often offer better therapeutic efficacy, less toxicity, and increased promise to successfully treat complex diseases. Success here will likely also be a pre-requisite to eventually allow for the expansion of complement therapeutics from rare to common complement-driven diseases. Lastly, and this is true particularly for patients with rare and hard-to-treat diseases whose quality of life is commonly greatly affected, therapies that do not meet established endpoints or outcomes of preventing disease or disease advancement, may still offer notable benefits by significantly enhancing patients' quality of life (QoL). Thus, including (prolonged) QoL tracking into the design of future intervention trials and studies may translate into real patient benefits even in the absence of a reduction in disease progression.

Although the points listed above represent some of the ongoing challenges and areas of focus for future complement drug developers, there is now unprecedented progress in treating patients with complement-associated pathologies successfully.

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## SEARCH STRATEGY AND SELECTION CRITERIA

We obtained citations for this publication through searches of PubMed up to May 31, 2023, using the terms ‘complement’, ‘disease’, ‘infection’, ‘COVID-19’, ‘autoimmunity’, ‘allergy’, ‘cancer’, ‘age-related macular degeneration, (AMD)’, ‘paroxysmal nocturnal haemoglobinuria (PNH)’, ‘atypical haemolytic uremic syndrome (HUS, aHUS)’, ‘vasculitis’, ‘cold agglutinin disease (CAD)’, ‘myasthenia gravis (MG)’, ‘neuromyelitis optica spectrum disorder (NMOSD)’, ‘therapeutics’, ‘drugs’, ‘clinical trials’, ‘Phase 3’, in different combinations. We also searched ClinicalTrials.gov, EudraCT, company websites and press releases, and conference abstracts for additional eligible studies, compounds, and trial information. We restricted the search to human studies and used no language restrictions.

### Panel 1. Current FDA approved complement drugs

**Antibodies**

- Eculizumab (Soliris) is a humanised anti-C5 antibody and approved for PNH, aHUS, NMOSD, and adult anti-AchR-positive gMG (IV infusion, weekly to bi-weekly).
- Ravulizumab (Ultomiris) is a humanised anti-C5 antibody engineered from eculizumab with an extended plasma half-life and approved for PNH, aHUS, and adult anti-AchR-positive gMG (IV infusion, weekly to bi-weekly).
- Sutimlimab (Enjaymo, sutimlimab-jome) is a humanised anti-C1s antibody and approved for CAD (IV infusion, bi-weekly).
- Vilobelimab is an anti-C5a antibody and with FDA Emergency Use Approval for critically ill patients with COVID-19 (IV infusion, days 1, 2, 4, 8, 15 and 22)

**Small molecule or peptide Inhibitors**

- Avacopan (Tavenos) is a small molecule C5aR1 antagonist and approved for use in ANCA-associated vasculitis (taken orally twice daily).
- Pegcetacoplan (a compstatin-derived C3 small peptide inhibitor) is approved for PNH (Empavali; applied subcutaneously twice weekly) and for GA secondary to AMD (Syfovre; applied by IV injection once every 25-60 days).

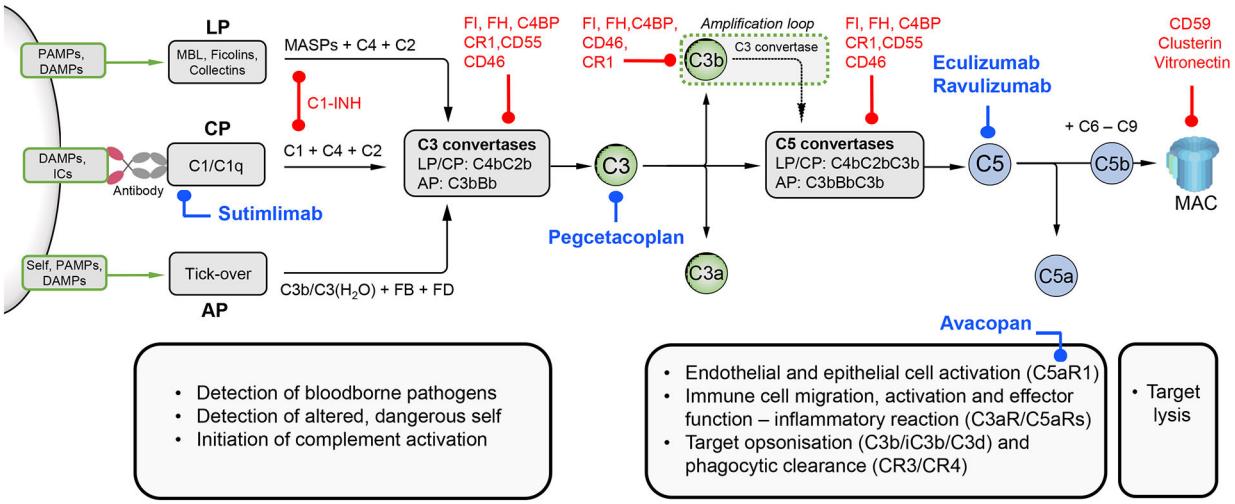


**Figure 1. The complement system – activation, function, and regulation.**

Complement can be activated through the lectin, classical, and alternative pathway. The pathways activate C3 into C3($H_2O$) via hydrolysis (AP) or recognize different PAMPs or DAMPs, or antigen-antibody immune complexes, as triggers, but all cumulate in the formation of initially C3 convertases and then C5 convertases (LP/CP or AP C3 and C5 convertases), which cleavage-activate C3 into C3a and C3b, and C5 into C5a and C5b, respectively. Because C3b can feed into all PW convertases, C3b generation is central to a (pathologically) important amplification loop. C3b opsonizes targets and mediates the phagocytic clearance of noxious antigens via engagement of receptors that recognize C3b (or breakdown products iC3b and C3d (not shown)). C5b, together with components C6 – C9, form the membrane attack complex (MAC) and kill target cells via direct lysis. C3a and C5a mediate several important activities (complement functions are listed in black boxes below) and are central to the general inflammatory reaction. Several fluid-phase or membrane bound complement regulators (depicted in red) control complement activation at central functional nodes of the complement cascade (target recognition, surface deposition, amplification, and MAC formation)). Complement functions depicted are not exhaustive but focused on currently know disease drivers. Approved complement drugs and respective targets are depicted in blue. AP, alternative pathway; C1-INH, C1 and MASP1/2 inhibitor; C4BP, C4b binding protein; CP, classical pathway; CR1, complement receptor 1; DAMP, danger-associated molecular pattern; F, factor; IC, antigen-antibody immune complexes; LP, lectin pathway; MAC, membrane attack complex; MASP1/2, MBL serine proteases 1 and 2; PAMP, pathogen-associated molecular pattern; pathway, PW.

**Table 1:**
**Complement-mediated diseases for which approved complement drugs currently exist.**

AP, alternative pathway; CNS, central nervous system; CP, classical pathway; IVH, intravascular haemolysis; EVH, extravascular haemolysis; FH, Factor H; GOF, gain of function; LOF, loss of function; LP, lectin pathway; MAC, membrane attack complex; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PR3, proteinase 3; RBC, red blood cell; ROS, reactive oxygen species; TMA, thrombotic microangiopathy.

| Disease | Affected complement component(s) | Complement-driven pathologies | Approved drug |
|---|---|---|---|
| Paroxysmal nocturnal haemogobinuria (PNH) | Lack of regulators CD55 and CD59 | Increased AP activity; MAC-mediated nocturnal lysis of RBCs (IVH); C3b/iC3b/C3d deposition on RBCs (EVH in the liver) | Eculizumab (anti-C5); Ravulizumab (anti-C5); Pegcetacoplan (C3 inhibitor) |
| Atypical haemolytic syndrome (aHUS) | LOF mutations in complement regulator genes (*CD46, CFH, CFI*); GOF mutations (*C3, CFB*); Autoantibodies against FH | Increased AP activity; MAC-mediated injury of kidney basal membrane; Platelet activation (C5aR1); Endothelial cell activation (C5aR1); TMA | Eculizumab (anti-C5); Ravulizumab (anti-C5) |
| Geographic atrophy (GA) secondary to age-related macular degeneration (AMD) | Rare variants in complement genes (*C3, C9, CFB, CFI, CFH, CD46, etc.*) | Increased AP activity; MAC-mediated death of RECs and photoreceptors; Increased ocular recruitment of immune cells (C3aR/C5aRs) | Pegcetacoplan (C3 inhibitor) |
| Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) | C1 activation by autoantibodies to proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) expressed by neutrophils | CP activation with subsequent AP activation; Neutrophil activation (ROS prod. and NET formation (C5aR1); Endothelial cell activation (C5aR1); | Avacopan (C5aR1 antagonist) |
| Neuromyelitis optica spectrum disorder (NMOSD) | C1 activation by autoantibodies to aquaporin 4 expressed on cells of the CNS | CP activation with subsequent AP activation; MAC-mediated injury of astrocytes and subsequent neuronal damage | Eculizumab (anti-C5); |
| Generalised myasthenia gravis (gMG) | C1 activation at neuro-muscular interfaces by autoantibodies to the acetylcholine receptor (anti-AChR) | CP activation with subsequent AP activation; MAC-mediated damage of cell membranes at the neuro-muscular junctions | Eculizumab (anti-C5); Ravulizumab (anti-C5) – both for anti-AChR-positive gMG |
| Cold agglutinins disease (CAD) | C1 activation by IgM antibodies recognising RBCs antigens at temperatures ≤ 32 °C. | CP activation with subsequent AP activation; MAC-mediated lysis of RBCs (IVH); C3b/iC3b/C3d deposition on RBCs (EVH in the liver) | Sutimlimab (anti-C1s) |
| Coronavirus disease 2019 (COVID-19) | Direct CP, LP, and AP activation by SARS-CoV2 spike protein; SARS-CoV2-induced type II pneumocyte local C3 production and activation | Endothelial and epithelial cell activation and injury (C5aR1, MAC); Activation of the clotting cascade; Immune cell recruitment and activation (C3aR/C5aRs) | Vilobelimab (anti-C5a); FDA Emergency Use Authorisation |

**TABLE 2:**

**Approved indications for eculizumab.**

Contains the published trial data used by the FDA for granting approval (not including extension study data or retrospective data). [1]No symptom control with previous treatment of ≥ 2 immunosuppressive therapies or chronic intravenous Ig/plasma exchange and 1 immunosuppressive therapy for 12 months. *** note that while no statistically significant changes in MG-ADL score were seen in the 26-week study (the primary endpoint), post-hoc analyses and secondary outcomes indicated an efficacy of eculizumab therapy. Interim results from the open-label extension trial of REGAIN also supported improved outcomes. aHUS, atypical haemolytic uremic syndrome; anti-AChR$^{+}$, anti-acetylcholine receptor antibody positive; LDH, lactate dehydrogenase; gMG, generalised myasthenia gravis; MG-ADL, MG activities of daily living; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria; PNH type III: complete loss of CD59; RBC, red blood cell; TMA, thrombotic microangiopathy.

| Disease | Trial (# of partic.) | Trial type | Main inclusion criteria | Endpoints | Summary data |
|---|---|---|---|---|---|
| PNH | TRIUMPH (n=87) Adults | Phase 3: Randomised, double-blind, placebo-controlled | *≥18 years old<br>*≥4 transfusions in last year<br>*≥10% PNH type III erythrocytes<br>*Elevated LDH levels | *26-week treatment<br>*Stable haemoglobin levels<br>*Absence of transfusions | *Haemoglobin stabilisation: eculizumab (21/43; 49%) vs. placebo (0/44; 0%)<br>*Median of Units of RBCs transfused: 0 eculizumab vs. 10 in placebo |
| | SHEPHERD (n=97) Adults | Phase 3: Open label, non-placebo controlled | *≥18 years old with PNH diagnosis more than 6 months prior<br>*≥1 transfusions in last 2 years<br>*≥10% PNH type III erythrocyte<br>*Elevated LDH levels<br>*Platelets ≥ 30x10$^{9}$/L | *52-week treatment<br>*Safety<br>*Haemolysis (LDH levels)<br>*Reduced fatigue (FACIT-Fatigue) | *87% reduction in haemolysis (LDH levels)<br>*Fatigue scores increased 12.2±1.1 (over baseline)<br>*52% reduction in transfusions |
| aHUS | C08-002 (n=17, 16 adults, 1 adolescent) | Phase 2: Prospective, single-arm | *≥12 years old with aHUS diagnosis<br>*Progressive TMA after ≥4 plasma exchanges or infusions in week prior | *26-week treatment (extension possible)<br>*Inhibition of TMA (change in platelet count)<br>*Normalisation of haematologic values (platelet count and LDH levels) | *Increase in platelet counts over baseline (mean increase: 73x10$^{9}$ per liter)<br>*Platelet count normalisation (87% of patients had normal counts at weeks 26 and 64 (extension))<br>*Dialysis discontinued in 4/5 patients |
| | C08-003 (n=20, 15 adults, 5 adolescents) | Phase 2: Prospective, single-arm | *≥12 years old with aHUS diagnosis<br>*<25% decrease in platelet count for at least 8 weeks<br>*Treated with plasma exchange/ infusion at least every 2 weeks, but <3 times per week | *26-week treatment (extension possible)<br>*TMA event free for ≥12 weeks<br>*Normalisation of haematologic values (platelet count and LDH levels) | *80% of patients had TMA event-free status<br>*Plasma exchange/infusion discontinued in all patients<br>*No new dialysis required |
| | C10-003 n=22 pediatric | Phase 2: Open-label, prospective, single-arm | *5 months to 17 years old with aHUS diagnosis<br>*Low platelet count<br>*Signs/symptoms of haemolysis | *26-week treatment<br>*Complete TMA response | *14/22 had a complete TMA response<br>*18/22 had haematologic normalisation<br>*16/22 had ≥25% improvement in serum creatinine |
| | C10-004 (n=41) Adults | Phase 2: Open-label, prospective, single-arm | *≥18 years old<br>*< Normal platelet count<br>*≤ Lower limit of normal haemoglobin<br>*Elevated LDH levels | *26-week treatment<br>*Platelet count normalisation<br>*LDH level normalisation | *73% had a complete TMA response with platelet count and LDH level normalisation and |

| Disease | Trial (# of partic.) | Trial type | Main inclusion criteria | Endpoints | Summary data |
|---|---|---|---|---|---|
| | | | *Elevated (or upper limit of normal) creatinine levels | *Preservation of kidney function (<25% increase in creatinine over baseline) | preservation of graft function |
| gMG (anti-AChR$^+$) | REGAIN *** (n=125) | Phase 3: Randomised, double-blind, placebo-controlled, multicenter study | *≥18 years of age<br>*MG-ADL score ≥ 6.<br>*Class II-IV disease<br>*Anti-AChR$^+$<br>*Previous immunosuppressive treatment without symptom control1 | *Week 26 change in MG-ADL score over baseline | *No statistically significant changes in MG-ADL score at 26 weeks(***)<br>*10% and 24% of patients had MG exacerbations in eculizumab and placebo groups, respectively<br>*10% and 19% of patients required rescue therapy in eculizumab and placebo groups respectively<br>*Eculizumab was well tolerated |
| NMOSD | PREVENT (n=143) | Phase 3: Randomised, double-blind, placebo controlled, time-to-event | *≥18 years of age<br>*Neuromyelitis optica or NMOSD diagnosis<br>*anti-AQP4 seropositive<br>*≥2 relapses or 3 relapses during previous 12 or 24 months, respectively | *First adjudicated relapse<br>*Adjudicated annual relapse rate<br>*Quality of life<br>*Expanded Disability Status Scale score | *Significantly lower relapse frequency (adjuncticated relapse occurred in 3% and 43% of patients in the eculizumab treated vs. placebo groups, respectively<br>*No difference in disability progression |

**TABLE 3:**

**Approved indications for ravulizumab.**

Table contains the published trial data used by the FDA for granting approval (not including extension study data or retrospective data). aHUS, atypical haemolytic uremic syndrome; anti-AChR$^{+}$, anti-acetylcholine receptor antibody positive; LDH, lactate dehydrogenase; gMG, generalised myasthenia gravis; MG-ADL, MG activities of daily living; PNH, paroxysmal nocturnal haemoglobinuria; QMG, quantitative MG total score; TMA, thrombotic microangiopathy.

| Disease | Trial (# of partic.) | Trial type | Main inclusion criteria | Endpoints | Summary data |
|---|---|---|---|---|---|
| PNH | CHAMPION-301 (n=246) | Phase 3: randomised, open-label; Assessing the noninferiority of ravulizumab to eculizumab; Ravulizumab every 8 weeks vs. eculizumab every 2 weeks at maintenance phase | *≥18 years of age with PNH diagnosis<br>*≥ 1 PNH symptom<br>*Elevated LDH levels<br>*Complement inhibitor naive | *26-weeks with possible extension up to 2 years<br>*Transfusion avoidance<br>*LDH normalization<br>*Reduced fatigue (FACIT-Fatigue)<br>*Breakthrough haemolysis<br>*Haemoglobin stabilisation | *Ravulizumab (R) was non-inferior to eculizumab (E)<br>*Transfusion avoidance (R: 73.6% vs. E: 66.1%) LDH normalisation (R: 53.6% vs. E: 49.4%)<br>*Reduced fatigue<br>*Reduced LDH<br>*Stabilised haemoglobin |
| | CHAMPION-302 (n=195) | Phase 3: randomised, open-label; Assessing the noninferiority of ravulizumab to eculizumab | *≥18 years of age with PNH diagnosis<br>*Clinically stable on eculizumab with ≥ 6 months eculizumab treatment | *26-weeks with possible extension up to 2 years<br>*% change in LDH from baseline<br>*Transfusion avoidance<br>*Reduced fatigue (FACIT-Fatigue)<br>*Breakthrough haemolysis | *Ravulizumab (R) was non-inferior to eculizumab (E)<br>*% change in LDH difference = 9.21%<br>*Transfusion avoidance difference = 5.5<br>*Breakthrough haemolysis difference = 5.1<br>*FACIT-fatigue score difference = 1.47<br>*Haemoglobin stabilisation difference = 1.4 |
| aHUS | ALXN1210-aHUS-311 (n=58) | Phase 3: Single-arm | *≥18 years of age with aHUS diagnosis<br>*Complement inhibitor naive | *26-weeks<br>*Complete TMA response (Platelet count and LDH normalisation & ≥25% improvement in serum creatinine)<br>*Renal function<br>*Haematologic changes | *Complete TMA response: 53.6%<br>*Platelet count normalisation: 83.9%<br>*LDH normalisation: 76.8%<br>improvement of serum creatinine ≥25%: 68.1% |
| aHUS | ALXN1210-aHUS-312 (n=21, n=18 full analysis) | Phase 3: Single-arm | *≤18 years of age with aHUS diagnosis<br>*Complement inhibitor naive | *26-weeks<br>*Complete TMA response (Platelet count and LDH normalisation & ≥25% improvement in serum creatinine)<br>*Renal function<br>*Haematologic changes | *Complete TMA response in 77.8% of patients<br>*Platelet count normalisation: 94.4%<br>*LDH normalisation: 88.9%<br>*Improvement of serum creatinine ≥25%: 83.3% |
| gMG | CHAMPION-MG (n=175) | Phase 3: Randomised, double-blind, placebo-controlled | *≥18 years of age<br>*MG-ADL score ≥ 6.<br>*Class II-IV disease<br>*anti-AchR$^{+}$ | *26-weeks with possible extension up to 4 years<br>*Week 26 change in MG-ADL score over baseline<br>*QMG | *Improved MG-ADL score (magnitude of mean changes from baseline: −3.1 vs. −1.4, ravulizumab and placebo, respectively<br>*≥5 point increased QMG in 30.0% vs. 11.3% of ravulizumab vs. placebo, respectively |

**TABLE 4:**
**Other (than eculizumab and ravulizumab) approved complement-targeting drugs.**

Contains the published trial data used by the FDA for granting approval (not including extension study data or retrospective data). ***Vilobelimab is currently only authorized for Emergency Use. AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; aHUS, atypical haemolytic uremic syndrome; AMG, age-related macular degeneration; CAD, cold agglutinins disease; COVID-19, coronavirus disease 2019; GA, geographic atrophy; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

| Mode of action | Drug | Disease | Trial (# of partic.) | Trial type | Main inclusion criteria | Endpoints | Summary data |
|---|---|---|---|---|---|---|---|
| C5aR1 antagonist | Avacopan | AAV | ADVOCATE (n=331) | Phase 3: Randomised, double-blind, double-dummy, controlled trial (avacopan vs. prednisone taper) | *Diagnosed with granulomatosis with polyangiitis or micro polyangiitis *Treatment with rituximab or cyclophosphamide indicated *anti-$PR3^+$ or anti-$MPO^+$ | *Remission at 26 weeks *Sustained remission at 52 weeks | *At 26 weeks Avacopan was noninferior to prednisone taper for remission (Avacopan= 120/166; 72.3% remission prednisone=115/164; 70.1% remission) *At 52 weeks Avacopan was superior to prednisone taper for sustained remission (Avacopan= 109/166; 65.7% remission prednisone=90/164; 54.9% remission) |
| C3 inhibitor | Pegcetacoplan | PNH | PEGASUS (n=80) | Phase 3: Open-label, randomised, controlled trial (Pegcetacoplan vs. eculizumab) | *≥ 18 years of age *PNH diagnosis *Haemoglobin < 10.5 g/dL while treated with eculizumab | *Mean change in haemoglobin at week 16 vs. baseline | *Change in haemoglobin levels: Pegcetacoplan was superior to eculizumab (least-squares mean change of 3.84 g/dL) *Transfusions no longer required in 35% vs. 6% of patients receiving Pegcetacoplan or eculizumab, respectively |
| | | GA secondary to AMD | OAKS (n=637) and DERBY (n=621) | Phase 3: Randomised, double-masked, sham-controlled; Treatment (tx) given every month or every other month | *≥ 60 years of age *≥ GA lesion area between 2.5-17.5 $mm^2$ | *12 and 24 months *Change in GA lesion size over baseline | *Reductions in GA lesion area in OAKS 22% (12 mo), 21.9% (24 mo) after monthly tx and 16% (12 mo), 18.1% (24 mo) after tx every other month *Reductions in GA lesion area in DERBY: 12% (12 mo), 18.1% (24 mo) after monthly tx and 11% (12 mo), 17.4% (24 mo) after tx every other month |
| Anti-C1s | Sutimlimab | CAD | CARDINAL (n=24) | Phase 3: Prospective, open-label, single-arm | *≥18 years of age *Diagnosed with CAD and recent transfusion history | *26-weeks with possible open-label extension | *Increase in haemoglobin levels (2.6 g/dL least-squares mean) |

| Mode of action | Drug | Disease | Trial (# of partic.) | Trial type | Main inclusion criteria | Endpoints | Summary data |
|---|---|---|---|---|---|---|---|
| | | | | | (within 6 months before enrollment) | *Norm. of haemoglobin (to ≥ 12g/dl or ≥ 2 g increase/ baseline)<br>*Absence of RBC transfusion from weeks 5-26<br>*No prohibited CAD medications | *Reduced need for transfusions (71% = no transfusions from weeks 526)<br>*Normalised bilirubin levels<br>*Decreased fatigue |
| | | | CADENZA (n=42) | Phase 3: Randomised, placebo controlled | *≥18 years of age<br>*Diagnosed with CAD and no recent transfusion history (no transfusions within 6 months before enrollment nor >1 transfusion/year) | *26-weeks<br>*Haemoglobin increase ≥ 1.5g/dL<br>*Transfusion avoidance<br>*Avoidance of prohibited CAD medications | *72.2% (sutimlimab) vs. 15% (placebo) of the patients met the responder criteria.<br>*Significantly increased mean haemoglobin<br>*Decreased fatigue<br>*Normalised bilirubin |
| Anti-C5a | Vilobelimab | COVID-19*** (adults) Emergency Use Authorisation | PANAMO (n=368) | Adaptive Phase 2/3 trial Phase 3 = randomized, double-blind, placebo controlled | *≥18 years of age<br>*Receiving invasive mechanical ventilation (within 48 hours pre-infusion)<br>*$PaO_2/FiO_2$ ratio = 60-200mm Hg<br>*SARS-CoV-2 diagnosis within last 14 days | *All-cause mortality at 28 days<br>*All-cause mortality at 60 days<br>*Freedom from acute kidney failure<br>*Freedom from any renal replacement therapy at 28 days | *All-cause mortality at 28 days was significantly reduced in the vilobelimab (32%) vs. placebo (42%) group<br>*All-cause mortality at 60 days was significantly reduced in the vilobelimab (35%) vs. placebo (46%) group<br>*No statistically significant difference in the proportion of patients with kidney failure, but vilobelimab protected against renal replacement therapy |

**Table 5:**
**Up-and-coming anti-complement therapies.**

Several current complement drugs (that are not authorized for any indications yet) with Orphan Status or Designation or with Breakthrough Therapy Designation. aHUS, atypical haemolytic uremic syndrome; AMD, age-related macular degeneration; C3G, C3 glomerulopathy; COVID-19, coronavirus disease 2019; IgAN, IgA nephropathy; MG, myasthenia gravis; PNH, paroxysmal nocturnal haemoglobinuria; TA-TMA, stem cell transplant associated (TA) thrombotic microangiopathy (TMA).

| Complement target | Drug | Disease/patient group | FDA designation | EMA designation | Additional information |
|---|---|---|---|---|---|
| Factor B inhibitor | Iptacopan (oral); Small molecule inhibitor | *PNH<br>*C3G<br>*IgAN | *Breakthrough therapy (PNH)<br>*Orphan Drug (PNH and C3G) | *Priority medicines designation (PRIME) for *C3G<br>*Orphan Designation for IgAN | *Recent Phase 3 trial data in PNH just released (APPOINT-PNH) |
| Factor D inhibitor | Danicopan (ALXN2040) (oral); Small molecule inhibitor | *PNH, add on to anti-C5 therapy in patients who experience clinically significant extravascular haemolysis | *Orphan Drug<br>*Breakthrough Therapy designation | *Priority medicines designation (PRIME)<br>*Orphan Designation | *ALPHA Phase 3 trial ongoing |
| Anti-MASP-2 | Narsoplimab (OMS721); Antibody | *TA - TMA in US<br>*aHUS in US<br>*Haematopoetic stem cell transplant in EU | *Orphan Drug - Prevention of complement-mediated TMAs and treatment of TMAs<br>*Breakthrough Therapy – high risk TA - TMA<br>*FDA fast track for aHUS | *Orphan product | *Ongoing Phase 3 trial in IgAN |
| Anti-MASP-3 | OMS906; Antibody | PNH | Orphan Drug | | *In trials for IgAN, aHUS, and COVID-19 |
| C3 inhibitor | AMY-101; Cyclic peptide | C3G | Orphan Drug | Orphan Designation | |
| C5 inhibitor | Zilucoplan (subcutaneous); Macrocyclic peptide | MG | Orphan Drug | Orphan Designation | |
| Inhibits C5 cleavage into C5a | Avacincaptad pegol (Zimura); PEGylated aptamer | GA | *Breakthrough Therapy Designation | | *Phase 3 trials near completion (GA)<br>*Phase 3 trials ongoing in AMD |
| Blocks C5 activation and inhibits leukotriene B4 activity | Nomacopan; Recombinant small protein | Bullous pemphigus | *Orphan Drug<br>*Fast Track Designation | Orphan Designation | |