# Supplementary Tables

**Supplementary Table S1. Inclusion criteria for studies 204 and 205**

|  |  |
| --- | --- |
| **Study 204 (C3G only)** | **Study 205 (C3G or IC-MPGN)** |
| * Must have biopsy-confirmed primary C3G * Must be 17 years of age or older and capable of swallowing tablets * Significant proteinuria ≥500 mg/day of protein in a 24-hour urine or equivalent on spot urine * eGFR ≥30 mL/min/1.73 m2 * Must have no more than 50% global fibrosis and no more than 50% of glomeruli with cellular crescents on kidney biopsy collected within approximately 6 months of the start of dosing and available for review * Stable dose of corticosteroids, anti-hypertensive medications, anti-proteinuric medications for at least 2 weeks | * Must have completed the ACH471-201 Proof of Mechanism study, followed by a washout period of at least 30 days   + OR * Must meet all the following criteria:   + Must have biopsy-confirmed primary C3G or IC-MPGN   + Must be 12 years of age or older and capable of swallowing tablets   + Significant proteinuria ≥500 mg/day of protein in a 24-hour urine   + eGFR ≥30 mL/min/1.73 m2   + If a pretreatment biopsy is obtained, or if a historical biopsy is available for review, it must have no more than 50% global fibrosis and no more than 50% of glomeruli with cellular crescents * Stable dose of corticosteroids, anti-hypertensive medications, anti-proteinuric medications for at least 2 weeks |

*C3G = C3 glomerulopathy; eGFR = estimated glomerular filtration rate; IC-MPGN = immune complex-mediated membranoproliferative glomerulonephritis.*

**Supplementary Table S2. Mean (SD) baseline PD parameters**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Mean (SD)** | | | | |
| **204**  **Placebo** N = 7 | **204**  **Danicopan** N = 6 | **205**  **Danicopan**  N=22 | **LLNa** | **ULNa** |
| **APW, normalized %b** | 40.3 (34.8) | 28.4 (43.1) | 18.0 (29.3) | 30 | 113 |
| **C3, µmol/L** | 3.671 (1.989) | 2.647 (2.300) | 2.170 (2.285) | 4.33–5.00 | 9.05–11.16 |
| **Bb, mg/L** | 1.789 (0.331) | 2.024 (0.559) | 2.252 (1.069) | 0.49 | 1.42 |
| **sC5b-9, ng/mL** | 641.857 (396.660) | 1342.637 (1552.238) | 1494.542 (1256.150) | 95 | 467 |
| **Factor D, µg/L** | 5184.7 (2006.47) | 4128.7 (1728.83) | 4206.1 (2282.61) | 1437 | 3966 |

*aThe LLN and ULN limits for serum AP activity were utilized as determined by the manufacturer (defined as ±2 SD from mean based on data from 120 donor samples; AP Wieslab, SVAR, Sweden); limits for serum C3 were determined independently by each local laboratory; limits for plasma Bb were determined by central clinical laboratories; limits for FD were calculated internally from results of phase I trial by Alexion of FD inhibitors (calculated internally as ±2 SD from mean based on data from three human volunteer studies conducted in 178 patients; data on file).*

*bAPW 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; C3 = complement component 3; Bb = activated Factor B; FD = Factor D; LLN = lower limit of normal; PD = pharmacodynamic; sC5b-9 = soluble complement 5b-9; SD = standard deviation; ULN = upper limit of normal.*

**Supplementary Table S3. Summary of AEs reported during the 6-month blinded treatment period and OLE in study 204**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **During the 6-month blinded treatment period**  **(full analysis set)** | | | | | **During the OLE period**  **(full analysis set)** | | | | |
|  | **Placebo** N = 7 | | **Danicopan** N = 6 | | | **Placebo/ Danicopan** N = 7 | | | **Danicopan/ Danicopan**  N=6 | |
|  | n (%) | Events | | n (%) | Events | | n (%) | Events | n (%) | Events |
| **Any AE** | 5 (71.4) | 31 | | 5 (83.3) | 34 | | 5 (71.4) | 12 | 3 (50.0) | 10 |
| **Any SAE** | 0 | 0 | | 0 | 0 | | 1 (14.3) | 1 | 0 | 0 |
| **Death** | 0 | 0 | | 0 | 0 | | 0 | 0 | 0 | 0 |
| **AE leading to withdrawal of study drug** | 0 | 0 | | 0 | 0 | | 0 | 0 | 0 | 0 |
| **SAE leading to withdrawal of study drug** | 0 | 0 | | 0 | 0 | | 0 | 0 | 0 | 0 |
| **AE by toxicity** | | | | | | | | | | |
| **Grade 1** | 5 (71.4) | 28 | | 5 (83.3) | 29 | | 5 (71.4) | 10 | 3 (50.0) | 7 |
| **Grade 2** | 3 (42.9) | 3 | | 3 (50.0) | 5 | | 1 (14.3) | 1 | 2 (33.3) | 3 |
| **Grade 3** | 0 | 0 | | 0 | 0 | | 1 (14.3) | 1 | 0 | 0 |
| **Grade 4** | 0 | 0 | | 0 | 0 | | 0 | 0 | 0 | 0 |
| **Grade 5** | 0 | 0 | | 0 | 0 | | 0 | 0 | 0 | 0 |

*AE = adverse event; OLE = open-label extension; SAE = serious AE.*

**Supplementary Table S4. Summary of AEs reported during study 205**

|  |  |  |
| --- | --- | --- |
|  | **During the study**  **(full analysis set)** | |
|  | **Danicopan** N = 22 | |
|  | n (%) | Events |
| **Any AE** | 22 (100) | 353 |
| **Any SAE** | 3 (13.6) | 4 |
| **Death** | 0 | 0 |
| **AE leading to withdrawal of study drug** | 0 | 0 |
| **SAE leading to withdrawal of study drug** | 0 | 0 |
| **AE by Toxicity** | | |
| **Grade 1** | 22 (100) | 288 |
| **Grade 2** | 16 (72.7) | 50 |
| **Grade 3** | 7 (31.8) | 15 |
| **Grade 4** | 0 | 0 |
| **Grade 5** | 0 | 0 |

*AE = adverse event; SAE = serious AE.*

**Supplementary Table S5. Study objectives and endpoints for study 201**

|  |  |
| --- | --- |
| **Objectives** | **Criteria for evaluation** |
| **Primary objective**  Determine whether danicopan can increase blood C3 levels in patients with low C3 levels due to either C3G or IC-MPGN | **Primary objective**  Change from baseline in serum C3 on Day 15 |
| **Secondary objectives**   * Evaluate the safety and tolerability of oral dosing with danicopan in patients with C3G or IC-MPGN * Evaluate the PK profile of danicopan following oral dosing in patients with C3G or IC-MPGN * Evaluate the effect of danicopan on biomarkers of AP activity in patients with C3G or IC-MPGN | **Secondary objective**   * Change from baseline after 14 days of treatment in AP activity   **Safety**   * Treatment-emergent AEs   **PD**   * Change from baseline to Day 14 in AP biomarker concentrations |

*AE = adverse event; AP = alternative complement pathway; C3 = complement component 3; C3G = C3 glomerulopathy; CP, classical complement pathway; IC-MPGN = immune complex-mediated membranoproliferative glomerulonephritis; PD = pharmacodynamic; SAE = serious AE.*

**Supplementary Table S6. Key inclusion and exclusion criteria for study 201**

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| * Patients aged 16–65 years with biopsy-confirmed clinical diagnosis of C3G or IC-MPGN * C3 <50% of the LLN * C4 >90% of the LLN * Up to date on routine vaccinations, or willing to be brought up to date, based on local guidelines * Compliance with study-specific vaccination requirements *for Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* strains ACWY | * History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant or kidney replacement therapy * History or presence of any clinically relevant comorbidities deemed inappropriate based on investigator assessment * Evidence of monoclonal gammopathy of unclear significance, infections, malignancy, autoimmune diseases, or other conditions to which C3G or IC-MPGN may be secondary * Presence or evidence of hepatobiliary cholestasis, Gilbert’s syndrome or kidney disease that would interfere with interpretation of the study * eGFR <45 mL/min/1.73 m2 at screening or over the preceding 4 weeks |

*C3/4 = complement component 3/4; C3G = C3 glomerulopathy; eGFR = estimated glomerular filtration rate; IC-MPGN = immune complex-mediated membranoproliferative glomerulonephritis; LLN = lower limit of normal*

**Supplementary Table S7. Baseline demographics and disease characteristics for patients in study 201**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Group 1**  **100 mg tid (n=2)** | **Group 2**  **200 mg tid (n=4)** | **Total**  **(n=6)** |
| **Mean (SD) age, years** | 25.5 (7.85) | 30.0 (12.68) | 28.5 (10.69) |
| **Mean (SD) body mass index, kg/m2** | 21.35 (2.051) | 23.15 (6.900) | 22.55 (5.502) |
| **Disease diagnosisa, n (%)** |  |  |  |
| C3GN | 1 (50.0) | 4 (100) | 5 (83.3) |
| IC-MPGN | 1 (50.0) | 0 | 1 (16.7) |
| **Mean (SD) duration of disease, days** | 274.5 (48.79) | 2270 (2274.08) | 1604.83 (2040.88) |
| **Mean (SD) serum C3, g/L** | 0.315 (0.064) | 0.555 (0.234) | 0.475 (0.221) |
| **Mean (SD) C4, mg/dL** | 31.5 (6.36) | 24.8 (11.03) | 27.0 (9.65) |
| **Mean (SD) serum creatinine, mg/dL** | 1.115 (0.2192) | 0.833 (0.3288) | 0.927 (0.3094) |
| **Mean (SD) eGFR, mL/min/1.73 m2** | 82.0 (12.73) | 122.5 (66.11) | 109.0 (55.60) |
| **Mean (SD) urine albumin, mg/L** | 2827.0 (980.05) | 2176.8 (1871.6) | 2393.6 (1551.3) |
| **Mean (SD) urine creatinine, mmol/L** | 7.150 (1.4849) | 8.815 (6.8227) | 8.260 (5.3954) |
| **Mean (SD) microalbumin:creatinine ratio, mg/mmol** | 418.60 (224.01) | 206.10 (102.11) | 276.93 (168.33) |
|  | | | |
| *aDisease diagnosis per biopsy. The reported medical history diagnosis was C3GN for both patients in Group 1; C3GN for three patients in Group 2, and IC-MPGN for one patient in Group 2.*  *C3/4 = complement component 3/4; eGFR = estimated glomerular filtration rate; SD = standard deviation; tid = three times daily.* | | | |

**Supplementary Table S8. Summary of AEs up to Day 49 in study 201**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Group 1**  **100 mg tid (N=2)** | **Group 2**  **200 mg tid (N=4)** | **Total**  **N=6** |
| **Patients with AEs, n (%)** | 2 (100) | 3 (75.0) | 5 (83.3) |
| **Number of AEs** | 6 | 8 | 14 |
| **Patients with SAEs, n (%)** | 0 | 1 (25.0) | 1 (16.7) |
| **Number of SAEs** | 0 | 1a | 1 |
| **Patients who discontinued due to AEs** | 0 | 0 | 0 |
| **Patients with related AEs, n (%)** | 1 (50.0) | 1 (25.0) | 2 (33.3) |
| **Number of related AEsb** | 1 | 2 | 3 |

*aOne SAE was reported: Grade 1 presyncope, which was considered not related to study drug and did not lead to treatment discontinuation.*

*bAll were considered possibly related; none were considered probably or definitely related.*

*AE = adverse event; SAEs = serious AE; tid = three times daily*