Clinical outcomes of patients with C3G or IC-MPGN treated with the factor D inhibitor Danicopan: final results from two phase 2 studies

Nester, C.; Appel, G.B.; Bomback, A.S.; Bouman, K.P.; Cook, H.T.; Daina, E.; ... ; Remuzzi, G.

AJN
American Journal
of Nephrology

Patient-Oriented, Translational Research:
Research Article

Am J Nephrol 2022;53:687–700
DOI: 10.1159/000527167

Received: June 16, 2022
Accepted: September 1, 2022
Published online: November 24, 2022

Clinical Outcomes of Patients with C3G or IC-MPGN Treated with the Factor D Inhibitor Danicopan: Final Results from Two Phase 2 Studies

Carla Nester[a] Gerald B. Appel[b] Andrew S. Bomback[b] Koenraad Peter Bouman[c] H. Terence Cook[d] Erica Daina[e] Bradley P. Dixon[f] Kara Rice[g] Nader Najafian[g] James Hui[g] Steven D. Podos[h] Craig B. Langman[i] Liz Lightstone[d] Samir V. Parikh[j] Matthew C. Pickering[d] C. John Sperati[k] Howard Trachtman[l] James Tumlin[m] Aiko PJ de Vries[n] Jack F.M. Wetzels[o] Giuseppe Remuzzi[e]

[a]Divisions of Nephrology, Stead Family Children's Hospital, University of Iowa, Iowa City, IA, USA; [b]Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, New York, NY, USA; [c]ZNA Nierkliniek, Antwerp, Belgium; [d]Department of Immunology and Inflammation, Centre for Inflammatory Disease, Faculty of Medicine, Imperial College London, London, UK; [e]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy; [f]Department of Pediatrics, Renal Section, University of Colorado School of Medicine, Aurora, CO, USA; [g]Alexion, AstraZeneca Rare Diseases, Boston, MA, USA; [h]Discovery research in small molecule research, Alexion, AstraZeneca Rare Diseases, New Haven, CT, USA; [i]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [j]Division of Nephrology, The Ohio State University Medical Center, Columbus, OH, USA; [k]Johns Hopkins University School of Medicine, Division of Nephrology, Baltimore, MD, USA; [l]Department of Pediatrics, NYU Grossman School of Medicine, New York, NY, USA; [m]Georgia Nephrology, Lawrenceville, GA, USA; [n]Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands; [o]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands

Keywords
C3 glomerulopathy · Factor D inhibitor · Complement alternative pathway · Danicopan · Clinical trial

Abstract
Introduction: C3 glomerulopathy (C3G) is an ultrarare, chronic and progressive nephropathy mediated by dysregulation of the alternative pathway of complement (AP), with poor prognosis and limited treatment options. Targeted inhibition of proximal AP through factor D (FD) blockade represents a rational treatment approach. We present two phase 2 proof-of-concept clinical studies of the orally active FD inhibitor danicopan in patients with C3G and immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) (NCT03369236 and NCT03459443). ***Methods:*** A double-blind, placebo-controlled study in patients with C3G and a single-arm, open-label study in patients with C3G or IC-MPGN treated with danicopan are reported. The studies evaluated pharmacokinetic/pharmacodynamic (PK/PD), efficacy, and safety outcomes. The co-primary endpoints were change from baseline in composite biopsy score and the proportion of patients with a 30% reduction in proteinuria relative to baseline at 6 or 12 months. ***Results:*** Optimal systemic concentrations of danicopan were not achieved

J. H. was an employee of Alexion, AstraZeneca Rare Disease, at the time of this study.
J. T. is now at Emory University School of Medicine, Atlanta, Georgia, and NephroNet Clinical Trials Consortium, Atlanta, Georgia.

Karger@karger.com
www.karger.com/ajn

Correspondence to:
Carla Nester, carla-nester@uiowa.edu

for complete and sustained inhibition of AP, although there was evidence that blockade of FD reduced AP activity shortly after drug administration. Consequently, limited clinical response was observed in key efficacy endpoints. While stable disease or improvement from baseline was seen in some patients, response was not consistent. The data confirmed the favorable safety profile of danicopan. ***Conclusion:*** While demonstrating a favorable safety profile, danicopan resulted in incomplete and inadequately sustained inhibition of AP, probably due to limitations in its PK/PD profile in C3G, leading to lack of efficacy. Complete and sustained AP inhibition is required for a clinical response in patients with C3G.

Introduction

C3 glomerulopathy (C3G) and immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) are ultrarare, chronic and progressive nephropathies. They are characterized by the deposition of varying amounts of immunoglobulin and/or complement component 3 (C3) in kidney glomeruli. IC-MPGN, also termed immune complex glomerulonephritis in the latest update of the KDIGO guidelines, is characterized by significant immunoglobulin deposition and is assumed to involve dysregulation of both the classical and alternative pathways of complement (AP) [1–4]. In contrast, C3G is a disease of AP overactivation, with either genetic or acquired drivers precipitating disease, and is further subdivided into C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) based on electron microscopy features [5, 6]. C3G onset often occurs in childhood or adolescence and while clinical presentation and progression are heterogenous, the overall prognosis of C3G is poor with ~50% of patients progressing to end-stage kidney disease by 10–15 years following diagnosis [7–14]. Both C3G and IC-MPGN share genetic, pathogenic, and clinical features [2, 3].

To date, no treatments are approved for C3G or IC-MPGN. Existing treatment strategies include supportive measures alone, with or without the addition of classic immunosuppression. These approaches have had limited efficacy in preventing or delaying progression of disease [15–20]. A rational treatment approach, based on the pathophysiology of these diseases, is the targeted inhibition of complement [19]. Terminal complement inhibition with the anti-C5 antibody eculizumab has demonstrated heterogeneous responses, presumably depending on the extent of terminal complement activation, which may vary substantially from patient to patient [21, 22]. Because C3G is driven by AP overactivation, which originates upstream of C5, inhibition of the proximal AP is anticipated to confer greater and more predictable efficacy in controlling pathologic C3 deposition in the kidney as compared to terminal complement blockade [23]. Several inhibitors of the proximal pathway are under investigation, with targets including MASP2, C3, and complement factors D and B [24]. Factor D (FD) is the rate-limiting step in the activation of the AP amplification loop. It mediates the cleavage of factor B to Ba and Bb, the latter being essential to the formation of C3 convertase. C3 convertase activity drives the amplification loop of the AP and is therefore critical to all subsequent functions of the AP [23, 25]. Inhibition of FD therefore has potential to prevent AP overactivation, reducing deposition of complement activation fragments in the kidney [23].

Early studies of danicopan (previously ACH-4471, ALXN2040), a first-generation, investigational, small molecule FD inhibitor, demonstrated a clinically relevant blockade of AP activity and highlighted the therapeutic potential of FD inhibition in AP-mediated diseases [23]. We present here the pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety outcomes of danicopan in patients with C3G and IC-MPGN obtained in two phase 2 proof-of-concept clinical studies (NCT03369236 and NCT03459443) [26, 27]. An investigation of baseline (BL) systemic and urinary biomarkers from these studies is presented in a separate publication (Podos et al. [manuscript submitted]).

Materials and Methods

Study Designs

The safety and efficacy of the FD inhibitor danicopan in the treatment of patients with C3G and IC-MPGN were investigated in two proof-of-concept, phase 2 studies. The first study (NCT03369236; study 204) was a double-blind, placebo-controlled study in patients with C3G [27], consisting of a 6-month, placebo-controlled, blinded treatment period, followed by a 6-month open-label extension (OLE) treatment period, and a long-term follow-up period of up to 21 months. The second study (NCT03459443; study 205) was a single-arm, open-label study in patients with C3G or IC-MPGN [26], consisting of an initial 12-month treatment period followed by a long-term extension treatment period. Studies 204 and 205 finished on December 18, 2020, and March 29, 2021, respectively (both dates were the last patient's last visit). Full study designs are shown in Figure 1. These studies were conducted at different centers, with no crossover of sites between studies.

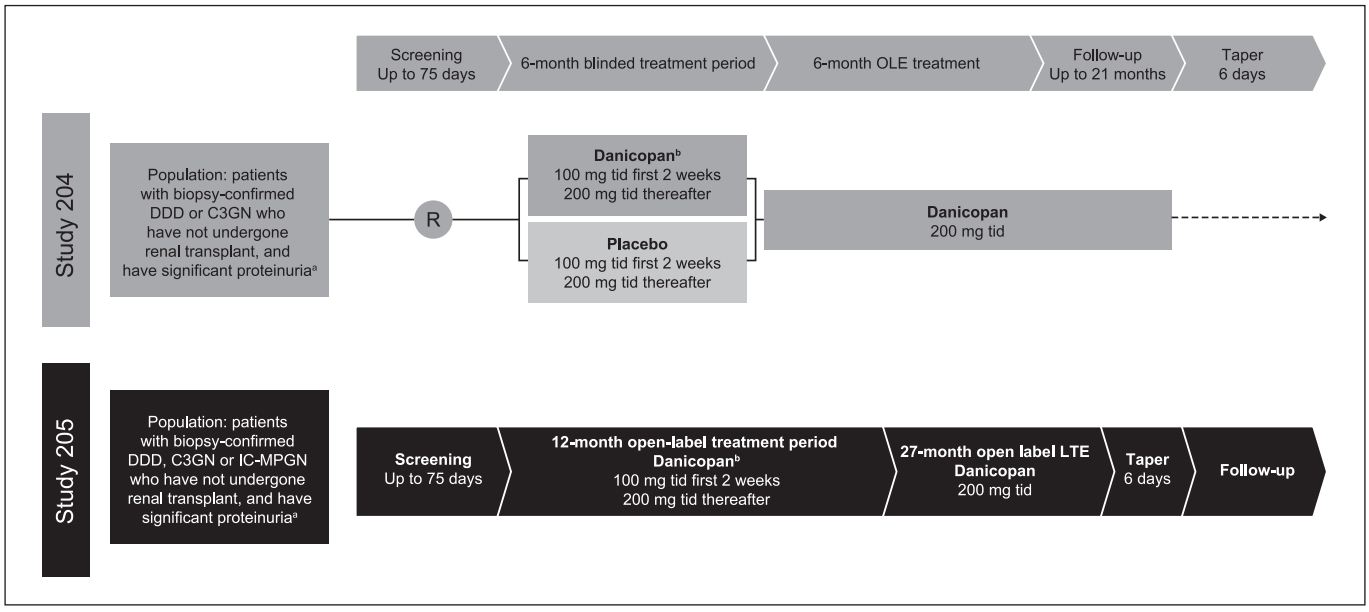


Fig. 1. Study designs of studies 204 and 205. [a]Proteinuria defined as ≥500 mg/day of protein in a 24-h urine or equivalent on spot urine. [b]The initial dosing regimen was chosen based on data from a small proof-of-mechanism study in patients with C3G and IC-MPGN, where similar exposures (100–200 mg t.i.d) had demonstrated AP inhibition (NCT03124368; study 201) [28]. Study 201 was a multicenter, open-label trial in which the effect of danicopan on C3 levels and AP activity in patients with C3G or IC-MPGN was assessed over 2 weeks of treatment followed by a 1-week taper. Full study design, objectives, inclusion/exclusion criteria, BL patient and disease characteristics, efficacy, and safety outcomes for study 201 are presented in online supplementary Figure S2 and in online supplementary Tables S5–S8, respectively. A total of 3 eligible patients from study 201 also participated in study 205 following a washout period (online suppl. Table S1). AP, alternative pathway of complement; BL, baseline; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; LTE, long-term extension; OLE, open-label extension; R, randomization; tid, three times daily.

Patients

Key eligibility criteria for the two studies are shown in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000527167). Briefly, adult and adolescent patients (≥17 years old with C3G in study 204 and ≥12 years with C3G or IC-MPGN in study 205) were eligible for inclusion. Both studies required proteinuria ≥500 mg/day and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2.

All patients were required to have a diagnosis of C3G or IC-MPGN established through kidney biopsy. Biopsy options included a screening period biopsy or a pre-study, historical biopsy obtained within 6 months before study enrollment. All biopsies obtained were subsequently re-evaluated at a central pathology laboratory (Centre for Inflammatory Disease, Department of Immunology and Inflammation, Faculty of Medicine, Imperial College London, London, UK).

Interventions

Vaccinations against *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* were required for all patients at least 2 weeks before danicopan dosing, and additional prophylactic measures, including the use of prophylactic antibiotics, could be administered based on investigator decision. Danicopan or placebo was administered orally, in tablet form, at a starting dosage of 100 mg three times daily (t.i.d). After 2 weeks of treatment, the dosage was increased to 200 mg t.i.d (or 150 mg t.i.d for patients weighing <60 kg in study 205). In study 204, all patients could continue into the 6-month OLE and receive danicopan following the blinded treatment period. During the OLE, all patients continued or were transitioned to danicopan at a starting dosage of 200 mg t.i.d. At the end of the OLE (week 52), patients could enter the long-term follow-up period while continuing on danicopan. For discontinuation, patients underwent dose tapering for 6 days with follow-up visits 2 and 4 weeks (±2 days) after the last dose (including the taper) in both studies.

Outcomes

Primary efficacy endpoints were assessed at 6 months in study 204 and at 12 months in study 205; safety outcomes were assessed throughout the duration of the studies. The co-primary endpoints were change from BL in composite biopsy score (see Histologic Assessments section for details on the scoring system and Podos et al. [manuscript submitted], for a full description) and the proportion of patients with a 30% reduction in proteinuria relative to BL for each study. For study 204, renal biopsy was mandated to occur between weeks 26 and 28 for primary endpoint assessment, while for study 205 renal biopsy was mandated at week 52; all renal biopsy procedures required further consent. An amendment was

also made to the study 205 protocol in response to the COVID-19 pandemic, which allowed for postponement of the week 52 biopsy until it was safe to attend the clinic. A 30% reduction in proteinuria relative to BL was selected for the co-primary endpoint in conjunction with regulatory authorities and was supported by recent understanding in the field, including the view that proteinuria changes of 30% appear clinically meaningful in other chronic kidney diseases [29–31].

Key secondary endpoints included changes in eGFR from BL and change in proteinuria from BL. Exploratory endpoints evaluated the effect of danicopan on complement biomarkers at 6 or 12 months relative to BL, including AP activity, FD, C3, Bb, and soluble C5b-9 (sC5b-9). Safety analyses of danicopan treatment in participants with C3G or IC-MPGN included the frequency of adverse events (AEs) and serious AEs (SAEs), frequency of AEs leading to discontinuation of the study medication, frequency of laboratory abnormalities by toxicity grade, and treatment-emergent abnormalities via electrocardiogram.

Histologic Assessments

Percutaneous kidney biopsies were performed according to local practices and centrally reviewed by light microscopy, immunofluorescence, and electron microscopy. The criteria for diagnosis of C3G required that C3 deposits were ≥2 orders of magnitude greater than any other immune reactants (IgG, IgA, IgM, and C1Q), while C3 deposits accompanied by significant Ig deposition confirmed a diagnosis of IC-MPGN [6]. Further classification of C3G into DDD or C3GN was based on the presence or absence of highly electron-dense intramembranous deposits upon electron microscopy, respectively [5, 6, 16].

Kidney tissue was evaluated using a novel composite biopsy score, which incorporated changes in the activity index (range 0–15), glomerular C3c staining (range 0–3), and glomerular macrophage infiltration (range 0–3) and a chronicity index (range 0–12), with higher scores indicating more active/advanced, severe disease [17, 32]. eGFR was calculated by the Modification of Diet in Renal Disease equation for patients ≥19 years and the bedside Schwartz equation for patients <19 years [33, 34].

Laboratory Assessments

Whole blood samples and 24-h urine samples (at least 7 days post-screening biopsy) were taken during screening (24-h urine) or just prior to dosing. Whole blood was processed to obtain serum or plasma and urine was cleared by centrifugation; samples were stored at −80°C until analyzed.

Collected urine samples were assayed for total protein concentration, albumin and creatinine concentrations, albumin:creatinine ratio, total protein:creatinine ratio, and total volume. Proteinuria was evaluated in both spot and 24-h urine collections.

Serum AP activity was evaluated by AP Wieslab functional assay using commercial ELISA kits (SVAR, Sweden). Serum C3 concentrations were determined by immunoturbidimetric assay (Tina-quant) on a Cobas analyzer (Roche Diagnostics, Switzerland). Commercial ELISA kits were used to determine concentrations of the complement components serum FD (Quantikine, R&D Systems, USA), plasma Bb, and sC5b-9 (MicroVue, Quidel, USA).

Analyses were performed by central clinical laboratories for the AP Wieslab, serum FD, plasma Bb, and sC5b-9 and by local clinical laboratories for serum C3 and urinary protein and creatinine concentrations. Danicopan concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry following protein precipitation with acetonitrile and centrifugation [35].

Statistical Analyses

Data were analyzed descriptively, with no statistical comparisons performed. Descriptive statistics included number of patients, mean, standard deviation (SD), median, interquartile range. Categorical data were summarized as frequency counts and percentages.

Results

Patient Disposition and BL Characteristics

A total of 13 patients were enrolled in study 204, with six in the danicopan group and seven in the placebo group. Of these, 1 patient in the placebo arm discontinued during the 6-month blinded treatment period due to accidental unblinding, and 4 patients discontinued during the OLE period: three for lack of efficacy and one due to acute kidney injury (Fig. 2).

In study 205, all 22 patients received danicopan. Of these, 3 patients discontinued due to lack of efficacy and one due to an AE (elevated creatine kinase) during the treatment period of the study. The study was closed early in consideration of a suboptimal clinical response. In 5 patients with documented favorable trend, treatment with danicopan was continued on an individual basis (named-patient basis), under the direct responsibility of the investigating physicians (Fig. 2).

BL demographics and characteristics in both studies are presented in Table 1. A total of 35 patients (13 in study 204; 22 in study 205) were enrolled. Thirty patients had their diagnoses confirmed by the central pathology laboratory, while 5 patients in study 205 who had been diagnosed and enrolled based on local biopsies performed previously did not consent to re-biopsy. Thirty-four of 35 (97%) patients had C3G and one of 35 (3%) had IC-MPGN. Overall, most patients were male, with a mean age of approximately 25 years. The patients had a long duration of disease, with mean values ranging from 4.4 to 7.4 years across studies. Most patients had a history of angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or immunosuppressant therapy; overall, 5 patients had received prior eculizumab. There were slight differences between patients in studies 204 and 205, especially with respect to markers of disease severity such as proteinuria, eGFR, or biopsy scores, which appeared to display a tendency toward more rapidly progressing disease in the patients in study 204. However, these differences were not formally analyzed.

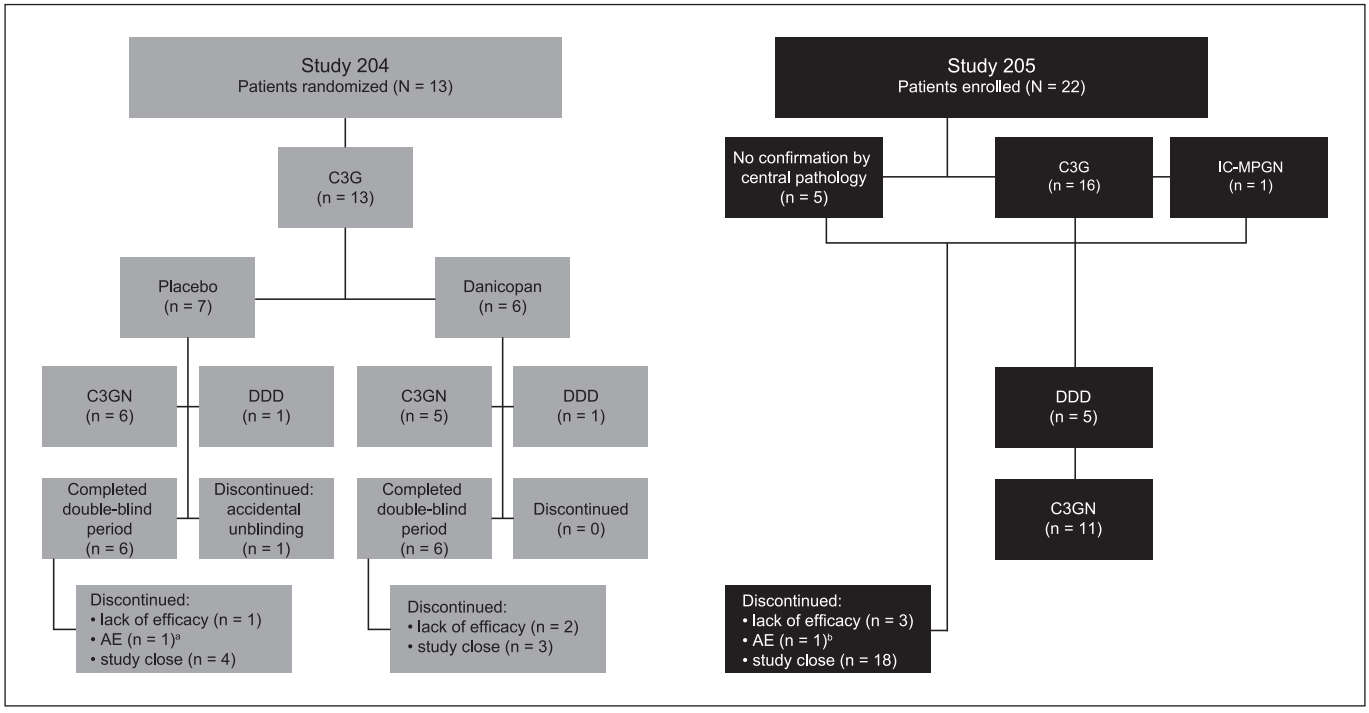


Fig. 2. Patient disposition in studies 204 and 205. [a]The AE leading to study discontinuation in 1 patient in study 204 was acute kidney injury. [b]The AE leading to study discontinuation in 1 patient in study 205 was elevated creatine kinase. Note that after discontinuation of studies 204 and 205, 5 patients continued on danicopan in a named-patient program. Note: In study 205, patients were diagnosed with C3G or IC-MPGN by local laboratory histology assessments, with no mandatory central confirmation of diagnosis using new biopsy samples required; 5 patients declined subsequent biopsies and therefore central pathology diagnosis confirmation was not completed in these participants. AE, adverse event; C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis.

PK and PD Results

Mean danicopan plasma C_{trough} values varied considerably over time (Fig. 3a) but did not reach concentrations sufficient to maintain ≥90% AP inhibition as had been projected from phase 1 studies (data not shown). Large inter-individual variations in plasma C_{trough} were also observed, potentially indicating that patients were not consistently exposed to danicopan. Inhibition was highly dependent on bioavailable drug concentration, as shown in the intensive day 10 sampling (every 2 h, at 100 mg t.i.d dosing) presented in online supplementary Figure S1, and plasma drug concentrations were largely suboptimal. While danicopan was able to reduce AP activity, the decrease was less robust at most trough timepoints, indicating that nearly complete AP inhibition was achieved but not sustained throughout the 8-h dose interval (Fig. 3b).

BL PD parameters showed significant inter-individual heterogeneity but indicated substantial AP dysregulation and C3 consumption across both studies (online suppl. Table S2). FD BL concentrations were on average above the upper limit of normal and fluctuated across patients (online suppl. Table S2), with higher concentrations seen in patients with lower eGFR (see Podos et al. [manuscript submitted]).

Consistent with a reduction in AP activation following danicopan administration, Bb – a cleavage product of complement factor B – concentration decreased from BL. Mean Bb concentrations following dosing remained below the mean BL concentration at all visits, falling within the normal range at most visits during the respective evaluation periods of the two studies (Fig. 3c). In study 204, danicopan but not placebo mediated modest but notable C3 elevations from BL through week 28 (day 196), while in study 205, mean C3 concentration following danicopan dosing marginally increased from BL to week 28 and week 52 (day 364; Fig. 3d). Mean soluble terminal complement complex (sC5b-9) concentration did not meaningfully decrease with danicopan treatment in either study (Fig. 3e). Neither C3 nor sC5b-9 concentrations achieved levels within their respective normal ranges.

Table 1. BL demographics and disease characteristics in studies 204 and 205

	Study 204 Placebo *N* = 7	Study 204 Danicopan *N* = 6	Study 205 Danicopan *N* = 22
Sex, *n* (%)			
N	7	6	22
Male	5 (71.4)	4 (66.7)	12 (54.5)
Female	2 (28.6)	2 (33.3)	10 (45.5)
Race, *n* (%)			
N	7	6	22
Asian	2 (28.6)	0	2 (9.1)
White	4 (57.1)	5 (83.3)	19 (86.4)
Other	1 (14.3)	1 (16.7)	1 (4.5)
Ethnicity, *n* (%)			
N	7	6	22
Hispanic or Latino	1 (14.3)	3 (50.0)	0
Age, years			
N	7	6	22
Mean (SD)	24.9 (4.9)	25.5 (10.5)	24.3 (9.9)
Disease duration, years			
N	6	6	21
Mean (SD)	7.4 (2.3)	5.4 (3.0)	4.4 (3.6)
BL composite biopsy score			
N	6	6	16
Mean (SD)	9.3 (3.5)	11.7 (4.2)	10.6 (3.6)
BL eGFR, mL/min/1.73 m^2			
N	7	6	22
Mean (SD)	68.4 (36.7)	79.9 (67.7)	90.7 (35.5)
BL 24-h urine protein, mg/day			
N	7	6	22
Mean (SD)	4,274.5 (2,992.8)	6,137.7 (2,904.4)	4,252.3 (2,685.0)
Prior use of ACE/ARB inhibitors[a], *n* (%)			
N	7	6	22
Yes	6 (85.7)	6 (100)	19 (86.4)
No	1 (14.3)	0	3 (13.6)
Prior use of immunosuppressants[a], *n* (%)			
N	7	6	22
Yes	5 (71.4)	5 (83.3)	14 (63.6)
No	2 (28.6)	1 (16.7)	8 (36.4)
Prior use of eculizumab, *n* (%)			
N	7	6	22
Yes	0	0	5 (22.7)
No	7 (100)	6 (100)	17 (77.3)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BL, baseline; eGFR, estimated glomerular filtration rate; SD, standard deviation. [a]Concomitant administration of corticosteroids, mycophenolate mofetil, or anti-proteinuric medications (e.g., ACE inhibitors or ARBs) is permitted if on a stable dose for at least 2 weeks prior to the first screening visit.

Safety

In study 204, many patients (*n* = 10 [76.9%]) had at least one treatment-emergent AE (TEAE) during the 6-month blinded treatment period, with most AEs not related to study treatment, of grade 1 severity, and with similar incidences between placebo and danicopan treatment groups. During the blinded treatment period, the most common AEs were nausea and vomiting, which were experienced by 2 (28.6%) patients in the placebo group and 1 (16.7%) patient in the danicopan group. The most common infections were upper respiratory tract infections experienced by 1 patient per treatment group in the 6-month blinded period and nasopharyngitis experienced by 2 patients in the placebo group during the OLE period. Other common AEs during the OLE period were diarrhea and acute kidney injury, each occurring in a total of 2 patients.

No SAEs were reported during the 6-month blinded treatment period in study 204. One SAE (acute kidney injury) leading to study withdrawal occurred in a patient in the placebo-to-danicopan crossover group during the OLE period. No deaths were recorded during the study period.

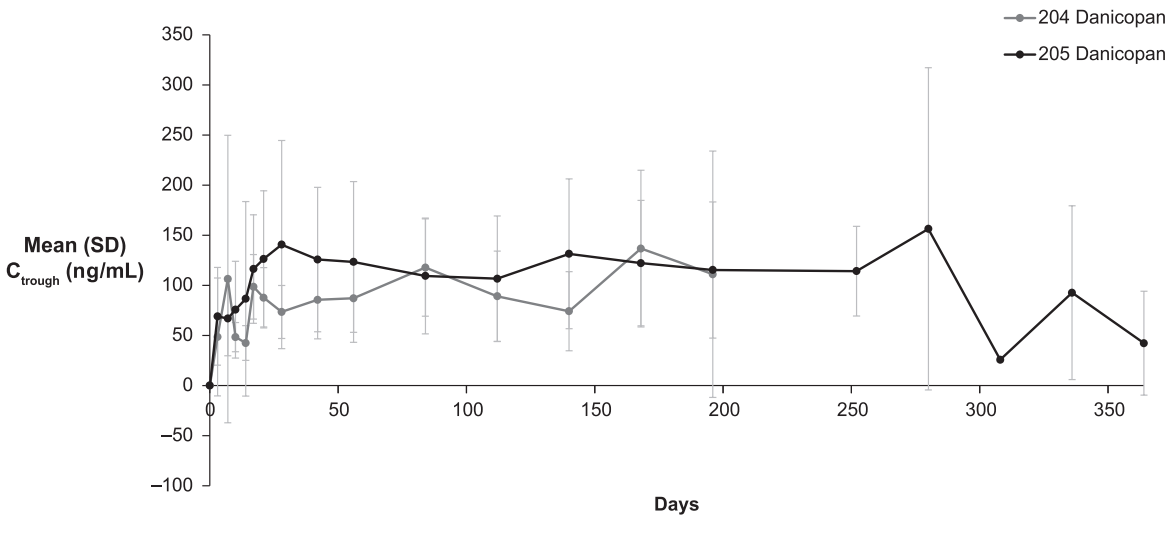
In study 205, while all patients had at least one TEAE, the majority of these were not related to study intervention and had a severity of grade 1 or 2. The most common TEAEs were pyrexia and peripheral edema, recorded in 11 (50%) and 8 (36.4%) patients, respectively. The most common infections reported were gastroenteritis and pharyngitis, both occurring in 6 (27.3%) patients.

Four SAEs were reported in 3 patients in study 205 (rhinovirus, pyrexia, renal impairment, and atrial fibrillation). All were determined to be unrelated to treatment drug. No deaths or TEAEs leading to drug withdrawal were observed. No meningococcal infections, *H. influenza* type B, or *S. pneumoniae* infections were reported during either study. The key safety results in studies 204 and 205 are presented in online supplementary Table S3 and S4, respectively.

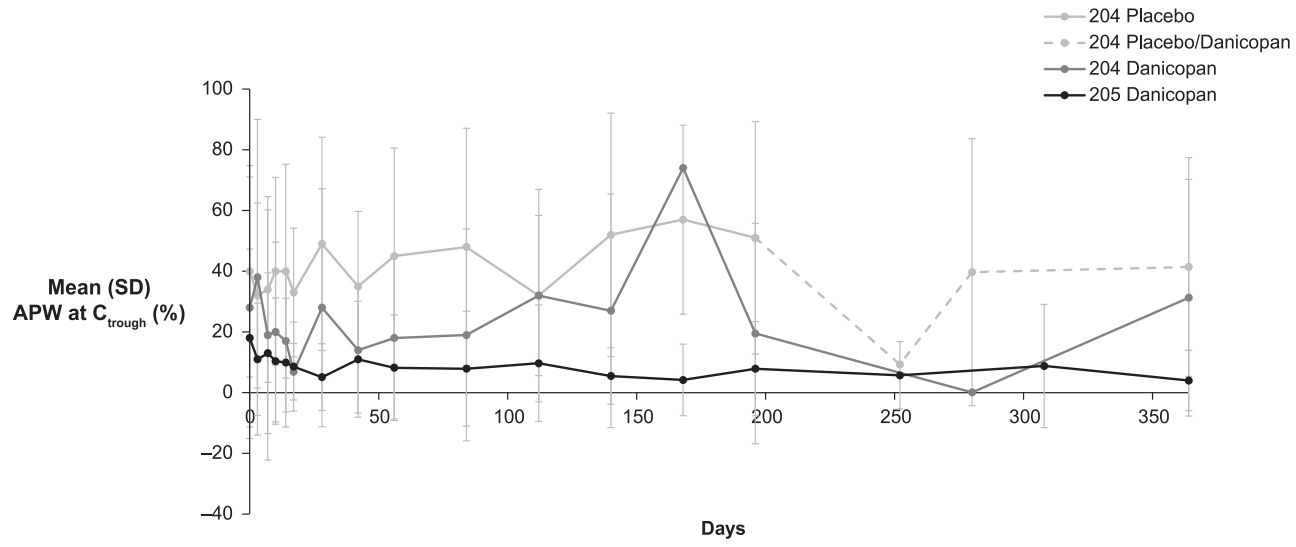
Efficacy Results

Co-Primary Endpoints

Composite biopsy score changes from BL to week 28 were evaluated for 6 patients receiving placebo and 5 patients receiving danicopan in study 204. Score changes from BL to week 52 were available for 8 patients in study 205. The changes from BL for each study are shown in Figure 4a, b. Higher scores indicate greater glomerular abnormalities. Biopsy scores marginally improved from BL in the danicopan-treated patients, but not in the pla-



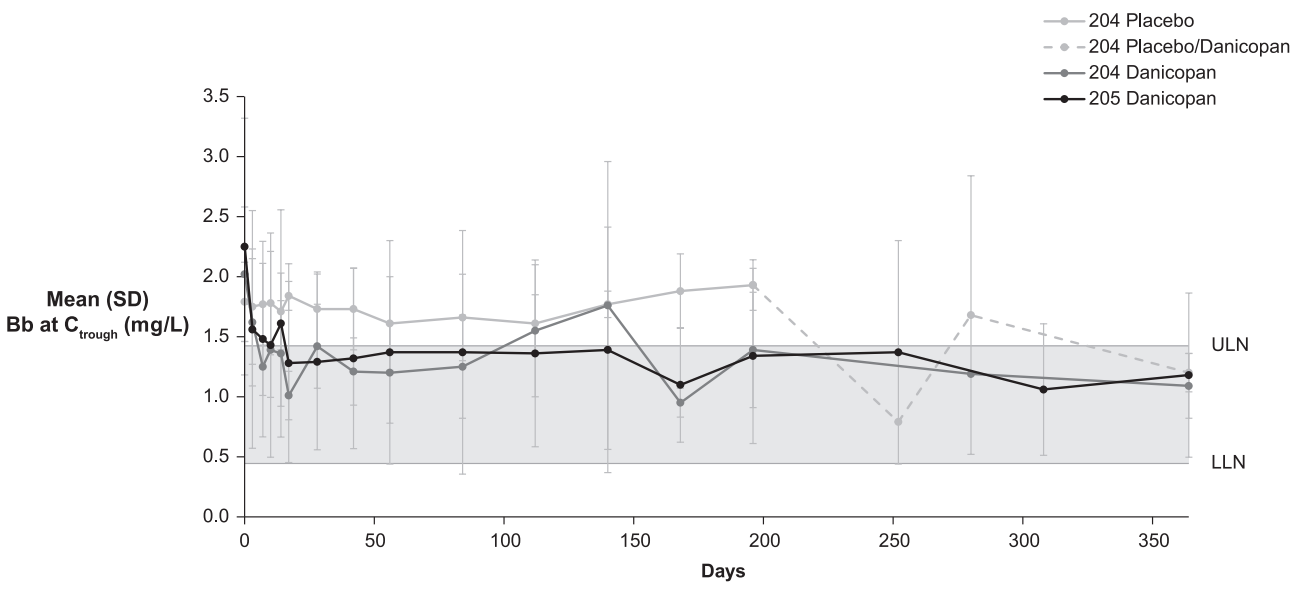
	Day	0	3	7	10	14	17	21	28	42	56	84	112	140	168	196	252	280	308	336	364
	204 Danicopan (n)	6	6	6	6	5	6	6	5	6	6	6	4	4	2	2					
a	205 Danicopan (n)	18	18	18	17	22	16	15	22	15	22	21	14	15	11	20	3	7	2	2	2



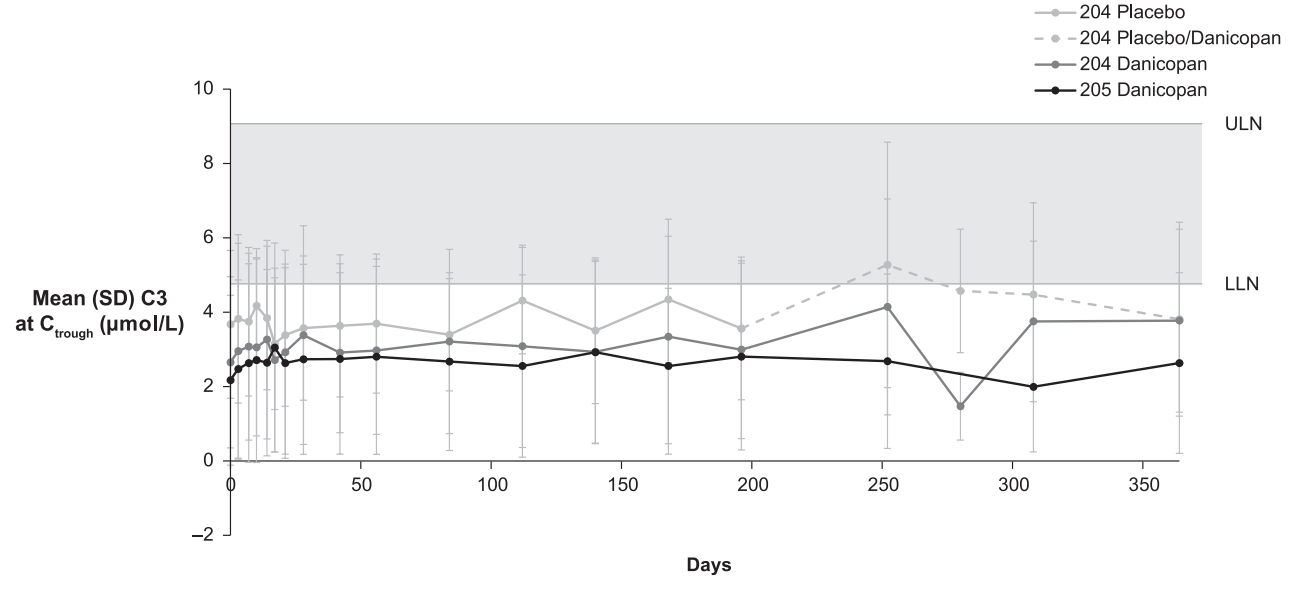
	Day	0	3	7	10	14	17	28	42	56	84	112	140	168	196	252	280	308	364
	204 Placebo (n)	7	6	6	6	7	5	6	5	6	6	2	5	2	5				
	204 Placebo/Danicopan (n)															1	2		3
	204 Danicopan (n)	6	5	6	6	5	6	5	6	6	6	4	5	2	6	0	1		5
b	205 Danicopan (n)	22	18	22	17	22	16	22	22	22	21	21	21	14	20	19		17	18

3

(Figure continued on next pages.)



	Day	0	3	7	10	14	17	28	42	56	84	112	140	168	196	252	280	308	364
	204 Placebo (n)	7	6	6	6	7	5	6	5	6	6	2	5	2	5				
	204 Placebo/Danicopan (n)															1	2		3
	204 Danicopan (n)	6	5	6	6	5	6	5	6	6	6	4	5	2	6	0	1		5
c	205 Danicopan (n)	22	18	22	17	22	16	22	22	22	21	21	21	13	20	19		17	17



	Day	0	3	7	10	14	17	21	28	42	56	84	112	140	168	196	252	280	308	364
	204 Placebo (n)	7	7	7	5	7	5	6	6	6	6	6	5	5	3	5				
	204 Placebo/Danicopan (n)																2	3	2	3
	204 Danicopan (n)	6	5	6	6	5	5	5	5	6	6	6	5	5	5	6	2	2	2	5
d	205 Danicopan (n)	22	22	22	17	22	16	21	22	22	22	19	20	18	14	20	19		13	18

3

(For legend see next page.)

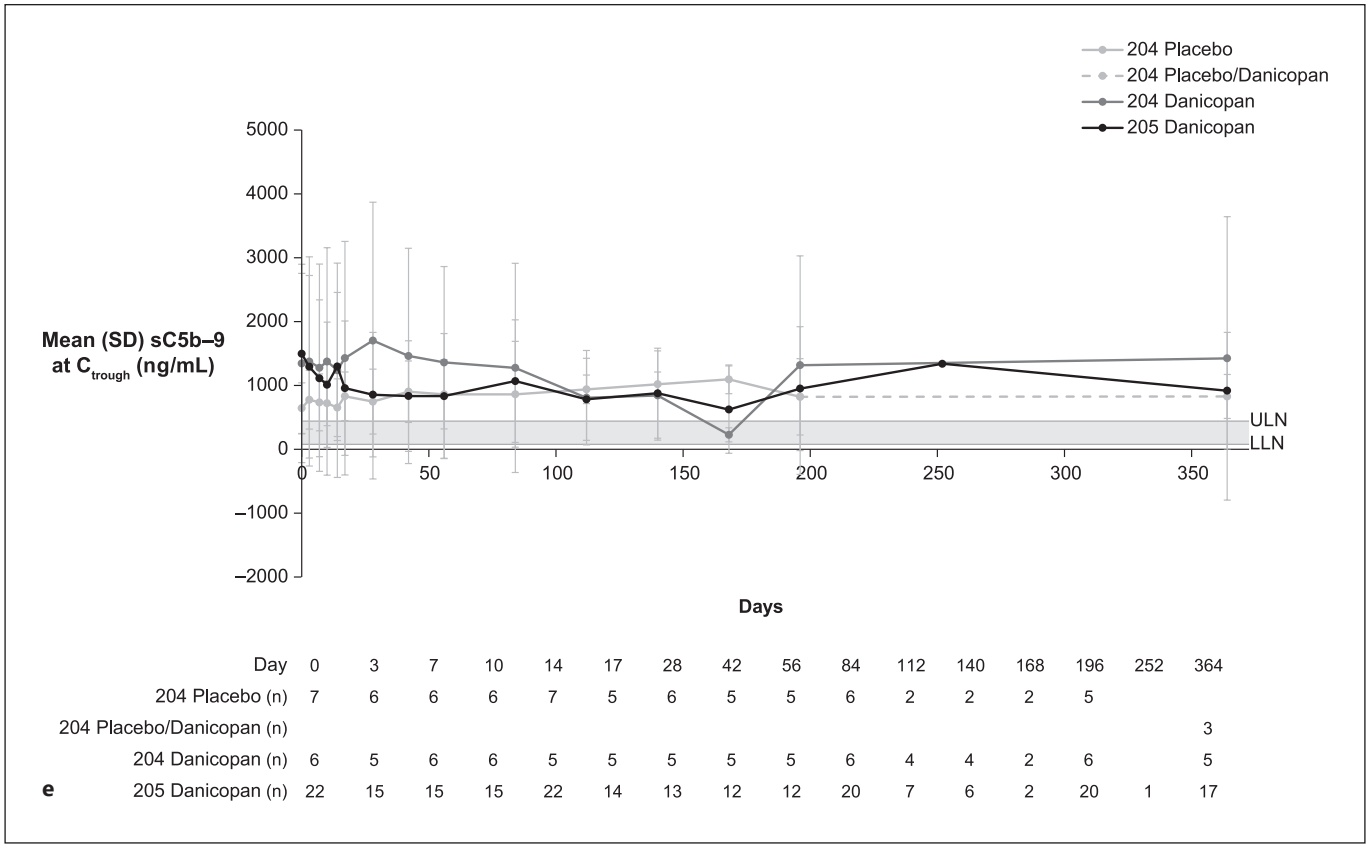


Fig. 3. PK and PD outcomes up to week 52 in studies 204 and 205: Mean (SD) C_{trough} (**a**); mean (SD) change (%) from BL in AP activity (APW) (**b**); mean (SD) Bb at C_{trough} (**c**); mean (SD) C3 at C_{trough} (**d**); mean (SD) sC5b-9 at C_{trough} (**e**). **a** At no timepoint were mean concentrations sufficient to maintain ≥90% AP inhibition as projected from phase 1 study and observed in the studies (data not shown). **b** APW activity values are provided on a scale such that 100% of activity is normal activity as per assay control. Full inhibition of AP corresponds to a value of 0. AP, alternative pathway; APW, alternative pathway Wieslab activity; Bb, activated factor B; C3, complement component 3; C_{trough}, trough plasma concentrations; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation; LLN, lower limit of normal (shown in **d**, highest of multiple LLN values); ULN, upper limit of normal (shown in **d**, lowest of multiple LLN values).

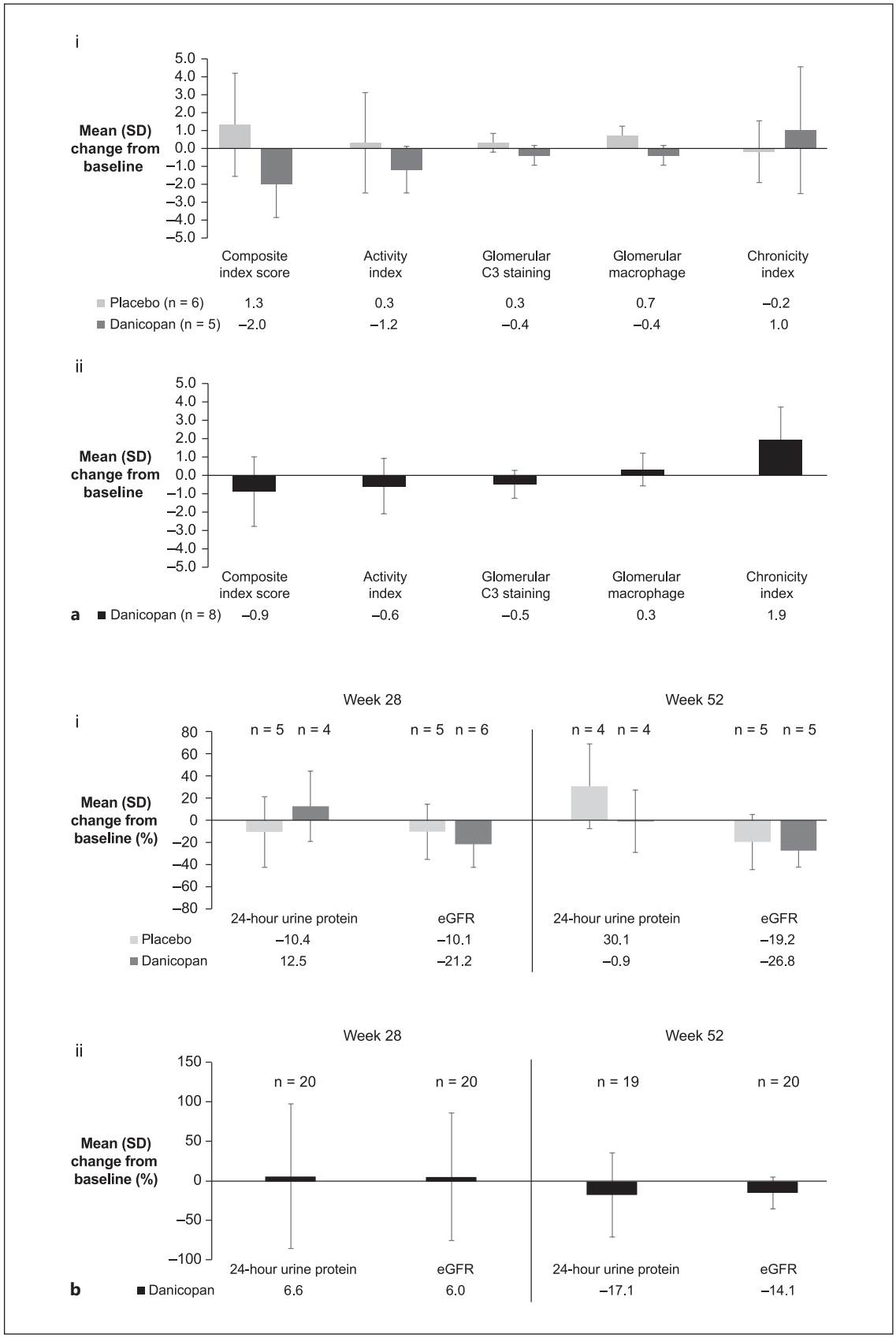
cebo group, over the respective evaluation periods of the two studies. However, mean chronicity indexes in the two studies either did not improve or deteriorated (index increased) from BL with danicopan treatment. Glomerular C3 staining, which is included in the composite biopsy score, did not change from BL to 6 months in either treatment group of study 204 or to 12 months in study 205.

All patients were evaluated for improvement in proteinuria, defined as ≥30% decrease in proteinuria (total protein/day) relative to BL from 24-h urine collection. In study 204, none of the patients treated with danicopan and 1 (20.0%) patient in the placebo group achieved the required proteinuria improvement. In study 205, 7 of 22 (31.8%) and 8 of 19 (42.1%) patients with available samples at weeks 28 and 52, respectively, experienced improvement in proteinuria.

Key Secondary Endpoints

At BL, in study 204, mean eGFR was slightly greater in the danicopan group than in the placebo group, and no significant increase in eGFR was observed over time in either treatment group. In study 205, eGFR fluctuated from BL over time.

In the 4 patients receiving danicopan in study 204 with samples available at week 28, proteinuria worsened by a mean of 12.5%. Conversely, in study 205, at the end of the 52-week evaluation period patients experienced a 17.1% decrease in proteinuria from a mean (SD) BL value of 4,252.28 (2,684.96) mg/day to 3,512.63 (3,335.77) mg/



4

(For legend see next page.)

day. The mean percent changes from BL in eGFR and proteinuria at weeks 28 and 52 in each study are shown in Figure 4.

Discussion

Herein, we report the first clinical assessment of FD inhibition in patients with C3G and IC-MPGN. Definitive clinical and histologic improvement was not demonstrated in these studies and, although danicopan had a good safety profile, the study was terminated early due to lack of efficacy in this patient population.

A critical evaluation for the observed lack of efficacy reveals that an optimal systemic bioavailability of the drug required to achieve complete and sustained blockade of the AP was not maintained with the dosing regimen investigated in these studies. Shortly after administration, danicopan was able to reduce AP activity even at the lower dose of 100 mg t.i.d; however, inhibition was not sustained, and AP activity levels recovered within a few hours. The observed PD response, characterized by limited inhibition of AP activity at PK troughs and incomplete restoration of C3, further supports the conclusion that systemic danicopan concentrations were insufficient for sustained inhibition of AP activity. The nature of C3G and IC-MPGN suggests that even minute breakthrough AP activation, which is rapidly amplified via the AP amplification loop, would maintain C3 convertase upregulation, C3b deposition, and subsequent progression of disease. These phenomena may account for the limited clinical response observed in the key efficacy endpoints. More robust PD responses were suggested in patients with more sustained systemic drug concentrations.

Across the 204 and 205 studies, efficacy outcomes, including results of the primary endpoints (changes from BL in biopsy score and patients with reduction in proteinuria at 6 and 12 months, respectively) were not clinically significant. In study 204, differences were not observed in efficacy outcomes between the danicopan and the placebo treatment groups. While study 205 showed some efficacy, responses were not consistent among patients. Stable disease or improvement from BL was seen in some patients, despite a prior history of immunosuppression and a BL of long disease duration.

Interestingly, patients with milder disease activity appeared to respond better to danicopan (data not shown), suggesting that FD inhibition may achieve some clinical benefits in this group even with a suboptimal PK/PD activity. However, whether milder disease is associated with lesser degrees of complement activation, and therefore less need for complement blockade, remains unknown. The small sample size and the inability to achieve adequate sustained complement suppression in these studies precludes generalizations, and these results would need to be confirmed in a larger dataset. With respect to inadequate dosing (despite phase 1 data), independent studies have indicated that a very high degree of FD inhibition is required to efficiently block the AP [36]. These findings are of relevance for C3G and IC-MPGN patients, who may require an even higher degree of FD inhibition to compensate for the hyperactivity of the AP due to C3 convertase dysregulation. In addition, circulating levels of FD are dependent on kidney function and an inverse correlation between plasma FD levels and eGFR has been documented [37, 38].

The patient population and severity of disease in these studies were highly heterogenous, reflective of the larger C3G population. Our results reinforce the need for a robust PK/PD profile to produce consistent clinical effects of treatment in all patients. Heterogeneity in patient characteristics may also help explain the observed differences in the results for danicopan-treated patients between studies 204 and 205.

The overall safety profile of danicopan was favorable with no significant serious infections, no reports of meningococcal infections, and no deaths or treatment discontinuations related to the study drug during the 6-month treatment period. This was also true for the patients in the phase 1 study of danicopan (study 201, in online suppl. Table S8).

Several trial-related limitations were noted across studies 204 and 205, including small sample sizes, multiple protocol amendments, and deviations relating to treatment compliance and laboratory assessments. Further, only 1 patient had central pathology-confirmed diagnosis of IC-MPGN; therefore, conclusions particular to this condition cannot be drawn. Lastly, not all patients in these studies provided biopsy samples for assessment of the co-

Fig. 4. Mean (SD) change from BL in composite biopsy index score and individual biopsy components (**a**) at week 28 (study 204 primary endpoint; **ai**) and week 52 (study 205 primary endpoint; **aii**) and mean (SD) percentage change from BL in proteinuria and eGFR (**b**) at weeks 28 and 52 in study 204 (**bi**) and study 205 (**bii**). Composite index score ranges from 0 to 21; activity index ranges from 0 to 15; glomerular C3 staining ranges from 0 to 3; glomerular macrophage infiltration ranges from 0 to 3; chronicity index ranges from 0 to 12. BL, baseline; eGFR, estimated glomerular filtration rate; C3, complement component 3; SD, standard deviation; UPCR, urine protein:creatinine ratio.

primary endpoint; reasons for this included early trial termination due to a lack of observable efficacy, early trial discontinuation, lack of consent, contraindication to biopsy, age, and trial disruption related to the COVID-19 pandemic. Although not all patients were assessed, a lack of efficacy had already been established in these studies.

The results from these studies suggest that a complete and sustained inhibition of the AP is required to control disease activity in C3G. Early, consistent inhibition of the AP in patients within these trials suggests that the greatest limitation observed may be related to the required PK/PD profile and dosing schedule of FD inhibitors and not to their mechanism of action.

FD remains an attractive treatment target in C3G. FD inhibition targets the central mechanism driving C3G, that of dysregulated AP activity – particularly at the level of amplification. This is in significant contrast to the current standard of care treatments [24, 39]. Although inhibition of the proximal/upstream AP is proposed as preferable to terminal complement blockade in a disease driven by AP dysregulation [23], the heterogeneity of C3G patients poses a significant therapeutic challenge. The possibility of variable efficacy in the setting of advanced kidney disease adds an additional challenge not considered previously. Individualized dosing and treatment duration may be required, all highlighting the importance of future studies to identify clinical, histologic, biochemical, and genetic factors predictive of those patients with C3G most likely to benefit from treatment with FD inhibitors. There are several ongoing studies designed to validate both clinical and complement biomarkers as measures of C3G disease activity and severity. The present data confirm the safety of FD inhibition; armed with the data from the biomarker studies, future studies of FD inhibition will be able to select and stratify patient populations who will most benefit from a specific, targeted therapy.

Acknowledgments

The authors would like to thank the patients who have enrolled in the two clinical trials and their families. In addition, we are grateful to Hetal Kocinsky and Mark Uknis of prior Achillion Pharmaceuticals, Inc., who participated in the early stages of the study, and Dr C. Duineveld, nephrology fellow at Radboud UMC, Nijmegen, for her assistance with clinical trial monitoring. Our gratitude also goes to Dr. Tom Barbour (who passed away) for his substantial contributions to these studies. The sponsor provided a formal review of the publication; however, the authors had final authority over the content. Medical writing support was provided by Alexandra Balaceanu of Bioscript, Macclesfield, UK, which was funded by Alexion, AstraZeneca Rare Disease, Inc.

Statement of Ethics

This clinical trial was evaluated and approved by the Institutional Review Board or Independent Ethics Committee at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. A full list of Institutional Review Boards/Independent Ethics Committees can be found in the online supplementary materials (S1). All participants provided written informed consent/assent prior to enrolling in the study.

Conflict of Interest Statement

Steven Podos, Kara Rice, and Nader Najafian are employees of Alexion, AstraZeneca Rare Diseases, and are shareholders in the company. James Hui was an employee and shareholder of Alexion, AstraZeneca Rare Disease, at the time this study was conducted. Carla Nester is the Associate Director for Molecular Otolaryngology and Renal Research Laboratory and has received a grant/contract from NIH. She has been a site investigator for ChemoCentryx, Achillion Pharmaceuticals, Alexion Pharmaceuticals, Novartis, Apellis Pharmaceuticals, Retrophin/Travere Therapeutics, and BioCryst. In addition, she has received advisory board honorarium from BioCryst and has participated in drug safety monitoring board/advisory board for Alexion Pharmaceuticals, Novartis, and BioCryst. Disclosures including royalties/licenses are provided in www.uptodate.com. Gerald Appel has received a research grant from Alexion Pharmaceuticals/Achillion Pharmaceuticals, which was paid to his institution (Columbia University, College of Physicians and Surgeons) and consultancy fees from Alexion Pharmaceuticals. Andrew Bomback has received consultancy fees from Achillion Pharmaceuticals/Alexion Pharmaceuticals, Catalyst, ChemoCentryx, Novartis, and Visterra. Terence Cook has received consultancy fees from Alexion Pharmaceuticals and Novartis and a grant from Alexion Pharmaceuticals, which was provided to his institution. Bradley P. Dixon has received consultancy fees from Alexion Pharmaceuticals and Apellis Pharmaceuticals. Craig B Langman has received study funding and support from Alexion Pharmaceuticals, which was provided to his institution. Liz Lightstone has been a consultant/advisor for Achillion, Alexion Pharmaceuticals, AstraZeneca, Aurinia, Bristol-Myers Squibb, GSK, Kezar Life Sciences, Novartis, and Pfizer. She has received honoraria/travel grants from Alexion Pharmaceuticals, Achillion Pharmaceuticals, GSK, and Novartis and has participated in drug safety monitoring/advisory boards for Novartis. She has received study funding/support from Alexion Pharmaceuticals, which were provided to her institution. Liz Lightstone has also participated as the deputy chair of the Western Europe Regional Board and on ISN ExComm, is a trustee for Kidney Research UK, and a council member for Women in Nephrology (all unpaid). Samir V. Parikh has received grants/funding from NIH-NIDDK, EMD Serono, and Aurinia Pharmaceuticals, which were paid to institution, and consultancy fees from Aurinia Pharmaceuticals, Alexion Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, and Kezar Life Sciences. Disclosures including royalties/licenses are provided in www.uptodate.com. Matthew C. Pickering has received consultancy fees from Alexion Pharmaceuticals, Achillion Pharmaceuticals, and Gyroscope Pharmaceuticals and study funding from

Achillion Pharmaceuticals. C. John Sperati has received honoraria from Alexion Pharmaceuticals for serving on the DMC of clinical trials and research grant/contract support from Achillion Pharmaceuticals, Alnylam Pharmaceuticals, and Novartis Pharmaceuticals (paid to institution). C. John Sperati has received consultancy fees from Alnylam Pharmaceuticals and Q32 Bio. Howard Trachtman has received consultancy fees from Travere Therapeutics, Akebia Therapeutics, Goldfinch Bio, Angion, and Natera and support for meeting attendance from Travere Therapeutics. He has participated in data safety monitoring or advisory boards for Otsuka and ChemoCentryx. Jack Wetzels has received consultancy fees from Novartis (paid to institution), Morphosys, and Travere. He has received study funding/support from Alexion Pharmaceuticals, which was provided to his institution, and grant support and honoraria from Alexion Pharmaceuticals. JW is a member of KDIGO guide working groups (unpaid). Giuseppe Remuzzi has received consultancy fees from Akebia Pharmaceuticals Inc., Alexion Pharmaceuticals Inc., AstraZeneca, BioCryst Pharmaceuticals, Janssen Research and Development LLC, Menarini Ricerche Spa, Otsuka, and Silence Therapeutics, which were all paid to his institution. He has also received honoraria and support for meeting attendance from Boehringer Ingelheim. Koenraad Peter Bouman, Erica Daina, Aiko PJ de Vries, and James Tumlin have no conflicts to declare. Achillion Pharmaceuticals Inc. was acquired by Alexion Pharmaceuticals. Alexion Pharmaceuticals is now Alexion, AstraZeneca Rare Diseases.

Funding Sources

This analysis and publication were funded by Alexion, AstraZeneca Rare Disease, Inc. (and formerly by Achillion Pharmaceuticals, Inc.), who provided overall study management, performed the statistical analyses, and verified data accuracy.

Author Contributions

Carla Nester, Gerald Appel, Andrew Bomback, Bradley Dixon, Jack Wetzels, Aiko P.J de Vries, and Guiseppe Remuzzi: design of study, patient recruitment, data acquisition, and interpretation of data. Koenraad Peter Bouman, Erica Daina, Craig Langman, Liz Lightstone, Samir Parikh, Matthew Pickering, C. John Sperati, Howard Trachtman, and James Tumlin: patient recruitment, data acquisition, and interpretation of data. H. Terence Cook: design of study, central pathology review, and scoring of kidney biopsies. Kara Rice and James Hui: development of statistical analysis plan and data analysis. Nader Najafian: development of statistical analysis plan, data analysis, and interpretation of data. Steven Podos: development of analysis plan, data analysis, and interpretation of data. All authors provided critical review of the content of the manuscript and approval for its submission.

Data Availability Statement

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law) and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development (link to Data Request Form [https://alexion.com/contact-alexion/medical-information]).

References

1 Frémeaux-Bacchi V, Weiss L, Brun P, Kazatchkine MD. Selective disappearance of C3NeF IgG autoantibody in the plasma of a patient with membranoproliferative glomerulonephritis following renal transplantation. Nephrol Dial Transplant. 1994;9(7):811–4.
2 Iatropoulos P, Noris M, Mele C, Piras R, Valoti E, Bresin E, et al. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. Mol Immunol. 2016 Mar;71:131–42.
3 Iatropoulos P, Daina E, Curreri M, Piras R, Valoti E, Mele C, et al. Cluster analysis identifies distinct pathogenetic patterns in C3 glomerulopathies/immune complex-mediated membranoproliferative GN. J Am Soc Nephrol. 2018 Jan;29(1):283–94.
4 Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney Int. 2021 Oct;100(4):753–79.
5 Sethi S, Nester CM, Smith RJH. Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. Kidney Int. 2012 Mar;81(5):434–41.
6 Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013 Dec;84(6):1079–89.
7 Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJH. Clinical features and outcomes of 98 children and adults with dense deposit disease. Pediatr Nephrol. 2012 May;27(5):773–81.
8 Servais A, Noel LH, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey MA, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int. 2012 Aug;82(4):454–64.
9 Barbour TD, Pickering MC, Terence Cook H. Dense deposit disease and C3 glomerulopathy. Semin Nephrol. 2013 Nov;33(6):493–507.
10 Kerns E, Rozansky D, Troxell ML. Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. Pediatr Nephrol. 2013 Nov;28(11):2227–31.
11 Mahajan V, Tewari R, Minz RW, Jindal G, D'Cruz S. Dense deposit disease: a rare cause of steroid resistant nephrotic syndrome. Indian J Pediatr. 2014 Jul;81(7):728–9.
12 Taranta-Janusz K, Wasilewska A, Szynaka B. Childhood-onset dense deposit disease: a rare cause of proteinuria. Ir J Med Sci. 2014 Sep;183(3):455–9.
13 Ravindran A, Fervenza FC, Smith RJH, Sethi S. C3 glomerulonephritis with a severe crescentic phenotype. Pediatr Nephrol. 2017 Sep;32(9):1625–33.
14 Marques da Costa P, Correia L, Correia LA. The complexity of renal involvment in IBD-C3 glomerulopathy in ulcerative colitis. Inflamm Bowel Dis. 2018 Apr 23;24(5):e4–e5.

15 Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, Traynor C, Flanagan M, Wong L, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol. 2014 Jan;9(1):46–53.
16 Goodship THJ, Cook HT, Fakhouri F, Fervenza FC, Fremeaux-Bacchi V, Kavanagh D, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: improving global outcomes" (KDIGO) controversies conference. Kidney Int. 2017 Mar;91(3):539–51.
17 Bomback AS, Santoriello D, Avasare RS, Regunathan-Shenk R, Canetta PA, Ahn W, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. Kidney Int. 2018 Apr;93(4):977–85.
18 Koopman JJE, Teng YKO, Boon CJF, van den Heuvel LP, Rabelink TJ, van Kooten C, et al. Diagnosis and treatment of C3 glomerulopathy in a center of expertise. Neth J Med. 2019 Jan;77(1):10–8.
19 Rovin BH, Caster DJ, Cattran DC, Gibson KL, Hogan JJ, Moeller MJ, et al. Management and treatment of glomerular diseases (part 2): conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int. 2019 Feb;95(2):281–95.
20 Schena FP, Esposito P, Rossini M. A narrative review on C3 glomerulopathy: a rare renal disease. Int J Mol Sci. 2020 Jan 14;21(2):E525.
21 Le Quintrec M, Lapeyraque AL, Lionet A, Sellier-Leclerc AL, Delmas Y, Baudouin V, et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis. 2018 Jul;72(1):84–92.
22 Ruggenenti P, Daina E, Gennarini A, Carrara C, Gamba S, Noris M, et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a single-arm clinical trial. Am J Kidney Dis. 2019 Aug;74(2):224–38.
23 Yuan X, Gavriilaki E, Thanassi JA, Yang G, Baines AC, Podos SD, et al. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Haematologica. 2017 Mar;102(3):466–75.
24 Zipfel PF, Wiech T, Rudnick R, Afonso S, Person F, Skerka C. Complement inhibitors in clinical trials for glomerular diseases. Front Immunol. 2019;10:2166.
25 Harboe M, Mollnes TE. The alternative complement pathway revisited. J Cell Mol Med. 2008 Aug;12(4):1074–84.
26 ClinicalTrials.gov. NCT03459443. A proof of concept study for a 12 month treatment in patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN). ClinicalTrials.gov; 2020. https://clinicaltrials.gov/ct2/show/NCT03459443.
27 ClinicalTrials.gov. A proof of concept study for 6 month treatment in patients with C3 Glomerulopathy (C3G). 2021.
28 ClinicalTrials.gov. NCT03124368. A proof-of-mechanism study to determine the effect of danicopan on C3 levels in participants with C3G or IC-MPGN. ClinicalTrials.gov; 2021. https://clinicaltrials.gov/ct2/show/NCT03124368.
29 Bakris GL. Slowing nephropathy progression: focus on proteinuria reduction. Clin J Am Soc Nephrol. 2008 Jan;3(Suppl 1):S3–10.
30 Thompson A, Carroll K, A Inker L, Floege J, Perkovic V, Boyer-Suavet S, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. Clin J Am Soc Nephrol. 2019 Mar 7;14(3):469–81.
31 Troost JP, Trachtman H, Spino C, Kaskel FJ, Friedman A, Moxey-Mims MM, et al. Proteinuria reduction and kidney survival in focal segmental glomerulosclerosis. Am J Kidney Dis. 2021 Feb;77(2):216–25.
32 Galbusera M, Noris M, Remuzzi G. Inherited thrombotic thrombocytopenic purpura. Haematologica. 2009 Feb;94(2):166–70.
33 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604–12.
34 Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629–37.
35 Kulasekararaj AG, Risitano AM, Maciejewski JP, Notaro R, Browett P, Lee JW, et al. Phase 2 study of danicopan in patients with paroxysmal nocturnal hemoglobinuria with an inadequate response to eculizumab. Blood. 2021 Nov 18;138(20):1928–38.
36 Wu X, Hutson I, Akk AM, Mascharak S, Pham CTN, Hourcade DE, et al. Contribution of adipose-derived factor D/adipsin to complement alternative pathway activation: lessons from lipodystrophy. J Immunol. 2018 Apr 15;200(8):2786–97.
37 Volanakis JE, Barnum SR, Giddens M, Galla JH. Renal filtration and catabolism of complement protein D. N Engl J Med. 1985 Feb 14;312(7):395–9.
38 Pascual M, Steiger G, Estreicher J, Macon K, Volanakis JE, Schifferli JA. Metabolism of complement factor D in renal failure. Kidney Int. 1988 Oct;34(4):529–36.
39 Smith RJH, Appel GB, Blom AM, Cook HT, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy: understanding a rare complement-driven renal disease. Nat Rev Nephrol. 2019 Mar;15(3):129–43.