(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2019 (12.12.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/236345 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61P 7/00* (2006.01)

(21) International Application Number:
PCT/US2019/034297

(22) International Filing Date:
29 May 2019 (29.05.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/680,121 04 June 2018 (04.06.2018) US
62/790,577 10 January 2019 (10.01.2019) US

(71) Applicant: **ALEXION PHARMACEUTICALS, INC.** [US/US]; 121 Seaport Boulevard, Boston, MA 02210 (US).

(72) Inventors: **SHAFNER, Lori**; 45 Wickford Place, Madison, CT 06443 (US). **DENKER, Andrew**; 119 Bleddyn Road, Ardmore, PA 19003 (US). **SWENSON, Eugene, Scott**; 102 Yankee Peddler Path, Madison, CT 06443 (US). **PRADHAN, Rajendra**; 254 College Street, Apt. 4B, New Haven, CT 06510 (US). **ORTIZ, Stephan**; 31 Dover Court, Guilford, CT 06437 (US). **VALLEE, Marc**; 33 Hayden Avenue, Lexington, MA 02412 (US). **MIX, Christian**; 24 Atwood Street, Wellesley, MA 02481 (US). **GAO, Xiang**; 7 Franklins Way, Guilford, CT 06437 (US).

(74) Agent: **REMILLARD, Jane, E.** et al.; Nelson Mullins Riley & Scarborough LLP, One Post Office Square, 30th Floor, Boston, MA 02109-2127 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title:** DOSAGE AND ADMINISTRATION OF ANTI-C5 ANTIBODIES FOR TREATMENT OF ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS) IN PEDIATRIC PATIENTS

(57) **Abstract:** Provided are methods for clinical treatment of Atypical Hemolytic Uremic Syndrome (aHUS) using an anti-C5 antibody, or antigen binding fragment thereof, in pediatric patients.

WO 2019/236345 A1

DOSAGE AND ADMINISTRATION OF ANTI-C5 ANTIBODIES FOR TREATMENT OF ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS) IN PEDIATRIC PATIENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/680,121 (filed June 4, 2018) and U.S. Provisional Application No. 62/790,577 (filed January 10, 2019). The entire contents of the aforementioned applications are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing that has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 21, 2019, is named AXJ-237PC_SL.txt and is 50,618 bytes in size.

BACKGROUND

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at over 30 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory and lytic functions.

While a properly functioning complement system provides a robust defense against infecting microbes, inappropriate regulation or activation of the complement pathways has been implicated in the pathogenesis of a variety of disorders, including atypical hemolytic uremic syndrome (aHUS). aHUS is an ultra-rare disorder driven by chronic uncontrolled complement activation. The resulting inflammation and cellular damage lead to the devastating clinical manifestations of these diseases.

Hemolytic uremic syndrome (HUS) is characterized by thrombocytopenia, microangiopathic hemolytic anemia and acute renal failure. HUS is classified as one of two

types: diarrheal-associated (D^+ HUS; also referred to as shiga toxin producing *E. coli* (STEC)-HUS or typical HUS) and non-diarrheal or atypical HUS (aHUS). D^+ HUS is the most common form, accounting for greater than 90% of cases and is caused by a preceding illness with a shiga-like toxin-producing bacterium, *e.g.*, *E. coli* O157:H7.

Patients with aHUS, particularly children and adolescents, are at risk of substantial morbidity and mortality. Accordingly, it is an object of the compositions and methods described herein to provide improved treatments for human pediatric patients with aHUS.

SUMMARY

Provided herein are compositions and methods for treating atypical hemolytic uremic syndrome (aHUS) in a pediatric patient (*e.g.*, a patient < 18 years of age), comprising administering to the patient an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody or antigen binding fragment thereof is administered (or is for administration) according to a particular clinical dosage regimen (*e.g.*, at a particular dose amount and according to a specific dosing schedule). In one embodiment, the pediatric patient has not previously been treated with a complement inhibitor (*e.g.,* the patient is a complement inhibitor treatment-naïve patient).

An exemplary anti-C5 antibody is ravulizumab (also known as ALXN1210 and antibody BNJ441) comprising the heavy and light chains having the sequences shown in SEQ ID NOs:14 and 11, respectively, or antigen binding fragments and variants thereof. In other embodiments, the antibody comprises the heavy and light chain complementarity determining regions (CDRs) or variable regions (VRs) of ravulizumab. The terms ravulizumab, BNJ441, and ALXN1210 may be used interchangeably throughout this document, but all refer to the same antibody. In one embodiment, the antibody comprises the CDR1, CDR2 and CDR3 domains of the heavy chain variable (VH) region of ravulizumab having the sequence shown in SEQ ID NO:12, and the CDR1, CDR2 and CDR3 domains of the light chain variable (VL) region of ravulizumab having the sequence shown in SEQ ID NO:8. In another embodiment, the antibody comprises CDR1, CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, and CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs:4, 5 and 6, respectively.

In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO:12 and SEQ ID NO:8, respectively.

In another embodiment, the antibody comprises a heavy chain constant region as set forth in SEQ ID NO:13.

In another embodiment, the antibody comprises a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn), wherein the variant human Fc CH3 constant region comprises Met429Leu and Asn435Ser substitutions at residues corresponding to methionine428 and asparagine434, each according to the EU numbering convention.

In another embodiment, the antibody comprises CDR1, CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, and CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs:4, 5 and 6, respectively and a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn), wherein the variant human Fc CH3 constant region comprises Met429Leu and Asn435Ser substitutions at residues corresponding to methionine 428 and asparagine 434, each according to the EU numbering convention.

In another embodiment, the anti-C5 antibody comprises the heavy and light chain CDRs or variable regions of the BNJ421 antibody (described in PCT/US2015/019225 and US Patent No. 9,079,949). In another embodiment, the anti-C5 antibody comprises the heavy and light chain CDRs or variable regions of the 7086 antibody (see US Patent Nos. 8,241,628 and 8,883,158). In another embodiment, the anti-C5 antibody comprises the heavy and light chain CDRs or variable regions of the 8110 antibody (see US Patent Nos. 8,241,628 and 8,883,158). In another embodiment, the anti-C5 antibody comprises the heavy and light chain CDRs or variable regions of the 305LO5 antibody (see US2016/0176954A1). In another embodiment, the anti-C5 antibody comprises the heavy and light chain CDRs or variable regions of the SKY59 antibody (Fukuzawa, T., *et al.*, *Sci. Rep.*, 7:1080, 2017).

In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on C5 as any of the antibodies described herein. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with any of the antibodies described herein (*e.g.,* at least about 90%, 95% or 99% variable region identity with SEQ ID NO:12 and SEQ ID NO:8). In another embodiment, the antibody binds to human C5 at pH 7.4

and 25C with an affinity dissociation constant (K_D) that is ≤ 1 nM (*e.g.*, from 0.1 nM to 1 nM). In another embodiment, the antibody binds to human C5 at pH 6.0 and 25C with a K_D ≥ 10 nM. In yet another embodiment, the [(K_D of the antibody or antigen-binding fragment thereof for human C5 at pH 6.0 and at 25C)/(K_D of the antibody or antigen-binding fragment thereof for human C5 at pH 7.4 and at 25C)] of the antibody is greater than 25.

In another embodiment, the patient has previously been treated with a different anti-C5 antibody or antigen binding fragment thereof (*e.g.*, eculizumab) prior to treatment.

The pediatric patients treated according to the methods described herein are ≤ 18 years of age. In one embodiment, the pediatric patient is ≤ 12 years of age. In another embodiment, the pediatric patient is ≤ 6 years of age. In another embodiment, the pediatric patient is ≤ 2 years of age. In another embodiment, the pediatric patient is less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 years of age.

In one embodiment, the dose of the anti-C5 antibody or antigen binding fragment thereof, is based on the weight of the pediatric patient. In one embodiment, for example, about 300 mg, about 600 mg, about 900 mg, about 1200 mg, about 2100 mg, about 2700 mg, about 3000 mg, about 3300 mg and/or about 3600 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a pediatric patient based on the patient's weight. In one embodiment, 300 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 5 to < 10 kg. In one embodiment, 600 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 5 to < 10 kg. In another embodiment, 600 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 10 to < 20 kg. In another embodiment, 900 mg or 2100 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 20 to < 30 kg. In another embodiment, 1200 mg or 2700 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 30 to < 40 kg. In another embodiment, 2400 mg or 3000 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 40 to < 60 kg. In another embodiment, 2700 mg or 3300 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 60 to < 100 kg. In another embodiment, 3000 mg or 3600 mg of the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing

≥ 100 kg. In certain embodiments, dosage regimens are adjusted to provide the optimum desired response (*e.g.,* an effective response).

In another embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered for one or more administration cycles. In one embodiment, the administration cycle is 26 weeks. In one embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered at a loading dose once on Day 1 of the administration cycle and then at a maintenance dose on Day 15 of the administration cycle and every four weeks thereafter. In another embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered at a loading dose once on Day 1 of the administration cycle and then at a maintenance dose on Day 15 of the administration cycle and every eight weeks thereafter.

In another embodiment, a method of treating a human pediatric patient with Atypical Hemolytic Uremic Syndrome (aHUS), the method comprising administering to the patient an effective amount of an anti-C5 antibody or antigen binding fragment thereof, comprising CDR1, CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, and CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs: 4, 5 and 6, respectively, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered: (a) once on Day 1 at a loading dose of: i. 600 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 900 mg to a patient weighing ≥ 20 to < 30 kg, iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg, v. 2400 mg to a patient weighing ≥ 40 to < 60 kg, vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3000 mg to a patient weighing ≥ 100 kg; and (b) on Day 15 at a maintenance dose of: i. 300 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg, iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg, v. 3000 mg to a patient weighing ≥ 40 to < 60 kg, vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3600 mg to a patient weighing ≥ 100 kg; wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter.

In one embodiment, the disclosure is directed to a method of treating a human pediatric patient with Atypical Hemolytic Uremic Syndrome (aHUS), the method comprising administering to the patient an effective amount of an anti-C5 antibody or antigen binding

fragment thereof, comprising CDR1, CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs:4, 5 and 6, respectively, and a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn), wherein the variant human Fc CH3 constant region comprises Met429Leu and Asn435Ser substitutions at residues corresponding to methionine 428 and asparagine 434, each according to the EU numbering convention, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered: (a) once on Day 1 at a loading dose of: i. 600 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 900 mg to a patient weighing ≥ 20 to < 30 kg, iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg, v. 2400 mg to a patient weighing ≥ 40 to < 60 kg, vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3000 mg to a patient weighing ≥ 100 kg; and (b) on Day 15 at a maintenance dose of: i. 300 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg, iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg, v. 3000 mg to a patient weighing ≥ 40 to < 60 kg, vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3600 mg to a patient weighing ≥ 100 kg; wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter. In a particular embodiment, the anti-C5 antibody comprises a heavy chain variable region set forth in SEQ ID NO:12 and a light chain variable region set forth in SEQ ID NO:8. In a particular embodiment, the anti-C5 antibody further comprises a heavy chain constant region set forth in SEQ ID NO:13. In a particular embodiment, the antibody comprises a heavy chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:14 and a light chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:11. In a particular embodiment, the anti-C5 antibody binds to human C5 at pH 7.4 and 25C with an affinity dissociation constant (K_D) that is in the range 0.1 nM to 1 nM. In a particular embodiment, the anti-C5 antibody binds to human C5 at pH 6.0 and 25C with a $K_D \geq 10$ nM. In a particular embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 100 μg/mL or greater. In a particular embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 200 μg/mL or greater. In a particular embodiment, the treatment maintains a free C5 concentration of 0.309

to 0.5 μg/mL or lower. In a particular embodiment, the anti-C5 antibody is administered at a dose of 300 mg or 600 mg every four weeks after the treatment for up to two years. In a particular embodiment, the anti-C5 antibody is administered at a dose of 2100 mg, 2700 mg, 3000 mg, 3300 mg or 3600 mg every eight weeks after the treatment for up to two years. In a particular embodiment, the anti-C5 antibody is formulated for intravenous administration. In a particular embodiment, the patient has not previously been treated with a complement inhibitor. In a particular embodiment, the patient is < 18 years of age. In a particular embodiment, the treatment is an administration cycle comprising a total of 26 weeks of treatment. In a particular embodiment, the treatment results in terminal complement inhibition. In a particular embodiment, the treatment results in a complete thrombotic microangiopathy (TMA) response (platelet count normalization, LDH normalization, and 25% improvement in serum creatinine from Baseline). In a particular embodiment, the treatment results in a ≥ 25% reduction in serum creatinine levels compared to baseline. In a particular embodiment, the treatment results in an increase in platelet count compared to baseline. In a particular embodiment, the treatment produces a reduction or cessation of at least one therapeutic marker selected from the group consisting of: severe hypertension, proteinuria, uremia, lethargy, fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia and renal function impairment, compared to baseline. In a particular embodiment, the treatment produces a shift toward normal levels of a marker selected from the group consisting of: Factor Ba, soluble tumor necrosis factor receptor 1 (sTNFR1), soluble vascular adhesion molecule 1 (sVCAM1), thrombomodulin, D-dimer and cystatin C, compared to baseline. In a particular embodiment, the treatment produces a reduction in the need for blood transfusions compared to baseline. In a particular embodiment, the treatment produces a reduction in major adverse vascular events (MAVEs) compared to baseline. In a particular embodiment, the treatment produces a change from baseline in quality of life, assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 or the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale compared to baseline.

In another embodiment, lactate dehydrogenase (LDH) levels are used to evaluate responsiveness to a therapy (*e.g.,* a reduction of hemolysis compared to baseline as assessed by LDH levels is indicative of an improvement in at least one sign of aHUS). In one embodiment,

patients treated according to the disclosed methods experience reductions in LDH levels compared to baseline to near normal levels or to within 10%, or within 20% above what is considered the normal level (*e.g.*, within 105-333 IU/L (international units per liter)). In another embodiment, the patient's LDH levels are normalized throughout maintenance period of treatment. In another embodiment, the treated patient's LDH levels are normalized at least at least 95% of the time while on the maintenance period of treatment. In another embodiment, the treated patient's LDH levels are normalized at least at least 90%, 85% or 80% of the time while on the maintenance period of treatment. In one embodiment, the patient's LDH levels are ≥ 1.5 fold above the upper limit of normal (LDH $\geq 1.5 \times$ ULN) prior to initiating treatment.

In one embodiment, the disclosure is directed to a kit for treating Atypical Hemolytic Uremic Syndrome (aHUS) in a human pediatric patient, the kit comprising: (a) a dose of an anti-C5 antibody or antigen binding fragment thereof, comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:12, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:8; and (b) instructions for using the anti-C5 antibody or antigen binding fragment thereof in the method of Claim 1 or 2. In a particular embodiment, the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 5 to < 10 kg: (a) once on Day 1 at a loading dose of 600 mg; and (b) once on Day 15 at a maintenance dose of 300 mg and every four weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 10 to < 20 kg: (a) once on Day 1 at a loading dose of 600 mg; and (b) once on Day 15 at a maintenance dose of 600 mg and every four weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 20 to < 30 kg: (a) once on Day 1 at a loading dose of 900 mg; and (b) once on Day 15 at a maintenance dose of 2100 mg and every eight weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 30 to < 40 kg: (a) once on Day 1 at a loading dose of 1200 mg; and (b) once on Day 15 at a maintenance dose of 2700 mg and every eight weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 40 to < 60 kg: (a) once on Day 1 at a loading dose of 2400 mg; and (b) once on Day 15 at a maintenance dose of 3000 mg and every

eight weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 60 to < 100 kg: (a) once on Day 1 at a loading dose of 2700 mg; and (b) once on Day 15 at a maintenance dose of 3300 mg and every eight weeks thereafter. In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 100 kg: (a) once on Day 1 at a loading dose of 3000 mg; and (b) once on Day 15 at a maintenance dose of 3600 mg and every eight weeks thereafter.

In one embodiment, the disclosure is directed to an anti-C5 antibody or antigen binding fragment thereof comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:12, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:8, wherein the anti-C5 antibody or antigen binding fragment thereof is administered: (a) once on Day 1 at a loading dose of: i. 600 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 900 mg to a patient weighing ≥ 20 to < 30 kg, iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg, v. 2400 mg to a patient weighing ≥ 40 to < 60 kg, vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3000 mg to a patient weighing ≥ 100 kg; and (b) on Day 15 at a maintenance dose of: i. 300 mg to a patient weighing ≥ 5 to < 10 kg, ii. 600 mg to a patient weighing ≥ 10 to < 20 kg, iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg, iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg, v. 3000 mg to a patient weighing ≥ 40 to < 60 kg, vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or vii. 3600 mg to a patient weighing ≥ 100 kg; wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter. In a particular embodiment, the antibody is determined to be safe, tolerable, efficacious and sufficiently non-immunogenic after multiple IV doses in aHUS patients.

In another embodiment, the anti-C5 antibody is administered on a monthly basis (*e.g.*, every four weeks) or every other month basis (*e.g.*, every eight weeks) after completion of the treatment (*e.g.*, administration cycle). In another embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered on a monthly basis or every other month basis for a year after completion of the treatment (*e.g.*, administration cycle). In another embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered on a monthly basis or every

other month basis for two, three, four, or five years after completion of the treatment (*e.g.*, administration cycle). In a particular embodiment, the anti-C5 antibody or antigen binding fragment thereof is administered on a monthly basis or every other month basis for up to two years after completion of the treatment (*e.g.*, administration cycle).

In another aspect, the treatment regimens described are sufficient to maintain particular serum trough concentrations of the anti-C5 antibody or antigen binding fragment thereof. In one embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 200, 205, 210, 215, 220, 225, 230, 240, 245, 250, 255, 260, 265, 270, 280, 290, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395 or 400 μg/mL or greater. In one embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 100 μg/mL or greater, 150 μg/mL or greater, 200 μg/mL or greater, 250 μg/mL or greater, or 300 μg/mL or greater. In another embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of between 100 μg/mL and 200 μg/mL. In another embodiment, the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of about 175 μg/mL.

In another embodiment, to obtain an effective response, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain at least 50 μg, 55 μg, 60 μg, 65 μg, 70 μg, 75 μg, 80 μg, 85 μg, 90 μg, 95 μg, 100 μg, 105 μg, 110 μg, 115 μg, 120 μg, 125 μg, 130 μg, 135 μg, 140 μg, 145 μg, 150 μg, 155 μg, 160 μg, 165 μg, 170 μg, 175 μg, 180 μg, 185 μg, 190 μg, 195 μg, 200 μg, 205 μg, 210 μg, 215 μg, 220 μg, 225 μg, 230 μg, 235 μg, 240 μg, 245 μg, 250 μg, 255 μg or 260 μg of antibody per milliliter of the patient's blood. In another embodiment, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain between 50 μg and 250 μg of antibody per milliliter of the patient's blood. In another embodiment, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain between 100 μg and 200 μg of antibody per milliliter of the patient's blood. In another embodiment, the anti-C5 antibody is administered to the

patient in an amount and with a frequency to maintain about 175 μg of antibody per milliliter of the patient's blood.

In another embodiment, to obtain an effective response, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain a minimum free C5 concentration. In one embodiment, for example, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain a free C5 concentration of 0.5 μg/mL, 0.4 μg/mL, 0.3 μg/mL, 0.2 μg/mL or lower. In another embodiment, the anti-C5 antibody is administered to the patient in an amount and with a frequency to maintain a free C5 concentration of 0.309 to 0.5 μg/mL or lower.

In another embodiment, the treatment results in a complete thrombotic microangiopathy (TMA) response. In another embodiment, the treatment results in a complete thrombotic microangiopathy response (cTMA) that is sustained for more than 170 days (*e.g.*, more than 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days, 185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

In another embodiment, the treatment results in reduction in serum creatinine levels compared to baseline. In a particular embodiment, the treatment results in a $\geq$ 25% reduction in serum creatinine levels compared to baseline.

In another embodiment, the treatment eliminates the need for the patient to receive dialysis. In another embodiment, the patient is weaned off dialysis within 35 days or fewer (*e.g.*, 35 days, 34 days, 33 days, 32 days, 31 days, 30 days, 29 days, 28 days, 27 days, 26 days, 25 days, 24 days, 23 days, 22 days, 21 days, 20 days, 19 days, 18 days, 17 days, 16 days, 15 days, 14 days, 13 days, 12 days, 11 days or 10 days) of initiating treatment.

In another embodiment, the treatment produces a change from baseline in quality of life as assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 and the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale. In one embodiment, the treatment produces a change from baseline in quality of life as assessed via the FACIT-Fatigue Scale by one or more (*e.g.*, 1, 2 or 3) points. In another embodiment, the treatment produces a change from baseline in quality of

life as assessed via the FACIT-Fatigue Scale by 3 points 150 days or more (*e.g.*, 150 days, 151 days, 152 days, 153 days, 154 days, 155 days, 156 days, 157 days, 158 days, 159 days, 160 days, 161 days, 162 days, 163 days, 164 days, 165 days, 166 days, 167 days, 168 days, 169 days, 170 days, 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days, 185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

In another embodiment, the patient's chronic kidney disease (CKD) improves by one or more stages after initiating treatment, *e.g.*, by one, two, three, four or five stages). In another embodiment, the patient's CKD improves by one or more stages 150 days or more (*e.g.*, 150 days, 151 days, 152 days, 153 days, 154 days, 155 days, 156 days, 157 days, 158 days, 159 days, 160 days, 161 days, 162 days, 163 days, 164 days, 165 days, 166 days, 167 days, 168 days, 169 days, 170 days, 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days, 185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic depicting the design of the dose regimen study.

FIG. 2 is a schematic depicting patient disposition.

FIG. 3 is a graph depicting primary complete thrombotic microangiopathy (cTMA) response.

FIG. 4 is a Venn diagram showing primary cTMA response.

FIG. 5 is a graph depicting time to cTMA response.

FIG. 6 is a graph depicting cTMA response, hematologic normalization, and cTMA response status components status over time.

FIG. 7 is a graph depicting observed values and model based values of changes in platelets over time during the initial evaluation period (Full Analysis Set).

FIG. 8 is a graph depicting observed values and model based values of changes in LDH over time during the initial evaluation period (Full Analysis Set).

FIG. 9 is a graph depicting observed values and model based values of changes in hemoglobin over time during the initial evaluation period (Full Analysis Set).

FIG. 10 is a diagram depicting dialysis status or events over time by patient among patients who had dialysis within five days of treatment start or after the first dose (Full Analysis Set).

FIG. 11 is a graph depicting observed values and model based values of changes in over time.

FIG. 12 is a graph depicting observed and model based values of changes in pediatric FACIT fatigue over time (Full Analysis Set).

FIG. 13 is a graph depicting mean (SD) ravulizumab serum concentration by dosing interval (Q4W and Q8W), linear scale (PK/PD Analysis Set).

FIG. 14 is a graph depicting serum free C5 concentration time profiles by dosing interval (Q4W and Q8W) (PK/PD Analysis Set).

FIG. 15 is a graph depicting mean (95% CI) serum total concentration time profile by dosing interval (Q4W and Q8W) (PK/PD Analysis Set).

DETAILED DESCRIPTION

I. Definitions

As used herein, the term "subject" or "patient" is a human patient (*e.g.,* a pediatric patient having aHUS).

As used herein, "effective treatment" refers to treatment producing a beneficial effect, *e.g.,* amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, *i.e.*, an improvement over a measurement or observation made prior to initiation of therapy according to the method. Effective treatment may refer to alleviation of at least one symptom of aHUS (*e.g.*, severe hypertension, proteinuria, uremia, lethargy/fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia, and renal function impairment (*e.g.*, acute renal failure)).

The term "effective amount" refers to an amount of an agent that provides the desired biological, therapeutic and/or prophylactic result. That result can be reduction, amelioration,

palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In one example, an "effective amount" is the amount of anti-C5 antibody, or antigen binding fragment thereof, clinically proven to alleviate at least one symptom of aHUS (*e.g.*, severe hypertension, proteinuria, uremia, lethargy/fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia and renal function impairment (*e.g.*, acute renal failure)). An "effective amount" can be administered in one or more administrations.

As used herein, the terms "induction" and "induction phase" are used interchangeably and refer to the first phase of treatment in the clinical trial setting or as part of a patient treatment regimen.

As used herein, the terms "maintenance" and "maintenance phase" are used interchangeably and refer to the second phase of treatment in the clinical trial setting or as part of a patient treatment regimen. In certain embodiments, treatment is continued as long as clinical benefit is observed or until unmanageable toxicity or disease progression occurs.

As used herein, the term "serum trough level" refers to the lowest level that the agent (*e.g.,* the anti-C5 antibody or antigen binding fragment thereof) or medicine is present in the serum. In contrast, a "peak serum level" refers to the highest level of the agent in the serum. The "average serum level" refers to the mean level of the agent in the serum over time.

The term "antibody" describes a polypeptide comprising at least one antibody-derived antigen binding site (*e.g.,* VH/VL region or Fv, or CDR). Antibodies include known forms of antibodies, *e.g.*, the antibody can be a human antibody, a humanized antibody, a bispecific antibody or a chimeric antibody. The antibody also can be a Fab, Fab'2, ScFv, SMIP, Affibody®, nanobody or a single-domain antibody. The antibody also can be of any of the following isotypes: IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgAsec, IgD, IgE or combinations thereof. The antibody can be a naturally occurring antibody or an antibody that has been altered by a protein engineering technique (*e.g.,* by mutation, deletion, substitution, conjugation to a non-antibody moiety). An antibody can include, for example, one or more variant amino acids (compared to a naturally occurring antibody) that change a property (*e.g.,* a functional property) of the antibody. Numerous such alterations are known in the art that affect, *e.g.,* half-life, effector function, and/or immune responses to the antibody in a patient. The term

antibody also includes artificial or engineered polypeptide constructs that comprise at least one antibody-derived antigen binding site.

II. Anti-C5 Antibodies

Anti-C5 antibodies described herein bind to complement component C5 (*e.g.,* human C5) and inhibit the cleavage of C5 into fragments C5a and C5b. As described above, such antibodies also have, for example, improved pharmacokinetic properties relative to other anti-C5 antibodies (*e.g.,* eculizumab) used for therapeutic purposes.

Anti-C5 antibodies (or VH/VL domains derived therefrom) suitable for use in the methods described herein can be generated using methods known in the art. Alternatively, art recognized anti-C5 antibodies can be used. Antibodies that compete for binding to C5 with any of these art recognized antibodies or antibodies described herein can also be used.

An exemplary anti-C5 antibody is ravulizumab comprising heavy and light chains having the sequences shown in SEQ ID NOs:14 and 11, respectively, or antigen binding fragments and variants thereof. Ravulizumab (also known as BNJ441 and ALXN1210) is described in PCT/US2015/019225 and US Patent No: 9,079,949, the entire teachings of which are hereby incorporated by reference. The terms ravulizumab, BNJ441, and ALXN1210 may be used interchangeably throughout this document, but all refer to the same antibody. Ravulizumab selectively binds to human complement protein C5, inhibiting its cleavage to C5a and C5b during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming membrane attack complex (MAC) C5b-9 while preserving the proximal or early components of complement activation (*e.g.,* C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes.

In other embodiments, the antibody comprises the heavy and light chain CDRs or variable regions of ravulizumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2 and CDR3 domains of the VH region of ravulizumab having the sequence set forth in SEQ ID NO:12, and the CDR1, CDR2 and CDR3 domains of the VL region of ravulizumab having the sequence set forth in SEQ ID NO:8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:19, 18 and 3, respectively, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:4, 5 and 6, respectively. In another

embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO:12 and SEQ ID NO:8, respectively.

Another exemplary anti-C5 antibody is antibody BNJ421 comprising heavy and light chains having the sequences shown in SEQ ID NOs:20 and 11, respectively, or antigen binding fragments and variants thereof. BNJ421 (also known as ALXN1211) is described in PCT/US2015/019225 and US Patent No.9,079,949, the entire teachings of which are hereby incorporated by reference.

In other embodiments, the antibody comprises the heavy and light chain CDRs or variable regions of BNJ421. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2 and CDR3 domains of the VH region of BNJ421 having the sequence set forth in SEQ ID NO:12, and the CDR1, CDR2 and CDR3 domains of the VL region of BNJ421 having the sequence set forth in SEQ ID NO:8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:19, 18 and 3, respectively, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:4, 5 and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO:12 and SEQ ID NO:8, respectively.

The exact boundaries of CDRs are defined differently according to different methods. In some embodiments, the positions of the CDRs or framework regions within a light or heavy chain variable domain are as defined by Kabat *et al.* [(1991) "Sequences of Proteins of Immunological Interest." NIH Publication No. 91-3242, U.S. Department of Health and Human Services, Bethesda, MD]. In such cases, the CDRs can be referred to as "Kabat CDRs" (*e.g.*, "Kabat LCDR2" or "Kabat HCDR1"). In some embodiments, the positions of the CDRs of a light or heavy chain variable region are as defined by Chothia *et al.* (*Nature*, 342:877-83, 1989). Accordingly, these regions can be referred to as "Chothia CDRs" (*e.g.*, "Chothia LCDR2" or "Chothia HCDR3"). In some embodiments, the positions of the CDRs of the light and heavy chain variable regions can be defined by a Kabat-Chothia combined definition. In such embodiments, these regions can be referred to as "combined Kabat-Chothia CDRs." Thomas, C. *et al.* (*Mol. Immunol.*, 33:1389-401, 1996) exemplifies the identification of CDR boundaries according to Kabat and Chothia numbering schemes.

Another exemplary anti-C5 antibody is the 7086 antibody described in US Patent Nos. 8,241,628 and 8,883,158. In one embodiment, the antibody comprises the heavy and light chain CDRs or variable regions of the 7086 antibody (*see* US Patent Nos. 8,241,628 and 8,883,158). In another embodiment, the antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:21, 22 and 23, respectively, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:24, 25 and 26, respectively. In another embodiment, the antibody, or antigen binding fragment thereof, comprises the VH region of the 7086 antibody having the sequence set forth in SEQ ID NO:27, and the VL region of the 7086 antibody having the sequence set forth in SEQ ID NO:28.

Another exemplary anti-C5 antibody is the 8110 antibody also described in US Patent Nos. 8,241,628 and 8,883,158. In one embodiment, the antibody comprises the heavy and light chain CDRs or variable regions of the 8110 antibody. In another embodiment, the antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:29, 30 and 31, respectively, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:32, 33 and 34, respectively. In another embodiment, the antibody comprises the VH region of the 8110 antibody having the sequence set forth in SEQ ID NO:35, and the VL region of the 8110 antibody having the sequence set forth in SEQ ID NO:36.

Another exemplary anti-C5 antibody is the 305LO5 antibody described in US2016/0176954A1. In one embodiment, the antibody comprises the heavy and light chain CDRs or variable regions of the 305LO5 antibody. In another embodiment, the antibody, or antigen binding fragment thereof, comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:37, 38 and 39, respectively, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NOs:40, 41 and 42, respectively. In another embodiment, the antibody comprises the VH region of the 305LO5 antibody having the sequence set forth in SEQ ID NO:43, and the VL region of the 305LO5 antibody having the sequence set forth in SEQ ID NO:44.

Another exemplary anti-C5 antibody is the SKY59 antibody (Fukuzawa, T. *et al.*, *Sci. Rep.*, 7:1080, 2017). In one embodiment, the antibody comprises the heavy and light chain

CDRs or variable regions of the SKY59 antibody. In another embodiment, the antibody, or antigen binding fragment thereof, comprises a heavy chain comprising SEQ ID NO:45 and a light chain comprising SEQ ID NO:46.

In some embodiments, an anti-C5 antibody described herein comprises a heavy chain CDR1 comprising, or consisting of, the following amino acid sequence: GHIFSNYWIQ (SEQ ID NO:19). In some embodiments, an anti-C5 antibody described herein comprises a heavy chain CDR2 comprising, or consisting of, the following amino acid sequence: EILPGSGHTEYTENFKD (SEQ ID NO:18). In some embodiments, an anti-C5 antibody described herein comprises a heavy chain variable region comprising the following amino acid sequence:

QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA
PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY
MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS
(SEQ ID NO:12).

In some embodiments, an anti-C5 antibody described herein comprises a light chain variable region comprising the following amino acid sequence:

DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP
GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP
EDFATYYCQN VLNTPLTFGQ GTKVEIK (SEQ ID NO:8).

An anti-C5 antibody described herein can, in some embodiments, comprise a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn) with greater affinity than that of the native human Fc constant region from which the variant human Fc constant region was derived. The Fc constant region can, for example, comprise one or more (*e.g.,* two, three, four, five, six, seven, or eight or more) amino acid substitutions relative to the native human Fc constant region from which the variant human Fc constant region was derived. The substitutions can increase the binding affinity of an IgG antibody containing the variant Fc constant region to FcRn at pH 6.0, while maintaining the pH dependence of the interaction. Methods for testing whether one or more substitutions in the Fc constant region of an antibody increase the affinity of the Fc constant region for FcRn at pH 6.0 (while maintaining pH dependence of the interaction) are known in the art and exemplified in the working examples.

See, *e.g.*, PCT/US2015/019225 and US Patent No.9,079949 the disclosures of each of which are incorporated herein by reference in their entirety.

Substitutions that enhance the binding affinity of an antibody Fc constant region for FcRn are known in the art and include, *e.g.,* (1) the M252Y/S254T/T256E triple substitution (Dall'Acqua, W. et al., *J. Biol. Chem.*, 281:23514-24, 2006); (2) the M428L or T250Q/M428L substitutions (Hinton, P. *et al.*, *J. Biol. Chem.*, 279:6213-6, 2004; Hinton, P. *et al.*, *J. Immunol.*, 176:346-56, 2006); and (3) the N434A or T307/E380A/N434A substitutions (Petkova, S. *et al.*, *Int. Immunol.*, 18:1759-69, 2006). The additional substitution pairings: P257I/Q311I, P257I/N434H and D376V/N434H (Datta-Mannan, A. *et al.*, *J. Biol. Chem.*, 282:1709-17, 2007), the disclosures of each of which are incorporated herein by reference in their entirety.

In some embodiments, the variant constant region has a substitution at EU amino acid posaition 255 for valine. In some embodiments, the variant constant region has a substitution at EU amino acid position 309 for asparagine. In some embodiments, the variant constant region has a substitution at EU amino acid position 312 for isoleucine. In some embodiments, the variant constant region has a substitution at EU amino acid position 386.

In some embodiments, the variant Fc constant region comprises no more than 30 (*e.g.,* no more than 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 or 2) amino acid substitutions, insertions, or deletions relative to the native constant region from which it was derived. In some embodiments, the variant Fc constant region comprises one or more amino acid substitutions selected from the group consisting of: M252Y, S254T, T256E, N434S, M428L, V259I, T250I and V308F. In some embodiments, the variant human Fc constant region comprises a methionine at position 428 and an asparagine at position 434 of a native human IgG Fc constant region, each in EU numbering. In some embodiments, the variant Fc constant region comprises a 428L/434S double substitution as described in, *e.g.,* U.S. Patent No. 8,088,376.

In some embodiments the precise location of these mutations may be shifted from the native human Fc constant region position due to antibody engineering. For example, the 428L/434S double substitution when used in a IgG2/4 chimeric Fc may correspond to 429L and 435S as in the M429L and N435S variants found in ravulizumab and described in US Patent Number 9,079,949 the disclosure of which is incorporated herein by reference in its entirety.

In some embodiments, the variant constant region comprises a substitution at amino acid position 237, 238, 239, 248, 250, 252, 254, 255, 256, 257, 258, 265, 270, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 325, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434 or 436 (EU numbering) relative to the native human Fc constant region. In some embodiments, the substitution is selected from the group consisting of: methionine for glycine at position 237; alanine for proline at position 238; lysine for serine at position 239; isoleucine for lysine at position 248; alanine, phenylalanine, isoleucine, methionine, glutamine, serine, valine, tryptophan, or tyrosine for threonine at position 250; phenylalanine, tryptophan, or tyrosine for methionine at position 252; threonine for serine at position 254; glutamic acid for arginine at position 255; aspartic acid, glutamic acid, or glutamine for threonine at position 256; alanine, glycine, isoleucine, leucine, methionine, asparagine, serine, threonine, or valine for proline at position 257; histidine for glutamic acid at position 258; alanine for aspartic acid at position 265; phenylalanine for aspartic acid at position 270; alanine, or glutamic acid for asparagine at position 286; histidine for threonine at position 289; alanine for asparagine at position 297; glycine for serine at position 298; alanine for valine at position 303; alanine for valine at position 305; alanine, aspartic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, valine, tryptophan, or tyrosine for threonine at position 307; alanine, phenylalanine, isoleucine, leucine, methionine, proline, glutamine, or threonine for valine at position 308; alanine, aspartic acid, glutamic acid, proline, or arginine for leucine or valine at position 309; alanine, histidine, or isoleucine for glutamine at position 311; alanine or histidine for aspartic acid at position 312;lysine or arginine for leucine at position 314; alanine or histidine for asparagine at position 315; alanine for lysine at position 317; glycine for asparagine at position 325; valine for isoleucine at position 332; leucine for lysine at position 334; histidine for lysine at position 360; alanine for aspartic acid at position 376; alanine for glutamic acid at position 380; alanine for glutamic acid at position 382; alanine for asparagine or serine at position 384; aspartic acid or histidine for glycine at position 385; proline for glutamine at position 386; glutamic acid for proline at position 387; alanine or serine for asparagine at position 389; alanine for serine at position 424; alanine, aspartic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, asparagine, proline, glutamine, serine, threonine, valine, tryptophan, or tyrosine for methionine at

position 428; lysine for histidine at position 433; alanine, phenylalanine, histidine, serine, tryptophan, or tyrosine for asparagine at position 434; and histidine for tyrosine or phenylalanine at position 436, all in EU numbering.

Suitable anti-C5 antibodies for use in the methods described herein, in some embodiments, comprise a heavy chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:14 and/or a light chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:11. Alternatively, the anti-C5 antibodies for use in the methods described herein, in some embodiments, comprise a heavy chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:20 and/or a light chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:11.

In one embodiment, the antibody binds to C5 at pH 7.4 and 25C (and, otherwise, under physiologic conditions) with an affinity dissociation constant (K_D) that is at least 0.1 (*e.g.,* at least 0.15, 0.175, 0.2, 0.25, 0.275, 0.3, 0.325, 0.35, 0.375, 0.4, 0.425, 0.45, 0.475, 0.5, 0.525, 0.55, 0.575, 0.6, 0.625, 0.65, 0.675, 0.7, 0.725, 0.75, 0.775, 0.8, 0.825, 0.85, 0.875, 0.9, 0.925, 0.95, or 0.975) nM. In some embodiments, the K_D of the anti-C5 antibody, or antigen binding fragment thereof, is no greater than 1 (*e.g.,* no greater than 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, or 0.2) nM.

In other embodiments, the [(K_D of the antibody for C5 at pH 6.0 at 25C)/(K_D of the antibody for C5 at pH 7.4 at 25C)] is greater than 21 (*e.g.,* greater than 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500 or 8000).

Methods for determining whether an antibody binds to a protein antigen and/or the affinity for an antibody to a protein antigen are known in the art. The binding of an antibody to a protein antigen, for example, can be detected and/or quantified using a variety of techniques such as, but not limited to, Western blot, dot blot, surface plasmon resonance (SPR) detection (*e.g.,* BIAcore system; Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.), or enzyme-linked immunosorbent assay (ELISA; Benny K. C. Lo (2004) "Antibody Engineering: Methods and Protocols," Humana Press (ISBN: 1588290921); Johne, B. *et al., J. Immunol.*

Meth., 160:191-8, 1993; Jönsson, U. et al., *Ann. Biol. Clin.*, 51:19-26, 1993; Jönsson, U. *et al.*, *Biotechniques*, 11:620-7, 1991). In addition, methods for measuring the affinity (*e.g.*, dissociation and association constants) are set forth in the working examples.

As used herein, the term "k_a" refers to the rate constant for association of an antibody to an antigen. The term "k_d" refers to the rate constant for dissociation of an antibody from the antibody/antigen complex. And the term "K_D" refers to the equilibrium dissociation constant of an antibody-antigen interaction. The equilibrium dissociation constant is deduced from the ratio of the kinetic rate constants, $K_D = k_a/k_d$. Such determinations can be measured, for example, at 25C or 37C (see the working examples). The kinetics of antibody binding to human C5 can be determined, for example, at pH 8.0, 7.4, 7.0, 6.5 and 6.0 via SPR on a BIAcore 3000 instrument using an anti-Fc capture method to immobilize the antibody.

In one embodiment, the anti-C5 antibody, or antigen binding fragment thereof, blocks the cleavage of C5 into C5a and C5b. Through this blocking effect, for example, the pro-inflammatory effects of C5a and the generation of the C5b-9 membrane attack complex (MAC) at the surface of a cell are inhibited.

Methods for determining whether a particular antibody described herein inhibits C5 cleavage are known in the art. Inhibition of human complement component C5 can reduce the cell-lysing ability of complement in a subject's body fluids. Such reductions of the cell-lysing ability of complement present in the body fluid(s) can be measured by methods known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay (Kabat and Mayer (eds.), "Experimental Immunochemistry, 2nd Edition," 135-240, Springfield, IL, CC Thomas (1961), pages 135-139), or a conventional variation of that assay such as the chicken erythrocyte hemolysis method (Hillmen, P. *et al.*, *N. Engl. J. Med.*, 350:552-9, 2004). Methods for determining whether a candidate compound inhibits the cleavage of human C5 into forms C5a and C5b are known in the art (Evans, M. *et al.*, *Mol. Immunol.*, 32:1183-95, 1995). The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured, for example, by methods known in the art. For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays known in the art can also be used. Using assays of these or other suitable types, candidate agents capable of inhibiting human complement component C5 can be screened.

Immunological techniques such as, but not limited to, ELISA can be used to measure the protein concentration of C5 and/or its split products to determine the ability of an anti-C5 antibody, or antigen binding fragment thereof, to inhibit conversion of C5 into biologically active products. In some embodiments, C5a generation is measured. In some embodiments, C5b-9 neoepitope-specific antibodies are used to detect MAC formation.

Hemolytic assays can be used to determine the inhibitory activity of an anti-C5 antibody, or antigen binding fragment thereof, on complement activation. To determine the effect of an anti-C5 antibody, or antigen binding fragment thereof, on classical complement pathway-mediated hemolysis in a serum test solution *in vitro*, for example, sheep erythrocytes coated with hemolysin or chicken erythrocytes sensitized with anti-chicken erythrocyte antibody are used as target cells. The percentage of lysis is normalized by considering 100% lysis equal to the lysis occurring in the absence of the inhibitor. In some embodiments, the classical complement pathway is activated by a human IgM antibody, for example, as utilized in the Wieslab® Classical Pathway Complement Kit (Wieslab® COMPL CP310, Euro-Diagnostica, Sweden). Briefly, the test serum is incubated with an anti-C5 antibody, or antigen binding fragment thereof, in the presence of a human IgM antibody. The amount of C5b-9 that is generated is measured by contacting the mixture with an enzyme conjugated anti-C5b-9 antibody and a fluorogenic substrate and measuring the absorbance at the appropriate wavelength. As a control, the test serum is incubated in the absence of the anti-C5 antibody, or antigen binding fragment thereof. In some embodiments, the test serum is a C5-deficient serum reconstituted with a C5 polypeptide.

To determine the effect of an anti-C5 antibody or antigen binding fragment thereof on alternative pathway-mediated hemolysis, unsensitized rabbit or guinea pig erythrocytes can be used as the target cells. In some embodiments, the serum test solution is a C5-deficient serum reconstituted with a C5 polypeptide. The percentage of lysis is normalized by considering 100% lysis equal to the lysis occurring in the absence of the inhibitor. In some embodiments, the alternative complement pathway is activated by lipopolysaccharide molecules, for example, as utilized in the Wieslab® Alternative Pathway Complement Kit (Wieslab® COMPL AP330, Euro-Diagnostica, Sweden). Briefly, the test serum is incubated with an anti-C5 antibody, or antigen binding fragment thereof, in the presence of lipopolysaccharide. The amount of C5b-9

that is generated is measured by contacting the mixture with an enzyme conjugated anti-C5b-9 antibody and a fluorogenic substrate and measuring the fluorescence at the appropriate wavelength. As a control, the test serum is incubated in the absence of the anti-C5 antibody, or antigen binding fragment thereof.

In some embodiments, C5 activity or inhibition thereof is quantified using a CH50eq assay. The CH50eq assay is a method for measuring the total classical complement activity in serum. This test is a lytic assay, which uses antibody-sensitized erythrocytes as the activator of the classical complement pathway and various dilutions of the test serum to determine the amount required to give 50% lysis (CH50). The percent hemolysis can be determined, for example, using a spectrophotometer. The CH50eq assay provides an indirect measure of terminal complement complex (TCC) formation, since the TCC themselves are directly responsible for the hemolysis that is measured. The assay is known and commonly practiced by those of skill in the art. Briefly, to activate the classical complement pathway, undiluted serum samples (*e.g.,* reconstituted human serum samples) are added to microassay wells containing the antibody-sensitized erythrocytes to thereby generate TCC. Next, the activated sera are diluted in microassay wells, which are coated with a capture reagent (*e.g.,* an antibody that binds to one or more components of the TCC). The TCC present in the activated samples bind to the monoclonal antibodies coating the surface of the microassay wells. The wells are washed and to each well is added a detection reagent that is detectably labeled and recognizes the bound TCC. The detectable label can be, *e.g.,* a fluorescent label or an enzymatic label. The assay results are expressed in CH50 unit equivalents per milliliter (CH50 U Eq/mL).

Inhibition, *e.g.,* as it pertains to terminal complement activity, includes at least a 5 (*e.g.,* at least a 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60) % decrease in the activity of terminal complement in, *e.g.,* a hemolytic assay or CH50eq assay as compared to the effect of a control antibody (or antigen-binding fragment thereof) under similar conditions and at an equimolar concentration. Substantial inhibition, as used herein, refers to inhibition of a given activity (*e.g.,* terminal complement activity) of at least 40 (*e.g.,* at least 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95 or greater) %. In some embodiments, an anti-C5 antibody described herein contains one or more amino acid substitutions relative to the CDRs of eculizumab (*i.e.*, SEQ ID NOs:1-6), yet retains at least 30 (*e.g.,* at least 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43,

44, 45, 46, 47, 48, 49, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 95) % of the complement inhibitory activity of eculizumab in a hemolytic assay or CH50eq assay.

An anti-C5 antibody described herein has a serum half-life in humans that is at least 20 (*e.g.,* at least 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 or 55) days. In another embodiment, the anti-C5 antibody described herein has a serum half-life in humans that is at least 40 days. In another embodiment, the anti-C5 antibody described herein has a serum half-life in humans that is approximately 43 days. In another embodiment, the anti-C5 antibody described herein has a serum half-life in humans that is between 39-48 days. Methods for measuring the serum half-life of an antibody are known in the art. In some embodiments, an anti-C5 antibody, or antigen binding fragment thereof, described herein has a serum half-life that is at least 20 (*e.g.,* at least 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 400 or 500) % greater than the serum half-life of eculizumab, *e.g.,* as measured in one of the mouse model systems described in the working examples (*e.g.,* the C5-deficient/NOD/scid mouse or hFcRn transgenic mouse model system).

In one embodiment, the antibody competes for binding with, and/or binds to the same epitope on C5 as an antibody described herein. The term "binds to the same epitope" with reference to two or more antibodies means that the antibodies bind to the same segment of amino acid residues, as determined by a given method. Techniques for determining whether antibodies bind to the same epitope on C5 with an antibody described herein include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen:antibody complexes, and hydrogen/deuterium exchange mass spectrometry (HDX-MS). Other methods monitor the binding of the antibody to peptide antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest to affinity isolate specific short peptides from combinatorial phage display peptide libraries. Antibodies having the same VH and VL or the same CDR1, CDR2 and CDR3 sequences are expected to bind to the same epitope.

Antibodies that "compete with another antibody for binding to a target" refer to antibodies that inhibit (partially or completely) the binding of the other antibody to the target. Whether two antibodies compete with each other for binding to a target, *i.e.*, whether and to what extent one antibody inhibits the binding of the other antibody to a target, may be determined using known competition experiments. In certain embodiments, an antibody competes with, and inhibits binding of another antibody to a target by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%. The level of inhibition or competition may be different depending on which antibody is the "blocking antibody" (*i.e.*, the antibody that is incubated first with the target). Competing antibodies can bind to, for example, the same epitope, an overlapping epitope or to adjacent epitopes (*e.g.*, as evidenced by steric hindrance).

Anti-C5 antibodies, or antigen-binding fragments thereof described herein, used in the methods described herein can be generated using a variety of art-recognized techniques. Monoclonal antibodies can be obtained by various techniques familiar to those skilled in the art. Briefly, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell (Köhler, G. & Milstein, C., *Eur. J. Immunol.*, 6:511-9, 1976)). Methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses or other methods known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences that encode a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells (Huse, W. *et al.*, *Science*, 246:1275-81, 1989).

III. Compositions

Also provided herein are compositions comprising an anti-C5 antibody or antigen binding fragment thereof. In one embodiment, the composition comprises an anti-C5 antibody comprising the CDR1, CDR2 and CDR3 domains in a heavy chain variable region having the sequence set forth in SEQ ID NO:12, and the CDR1, CDR2 and CDR3 domains in a light chain variable region having the sequence set forth in SEQ ID NO:8. In another embodiment, the anti-C5 antibody comprises heavy and light chains having the sequences shown in SEQ ID

NOs:14 and 11, respectively. In another embodiment, the anti-C5 antibody comprises heavy and light chains having the sequences shown in SEQ ID NOs:20 and 11, respectively.

The compositions can be formulated as a pharmaceutical solution, *e.g.,* for administration to a subject for the treatment or prevention of a complement-associated disorder. The pharmaceutical compositions generally include a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" refers to, and includes, any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The compositions can include a pharmaceutically acceptable salt, *e.g.,* an acid addition salt or a base addition salt, sugars, carbohydrates, polyols and/or tonicity modifiers.

The compositions can be formulated according to standard methods. Pharmaceutical formulation is an established art (see, for example, Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th Edition, Lippincott, Williams & Wilkins (ISBN: 0683306472); Ansel *et al.* (1999) "Pharmaceutical Dosage Forms and Drug Delivery Systems," 7th Edition, Lippincott Williams & Wilkins Publishers (ISBN: 0683305727); and Kibbe (2000) "Handbook of Pharmaceutical Excipients American Pharmaceutical Association," 3rd Edition (ISBN: 091733096X)). In some embodiments, a composition can be formulated, for example, as a buffered solution at a suitable concentration and suitable for storage at 2-8C (*e.g.,* 4C). In some embodiments, a composition can be formulated for storage at a temperature below 0C (*e.g.,* -20C or -80C). In some embodiments, the composition can be formulated for storage for up to 2 years (*e.g.,* 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 1½ years or 2 years) at 2-8C (*e.g.,* 4C). Thus, in some embodiments, the compositions described herein are stable in storage for at least 1 year at 2-8C (*e.g.,* 4C).

The pharmaceutical compositions can be in a variety of forms. These forms include, *e.g.,* liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.,* injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends, in part, on the intended mode of administration and therapeutic application. Compositions containing a composition intended for systemic or local delivery, for example, can be in the form of injectable or infusible solutions. Accordingly, the compositions

can be formulated for administration by a parenteral mode (*e.g.*, intravenous, subcutaneous, intraperitoneal, or intramuscular injection). "Parenteral administration," "administered parenterally" and other grammatically equivalent phrases, as used herein, refer to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intranasal, intraocular, pulmonary, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intrapulmonary, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, intracerebral, intracranial, intracarotid and intrasternal injection and infusion.

IV. Outcomes

aHUS is an ultra-rare disorder driven by chronic uncontrolled complement activation. Ongoing complement dysregulation leads to increased activation of C5 systemically with consequent terminal complement activation, resulting in the devastating clinical manifestations of this disorder. Patients with aHUS are at risk of substantial morbidity and mortality.

aHUS can be genetic, acquired, or idiopathic. Hereditable forms of aHUS can be associated with mutations in a number of human complement components including, *e.g.*, complement factor H (CFH), membrane cofactor protein (MCP), complement factor I (CFI), C4b-binding protein (C4BP), complement factor B (CFB), and complement component 3 (C3) (Caprioli, J. *et al.*, *Blood*, 108:1267-79, 2006). Certain mutations in the gene encoding CD55, though not yet implicated in aHUS, are associated with the severity of aHUS (Esparza-Gordillo, J. *et al.*, *Hum. Mol. Genet.*, 14:703-12, 2005). aHUS can be considered genetic when two or more (*e.g.*, three, four, five or six or more) members of the same family are affected by the disease at least six months apart and exposure to a common triggering agent has been excluded, or when one or more aHUS-associated gene mutations (*e.g.*, one or more mutations in CFH, MCP/CD46, CFB, or CFI) are identified in a subject. A subject can have CFH-associated aHUS, CFB-associated aHUS, CFI-associated aHUS or MCP-associated aHUS, for example. Up to 30% of genetic aHUS is associated with mutations in CFH, 12% with mutations in MCP, 5-10% with mutations in CFI, and less than 2% with mutations in CFB. Genetic aHUS can be multiplex (*i.e.*, familial; two or more affected family members) or simplex (*i.e.*, a single occurrence in a family). aHUS can be considered acquired when an underlying environmental factor (*e.g.*, a drug, systemic disease or viral or bacterial agents that do not result in Shiga-like exotoxins) or

trigger can be identified. aHUS can be considered idiopathic when no trigger (genetic or environmental) is evident.

aHUS is rare and has a mortality rate of up to 25%. Many patients with this disease will sustain permanent neurological or renal impairment, *e.g.*, at least 50% of aHUS patients progress to end-stage renal failure (ESRF) (Kavanagh, D. *et al.*, *Br. Med. Bull.*, 77-78:5-22, 2006). Until recently, treatment options for patients with aHUS were limited and often involved plasma infusion or plasma exchange. In some cases, aHUS patients undergo uni- or bilateral nephrectomy or renal transplantation (Artz, M. *et al.*, *Transplantation*, 76:821-6, 2003). Recurrence of the disease in treated patients is common, however.

Laboratory tests can be performed to determine whether a human subject has thrombocytopenia, microangiopathic hemolytic anemia, or acute renal insufficiency. Thrombocytopenia can be diagnosed by a medical professional as one or more of: (i) a platelet count that is less than 150,000/mm^3 (*e.g.*, less than 60,000/mm^3); (ii) a reduction in platelet survival time that is reduced, reflecting enhanced platelet disruption in the circulation; and (iii) giant platelets observed in a peripheral smear, which is consistent with secondary activation of thrombocytopoiesis. Microangiopathic hemolytic anemia can be diagnosed by a medical professional as one or more of: (i) hemoglobin concentrations that are less than 10 mg/dL (*e.g.*, less than 6.5 mg/dL); (ii) increased serum lactate dehydrogenase (LDH) concentrations (> 460 U/L); (iii) hyperbilirubinemia, reticulocytosis, circulating free hemoglobin, and low or undetectable haptoglobin concentrations; and (iv) the detection of fragmented red blood cells (schistocytes) with the typical aspect of burr or helmet cells in the peripheral smear together with a negative Coombs test (Kaplan *et al.* (1992) "Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura," Informa Health Care (ISBN 0824786637) and Zipfel (2005) "Complement and Kidney Disease," Springer (ISBN 3764371668)). Blood concentrations of C3 and C4 can also be used as a measure of complement activation or dysregulation. In addition, a subject's condition can be further characterized by identifying the subject as harboring one or more mutations in a gene associated with aHUS such as CFI, CFB, CFH, or MCP (*supra*). Suitable methods for detecting a mutation in a gene include, *e.g.,* DNA sequencing and nucleic acid array techniques (Breslin, E. *et al.*, *Clin. Am. Soc. Nephrol.*, 1:88-99, 2006; Goicoechea de Jorge, E. *et al.*, *Proc. Natl. Acad. Sci. USA*, 104:240-5, 2007).

Provided herein are methods for treating aHUS in a pediatric patient comprising administering to the patient an anti-C5 antibody. Symptoms of aHUS include, but are not limited to severe hypertension, proteinuria, uremia, lethargy/fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia, and renal function impairment (*e.g.*, acute renal failure). Patients treated according to the methods disclosed herein preferably experience improvement in at least one sign of aHUS. The treatment may produce, for example, at least one therapeutic effect selected from the group consisting of a reduction or cessation in severe hypertension, proteinuria, uremia, lethargy/fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia and renal function impairment (*e.g.*, acute renal failure) compared to baseline.

In another embodiment, the treatment results in a substantial or complete thrombotic microangiopathy (TMA) inhibtion In another embodiment, the treatment results in a substantial or complete thrombotic microangiopathy inhibition that is sustained for more than, for example, 170 days (*e.g.*, more than 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days, 185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

In another embodiment, the treatment results in an increase in platelet count compared to baseline. In another embodiment, the treatment results in reduction in serum creatinine levels compared to baseline. In a particular embodiment, the treatment results in a $\geq$ 25% reduction in serum creatinine levels compared to baseline.

In another embodiment, the treatment produces a shift toward normal levels of Factor Ba, soluble tumor necrosis factor receptor 1 [sTNFR1]), soluble vascular adhesion molecule 1 [sVCAM1], thrombomodulin, D-dimer, and cystatin C.

In another embodiment, the treatment produces a reduction in the need for blood transfusions compared to baseline.

In another embodiment, the treatment eliminates the need for the patient to receive dialysis. In another embodiment, the patient is weaned off dialysis within 35 days or less (*e.g.*, 35 days, 34 days, 33 days, 32 days, 31 days, 30 days, 29 days, 28 days, 27 days, 26 days, 25

days, 24 days, 23 days, 22 days, 21 days, 20 days, 19 days, 18 days, 17 days, 16 days, 15 days, 14 days, 13 days, 12 days, 11 days or 10 days) of initiating treatment.

In another embodiment, the treatment produces a reduction in major adverse vascular events (MAVEs) (*e.g.*, thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis/renal artery thrombosis/glomerular thrombosis, renal infarction, acute peripheral vascular occlusion, mesenteric/visceral vein/arterial thrombosis or infarction, hepatic/portal vein thrombosis, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, renal arterial thrombosis, or multi-infarct dementia).

In another embodiment, the treatment produces a change from baseline in quality of life as assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 and the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale. In one embodiment, the treatment produces a change from baseline in quality of life as assessed via the FACIT-Fatigue Scale by one or more (*e.g.*, 1, 2 or 3) points. In another embodiment, the treatment produces a change from baseline in quality of life as assessed via the FACIT-Fatigue Scale by 3 points 150 days or more (*e.g.*, 150 days, 151 days, 152 days, 153 days, 154 days, 155 days, 156 days, 157 days, 158 days, 159 days, 160 days, 161 days, 162 days, 163 days, 164 days, 165 days, 166 days, 167 days, 168 days, 169 days, 170 days, 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days, 185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

In another embodiment, the patient's chronic kidney disease (CKD) improves by one or more stages after initiating treatment. For example, the patient's CKD improves by one, two, three, four, or five stages). In another embodiment, the patient's CKD improves by one or more stages 150 days or more (*e.g.*, 150 days, 151 days, 152 days, 153 days, 154 days, 155 days, 156 days, 157 days, 158 days, 159 days, 160 days, 161 days, 162 days, 163 days, 164 days, 165 days, 166 days, 167 days, 168 days, 169 days, 170 days, 171 days, 172 days, 173 days, 174 days, 175 days, 176 days, 177 days, 178 days, 179 days, 180 days, 181 days, 182 days 183 days, 184 days,

185 days, 186 days, 187 days, 188 days, 189 days, 190 days, 191 days, 192 days, 193 days, 194 days, 195 days, 196 days, 197 days, 198 days, 199 days, 200 days, 205 days, 210 days, 215 days, 220 days or 225 days) after initiating treatment.

In another embodiment, lactate dehydrogenase (LDH) levels can be used to evaluate responsiveness to a therapy (*e.g.,* a reduction of hemolysis as assessed by lactate dehydrogenase (LDH) levels is indicative of an improvement in at least one sign of aHUS). LDH is a marker of intravascular hemolysis (Hill, A. *et al.*, *Br. J. Haematol.*, 149:414-25, 2010; Hillmen, P. *et al.*, *N. Engl. J. Med.*, 350:552-9, 2004; Parker, C. *et al.*, *Blood*, 106:3699-709, 2005). Red blood cells contain large amounts of LDH, and a correlation between cell-free hemoglobin and LDH concentration has been reported *in vitro* (Van Lente, F. *et al.*, *Clin. Chem.*, 27:1453-5, 1981) and *in vivo* (Kato, G. *et al.*, *Blood*, 107:2279-85, 2006). The consequences of hemolysis are independent of anemia (Hill, A. *et al.*, *Haematologica*, 93(s1):359 Abs.0903, 2008; Kanakura, Y. *et al.*, *Int. J. Hematol.*, 93:36-46, 2011). LDH concentration obtained at baseline and then serially throughout a treatment period, is an important measure of hemolysis. Baseline levels of cell-free plasma hemoglobin are highly elevated in patients with aHUS with LDH ≥1.5-fold above the upper limit of normal (LDH ≥ 1.5 × ULN), with a significant correlation between LDH and cell-free plasma hemoglobin (Hillmen, P. *et al.*, *N. Engl. J. Med.*, 355:1233-43, 2006). The normal LDH value range is 105-333 IU/L (international units per liter).

LDH levels can be measured using any suitable test or assay, such as those described by Ferri FF, ed. *Ferri's Clinical Advisor 2014.* Philadelphia: Pa: Elsevier Mosby; 2014: Section IV–Laboratory tests and interpretation of results. LDH concentration can be measured in various samples obtained from a patient, in particular, serum samples. As used herein, the term "sample" refers to biological material from a subject. Although serum LDH concentration is of interest, samples can be derived from other sources, including, for example, single cells, multiple cells, tissues, tumors, biological fluids, biological molecules or supernatants or extracts of any of the foregoing. Examples include tissue removed for biopsy, tissue removed during resection, blood, urine, lymph tissue, lymph fluid, cerebrospinal fluid, mucous and stool samples. The sample used can vary based on the assay format, the detection method and the nature of the tumors, tissues, cells or extracts to be assayed. Methods for preparing samples are known in the art and can be readily adapted to obtain a sample that is compatible with the method utilized.

In one embodiment, patients treated according to the disclosed methods experience reductions in LDH levels to normal levels or to within 10%, or within 20% above what is considered the normal level (*e.g.*, within 105-333 IU/L). In one embodiment, the patient's LDH levels are ≥ 1.5 fold above the upper limit of normal (LDH ≥ 1.5 × ULN) prior to initiating treatment.

V. Kits and Unit Dosage Forms

Also provided herein are kits that include a pharmaceutical composition containing an anti-C5 antibody or antigen binding fragment thereof, such as ravulizumab or BNJ421, and a pharmaceutically acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods. The kits optionally also can include instructions, *e.g.,* comprising administration schedules, to allow a practitioner (*e.g.,* a physician, nurse, or patient) to administer the composition contained therein to administer the composition to a patient having aHUS. The kit also can include a syringe.

Optionally, the kits include multiple packages of the single-dose pharmaceutical compositions each containing an effective amount of the anti-C5 antibody, or antigen binding fragment thereof, for a single administration in accordance with the methods provided above. Instruments or devices necessary for administering the pharmaceutical composition(s) also may be included in the kits. A kit may provide, for example, one or more pre-filled syringes containing an amount of the anti-C5 antibody or antigen binding fragment thereof.

In one embodiment, a kit for treating aHUS in a human patient, the kit comprises: (a) a dose of an anti-C5 antibody or antigen binding fragment thereof comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:12, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:8; and (b) instructions for using the anti-C5 antibody or antigen binding fragment thereof according to any of the methods described herein.

In one embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a pediatric patient weighing ≥ 5 to < 10 kg: (a) once on Day 1 at a dose of 300 mg; and (b) once on Day 15 at a dose of 300 mg and every four weeks thereafter.

In one embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered to a patient weighing ≥ 5 to < 10 kg: (a) once on Day 1 at a dose of 600 mg; and (b) on Day 15 and every four weeks thereafter at a dose of 300 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered to a patient weighing ≥ 10 to < 20 kg: (a) once on Day 1 at a dose of 600 mg; and (b) on Day 15 and every four weeks thereafter at a dose of 600 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 20 to < 30 kg: (a) once on Day 1 at a dose of 900 mg; and (b) on Day 15 and every eight weeks thereafter at a dose of 2100 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 30 to < 40 kg: (a) once on Day 1 at a dose of 1200 mg; and (b) on Day 15 and every eight weeks thereafter at a dose of 2700 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody, or antigen binding fragment thereof, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 40 to < 60 kg: (a) once on Day 1 at a dose of 2400 mg; and (b) on Day 15 and every eight weeks thereafter at a dose of 3000 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 60 to < 100 kg: (a) once on Day 1 at a dose of 2700 mg; and (b) on Day 15 and every eight weeks thereafter at a dose of 3300 mg.

In another embodiment, the kit comprises a dose of an anti-C5 antibody or antigen binding fragment thereof, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 100 kg: (a) once on Day 1 at a dose of 3000 mg; and (b) on Day 15 and every eight weeks thereafter at a dose of 3600 mg.

The following examples are merely illustrative and should not be construed as limiting the scope of this disclosure in any way as many variations and equivalents will become apparent to those

skilled in the art upon reading the present disclosure. The contents of all references, Genbank entries, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

EXAMPLE 1: A Phase 3, Open-Label, Multicenter Study of Ravulizumab in Children and Adolescent Patients with aHUS

A Phase 3, single-treatment arm, multicenter study is conducted to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of ravulizumab administered by intravenous (IV) infusion to approximately 23 to 28 pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS. The study has 2 cohorts. Cohort 1 includes complement inhibitor treatment-naïve patients. Cohort 2 includes eculizumab-experienced adolescent patients (12 to < 18 years of age). The study consists of a Screening Period (of up to 7 days for Cohort 1 or up to 28 days for Cohort 2), a 26-week Initial Evaluation Period, and a 2-year Extension Period. The study design is depicted in FIG. 1.

Approximately 23 to 28 pediatric patients with documented aHUS are planned. The minimum number of patients for each age category is as follows: (1) Birth to < 2 years: 4 patients, (2) 2 to < 6 years: 4 patients, (3), 6 to < 12 years: 4 patients, and (4) 12 to < 18 years: 8 patients. Cohort 2 patients must be 12 to < 18 years of age.

Consenting patients in Cohort 1 are screened for study eligibility up to 7 days prior to Day 1. Consenting patients in Cohort 2 are screened for study eligibility up to 28 days prior to Day 1; the first dose of study drug is given 14 days from the eligible patient's last dose of eculizumab. Patients who are eligible based on the Inclusion and Exclusion Criteria are enrolled into the Initial Evaluation Period and receive a weight-based loading dose of ravulizumab on Day 1, followed by weight-based maintenance treatment with ravulizumab on Day 15 and once every eight weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of treatment. Weight-based dosing is based on the patient's body weight recorded on Dose Regimen Decision Days (if the Dose Regimen Day is a dosing day, body weight is recorded predose), as shown in Table 1 below.

Table 1: Weight-Based Dosing

Body Weight Range (kg)[a]	**Loading Dose (mg)**	**Maintenance Doses (mg)**	**Maintenance Dosing Frequency**
≥ 5 to < 10	600	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks

[a] Body weight Z recorded on dose Regimen Decision Days. If the Dose Regimen day is also dosing day, body weight is recorded predose with dosing that day based on the previous Dose regimen day body weight.

An initial analysis, including review of ravulizumab PK and serum free C5 levels, is conducted after four complement inhibitor treatment-naïve (*i.e.*, Cohort 1) patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. In addition, safety data are reviewed. Enrollment of patients proceeds without interruption while the analysis is ongoing. The primary purpose of this review is to assure patients are achieving adequate complement inhibition during this study with the goal of achieving complete terminal complement blockade. Based on this review, if dose adjustment is considered needed and tolerable, subsequent treatment for all patients continues at the adjusted dose regimen. After the Initial Evaluation Period, patients roll over into an Extension Period in which all patients continue their weight-based maintenance dose of ravulizumab on Day 183 and once every eight weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every four weeks (q4w) for patients weighing < 20 kg, until the product is registered or approved (in accordance with country specific regulation) or for up to 2 years, whichever occurs first. Note that q4w visits during the Extension Period are not applicable for patients weighing ≥ 20 kg and receiving ravulizumab q8w. The end of trial is defined as the last patient's last visit or follow-up (whether on site or via phone call) of the 2-year Extension Period, whichever is later.

1. Objectives

The primary objective of the study is to assess the efficacy of ravulizumab in complement inhibitor treatment-naïve pediatric patients (*i.e.*, Cohort 1) with aHUS to inhibit

complement-mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis and renal impairment.

Secondary objectives for complement inhibitor treatment-naïve patients (*i.e.*, Cohort 1) are to (1) characterize the safety and tolerability of ravulizumab, (2) evaluate the efficacy of ravulizumab by dialysis requirement status, time to complete TMA response, complete TMA response status over time, observed value and change from baseline in estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline, observed value and change from baseline in hematologic parameters (platelets, lactate dehydrogenase [LDH], hemoglobin), increase in hemoglobin of $\geq$ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, and change from baseline in quality of life (QoL), as measured by the pediatric FACIT-Fatigue questionnaire, (3) characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ravulizumab, including changes in serum ravulizumab concentration over time and changes in serum free complement component 5 (C5) concentrations over time, and (4) evaluate the long-term safety and efficacy of ravulizumab.

Secondary objectives for eculizumab-experienced patients (*i.e.*, Cohort 2) are to (1) characterize the safety and tolerability of ravulizumab, (2) evaluate the efficacy of ravulizumab by dialysis requirement status, observed value and change from baseline in eGFR, CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline, observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin), and change from baseline in QoL, as measured by the pediatric FACIT-Fatigue questionnaire, (3) to characterize the PK/PD of ravulizumab, including changes in serum ravulizumab concentration over time and changes in serum free C5 concentrations over time, and (4) and evaluate the long-term safety and efficacy of ravulizumab.

2. Diagnosis and Main Criteria for Inclusion and Exclusion

Patients must satisfy all inclusion and exclusion criteria to have a confirmed diagnosis of aHUS and be eligible for the study. Patients who fail any of the eligibility criteria can be rescreened. Patients can be rescreened a maximum of two times. For Cohort 1, samples collected at Screening can be tested at either a local or central laboratory. If a local laboratory is used to define eligibility,

additional samples are collected during the Screening Period for LDH, platelet count, hemoglobin and serum creatinine and tested at the central laboratory. All analyses in this study are based on results from the central laboratory (unless the result is missing). If Cohort 1 patients are found not to satisfy the eligibility criteria for serum creatinine (Inclusion Criterion 2c) based on central laboratory results, they must not be enrolled into the study; if the subject has received the first dose of ravulizumab, the patient must be withdrawn from the study, and may be replaced. For Cohort 1 patients, laboratory results for Exclusion Criterion number 1 and/or Exclusion Criterion number 2 may not be available prior to first dose. Later results for Exclusion Criterion number 1 and/or Exclusion Criterion number 2 could lead to discontinuation and replacement of the patient.

For Cohort 2, samples collected at Screening must be tested at a central laboratory. Hhistorical test results via chart review, however, should be utilized for Inclusion Criterion 3 and Exclusion Criteria 1, 2, 3 and 24.

The following entry criteria are applicable for patients in both cohorts unless otherwise noted as specific for Cohort 1 or Cohort 2.

Inclusion Criteria are as follows:

1. Patients from birth up to < 18 years of age and weighing ≥ 5 kg at the time of consent who:
    a. For Cohort 1 patients, have not been previously treated with complement inhibitors
    b. For Cohort 2 patients, are between 12 and < 18 years of age and have been treated with eculizumab according to the labeled dosing recommendation for aHUS for at least 90 days prior to Screening
2. For Cohort 1 patients, evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:
    a. Platelet count < 150,000 per microliter (μL) during the Screening Period or within 28 days prior to the start of the Screening Period, and
    b. LDH ≥ 1.5× upper limit of normal (ULN) during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin ≤ lower limit of normal (LLN) for age and gender during the Screening Period or within 28 days prior to the start of the Screening Period, and

c. Serum creatinine level ≥ 97.5th percentile for age at Screening (patients who require dialysis for acute kidney injury are also eligible regardless of serum creatinine level).

3. For Cohort 2 patients, documented diagnosis of aHUS including:

a. Increase in LDH > ULN and creatinine > ULN, and decrease in platelets < LLN documented by local laboratories at the time of the TMA event

4. For Cohort 2 patients, clinical evidence of response to eculizumab indicated by stable TMA parameters (via central laboratory results) at Screening, including:

a. LDH < 1.5 × ULN, and

b. Platelet count ≥ 150,000/μL, and

c. eGFR > 30 mL/min/1.73m^2 using the Schwartz formula

5. Among patients with a kidney transplant:

a. Known history of aHUS prior to current kidney transplant, or

b. No known history of aHUS, and persistent evidence of TMA at least four days after modifying the immunosuppressive regimen (*e.g.*, suspending or reducing the dose) of calcineurin inhibitor ([CNI]; *e.g.*, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor ([mTORi]; *e.g.*, sirolimus, everolimus).

6. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.

7. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within three years prior to, or at the time of, initiating study drug. Patients who receive a meningococcal vaccine less than two weeks before initiating ravulizumab treatment must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination. Patients who have not been vaccinated prior to initiating ravulizumab treatment should receive prophylactic antibiotics prior to and for at least two weeks after meningococcal vaccination. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for eight months following last dose.

8. Patients must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines.

9. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.

10. Patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]) and comply with the study visit schedule.

Exclusion criteria are as follows:

1. Known familial or acquired 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13' (ADAMTS13) deficiency (activity < 5%).

2. Known Shiga toxin-related hemolytic uremic syndrome (STEC-HUS) as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin producing bacteria.

3. Positive direct Coombs test.

4. Known Human Immunodeficiency Virus (HIV) infection.

5. Unresolved meningococcal disease.

6. Patients with a confirmed diagnosis of ongoing sepsis defined as positive blood cultures within seven days prior to the start of Screening and untreated with antibiotics.

7. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.

8. Females who plan to become pregnant during the study or are currently pregnant or breastfeeding.

9. Heart, lung, small bowel, pancreas or liver transplant.

10. Among patients with a kidney transplant, acute kidney dysfunction within four weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria.

11. Among patients without a kidney transplant, history of kidney disease other than aHUS, such as known kidney biopsy finding suggestive of underlying disease other than aHUS, known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (*e.g.*, small kidneys for age), known family history and/or genetic diagnosis of non-complement mediated genetic renal disease (*e.g.*, focal segmental glomerulosclerosis).

12. Identified drug exposure-related HUS.

13. For Cohort 1 patients, receiving plasma exchange/plasma infusion (PE/PI), for 28 days or longer, prior to the start of Screening for the current TMA.

14. History of malignancy within five years of Screening with the exception of a non-melanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.

15. Bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) within the last six months prior to the start of Screening.

16. HUS related known genetic defects of cobalamin C metabolism.

17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), or antiphospholipid antibody positivity or syndrome.

18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for end-stage kidney disease).

19. Patients receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (*e.g.*, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening.

20. Patients receiving other immunosuppressive therapies such as steroids, mTORi (*e.g.*, sirolimus,everolimus), CNI (*e.g.*, cyclosporine or tacrolimus) are excluded unless part of an established post-transplant antirejection regimen, or a patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or steroids are being used for a condition other than aHUS (*e.g.*, asthma).

21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.

22. For Cohort 1 patients, prior use of any complement inhibitors.

23. For Cohort 2 patients, prior use of complement inhibitors other than eculizumab.

24. For Cohort 2 patients, any known abnormal TMA parameters within 90 days prior to Screening (*e.g.*, LDH $\geq 1.5 \times$ ULN, or platelet count < 150,000/μL, or eGFR ≤ 30 mL/min/1.73m^2 using the Schwartz formula).

25. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.

26. Any medical or psychological condition that, in the opinion of the Investigator or Sponsor, could increase the risk to the patient by participating in the study or confound the outcome of the study.

27. Known or suspected history of drug or alcohol abuse or dependence within one year prior to the start of Screening.

28. Use of tranexamic acid within seven days prior to Screening is prohibited.

3. Investigational Product, Dosage and Mode of Administration

Ravulizumab, a humanized anti-C5 monoclonal antibody composed of two 448 amino acid heavy chains and two 214 amino acid light chains, is an IgG2/4 kappa immunoglobulin consisting of human constant regions, and murine complementarity-determining regions grafted onto human framework light- and heavy-chain variable regions.

Ravulizumab drug product is supplied for clinical studies as a sterile, preservative-free 10 mg/mL solution in single-use vials and designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion. Table 2 and the current IB provide additional information.

Table 2: Study Drug

Product Name	**Ravulizumab**
Dosage Form	Concentrated solution (10 mg/mL) for infusion

Product Name	Ravulizumab
Route of Administration	Intravenous infusion
Physical Description	Clear to translucent, slight whitish color, practically free from particles
Manufacturer	Alexion Pharmaceuticals, Inc. or Contracted Manufacturing Organization

Ravulizumab is packaged in United States Pharmacopeia (USP)/ European Union Pharmacopeia (EP) Type 1 borosilicate glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug is supplied in kits. Ravulizumab is released to each site upon receipt of all required essential documents based upon applicable regulations.

Upon arrival of the study drug kits at the study site, the pharmacist (or trained designee) promptly removes the study drug kits from the shipping cooler and stores them in their original cartons under refrigerated conditions at 2C to 8C and protected from light. Ravulizumab is not frozen. Study drug is stored in a secure, limited-access storage area, and the temperature is monitored daily.

The admixed drug product is at room temperature prior to administration. The material is not heated (*e.g.*, by using a microwave or other heat source) other than by ambient air temperature.

Ravulizumab is not administered as an IV push or bolus injection. Infusions of study drug are prepared using aseptic technique. The patient's required dose of ravulizumab is further diluted into commercially available saline (0.9% sodium chloride; country-specific pharmacopeia) at the volume specified in Table 3. Ravulizumab admixture is administered to the patient using an IV tubing administration set via an infusion pump. Use of a 0.2 micron filter for infusion is required.

Table 3: Dosing Reference Chart for Ravulizumab Dose Preparation

Dose Type	**Body Weight (kg)[a]**	**Dose (mg)**	**Ravuliz-umab Volume (mL)**	**Saline Volume (mL)**	**Total Volume (mL)**	**Min. Infusion Duration minutes (hours)**	**Max. Infusion Rate (mL/hour)**
Loading	≥ 5 to < 10	600	60	60	120	228 (3.8)	31.5
	≥ 10 to < 20	600	60	60	120	113 (1.9)	63.1
	≥ 20 to < 30	900	90	90	180	86 (1.5)	120.0
	≥ 30 to < 40	1200	120	120	240	77 (1.3)	184.6
	≥ 40 to < 60	2400	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700	270	270	540	102 (1.7)	318
	≥ 100	3000	300	300	600	108 (1.8)	333
Maintenance	≥ 5 to < 10	300	30	30	60	113 (1.9)	31.5
	≥ 10 to < 20	600	60	60	120	113 (1.9)	63.1
	≥ 20 to < 30	2100	210	210	420	194 (3.3)	127.2
	≥ 30 to < 40	2700	270	270	540	167 (2.8)	192.8
	≥ 40 to < 60	3000	300	300	600	140 (2.4)	250
	≥ 60 to < 100	3300	330	330	660	120 (2.0)	330
	≥ 100	3600	360	360	720	132 (2.2)	328

Refer to the Pharmacy Manual for additional dose preparation instructions.

[a] Body weight as recorded on Dose Regimen Decision Days. If the Dose Regimen Day is also dosing day, body weight is recorded predose with dosing that day based on the previous Dose Regimen Day body weight.

Doses of study drug are only prepared and dispensed by a pharmacist or a medically qualified study personnel. Study drug is dispensed only to enrolled patients who are confirmed eligible for participation in this study. Once study drug is prepared for a patient, it is only administered to that patient. Vials of study drug are for one-time use only and any drug product remaining in the vial is not used for another patient. Any drug remaining in the infusion tubing or infusion bag is not used for another patient.

All clinical study material is stored in a secure place and allocated and dispensed by appropriately trained persons. Detailed records of the amounts of the investigational product received, dispensed and destroyed are maintained. Unless otherwise notified, empty vials and vials with residual materials are kept for inspection and accountability by the study monitor prior to their destruction or handled per local pharmacy standard operating procedures (SOPs) for

clinical study drugs. To satisfy regulatory requirements regarding drug accountability, at the end of the study all remaining ravulizumab inventory is reconciled and destroyed or returned according to applicable regulations.

For Cohort 1 and Cohort 2, ravulizumab loading doses on Day 1 and maintenance doses on Day 15 and once every eight weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every four weeks (q4w) for patients weighing < 20 kg are administered by IV infusion. Dosages are based on the patient's body weight recorded on Dose Regimen Decision Days (if the Dose Regimen Day is a dosing day, body weight is recorded predose), as shown in Table 3.

During the Initial Evaluation Period, changes to dose regimen (dose level or dose frequency [*e.g.*, q4w vs q8w]) are based on the patient's body weight on the "Dose Regimen Decision Day (patients on q4w or q8w schedules)" preceding the day of administration. Patients changing from q4w to q8w are administered their first q8w dose on the ravulizumab administration day ("ravulizumab administration [patients weighing > 20 kg]") following the "Dose Regimen Decision Day (patients on q4w or q8w schedules)." Patients changing from q8w to q4w are administered their first q4w dose on the ravulizumab administration day ("ravulizumab administration [patients weighing < 20 kg]") following the "Dose Regimen Decision Day (patients on q4w or q8w schedules)."

During the Extension Period, the dose of ravulizumab is based on the patient's body weight on the preceding "Dose Regimen Decision Day (patients on q4w schedule)" or "Dose Regimen Decision Day (patients on q8w schedule)." Patients changing from q4w to q8w are administered their first q8w dose on the ravulizumab administration day ("ravulizumab administration [patients weighing > 20 kg]") following the "Dose Regimen Decision Day (patients on q4w schedule)." Patients changing from q8w to q4w are administered their first q4w dose on the ravulizumab administration day ("ravulizumab administration [patients weighing < 20 kg]") 8 weeks after the "Dose Regimen Decision Day (patients on q8w schedule)."

4. Endpoints: Efficacy Assessments

As patients previously treated with eculizumab have stabilized TMA parameters at study entry, Cohort 2 patients are excluded from the following efficacy assessments: Complete TMA Response, Time to Complete TMA Response, Complete TMA Response status over time, and increase in hemoglobin from baseline.

The primary efficacy endpoint for Cohort 1 is Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at two separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

The secondary efficacy endpoints for Cohort 1 are the following and are measured through 26 weeks and over the entire study period: (1) dialysis requirement status, (2) time to Complete TMA Response, (3) complete TMA Response status over time, (4) observed value and change from baseline in eGFR, (5) CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline, (6) observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin), (7) increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, and (8) change from baseline in QoL, as measured by pediatric FACIT-Fatigue questionnaire (patients ≥ 5 years of age).

The secondary efficacy endpoints for Cohort 2 are the following and are measured through 26 weeks and over the entire study period: (1) dialysis requirement status, (2) observed value and change from baseline in eGFR, (3) CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline, (4) observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin), and (5) change from baseline in QoL, as measured by Pediatric FACIT-Fatigue questionnaire (patients ≥ 5 years of age).

The following PK/PD endpoints are applicable for Cohort 1 and Cohort 2: (1) changes in serum ravulizumab concentration over time and (2) changes in serum free C5 concentrations over time.

Biomarker, genetic, and extra-renal signs or symptoms of aHUS are exploratory endpoints that are applicable for Cohort 1 and Cohort 2. Exploratory biomarkers of PD effect may include, but are not limited to, change from baseline in levels of markers of complement dysregulation (*e.g.*, factor Ba), vascular inflammation (*e.g.*, soluble tumor necrosis factor receptor 1 [sTNFR1]), endothelial activation/damage (*e.g.*, soluble vascular adhesion

molecule 1 [sVCAM-1], thrombomodulin), coagulation (*e.g.*, D-dimer), and renal injury (*e.g.*, cystatin C). Additional assessments may include measurements of ravulizumab excretion in urine, chicken red blood cell (cRBC) hemolysis, total C5, autoantibodies to complement proteins (*e.g.*, anti-factor H).

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ravulizumab. Patients (or legal guardians) may decline from providing a sample for exploratory genetics and still participate in the study.

The Investigator evaluates extra-renal signs or symptoms of aHUS using clinical laboratory measurements, vital signs, and an organ system review.

For Cohort 1 and Cohort 2, the long-term safety and tolerability of ravulizumab are evaluated by physical examinations, vital signs, physical growth (height, weight, and head circumference [the latter only in patients ≤ 2 years of age]), electrocardiograms (ECG), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADA) are also assessed.

5. Statistical Methods

Continuous variables are summarized using descriptive statistics, including number of observations and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables are summarized by frequency counts and percentage of patients. The analyses for Cohort 1 and Cohort 2 are conducted and reported separately. Analyses specific to Cohort 1 are indicated as such below; all other endpoints are performed for both cohorts. Tabulated summaries do not include a direct comparison between Cohort 1 and Cohort 2.

An interim clinical study report (CSR) is prepared when 12 to 14 complement inhibitor treatment-naïve (*i.e.*, Cohort 1) patients have completed or withdrawn from the 26-week Initial Evaluation Period. An additional interim CSR is prepared when all study patients have completed or withdrawn from the 26-week Initial Evaluation Period. Each interim CSR includes efficacy, safety and PK/PD analyses. A final CSR to summarize long-term efficacy, safety and PK/PD is produced at study completion. Available exploratory data are summarized after study completion, but may not be included in the CSR. All data collected are presented using summary tables,

figures and data listings. Planned summaries are presented overall and by age groups when applicable.

Efficacy analyses are performed on the Full Analysis Set (FAS). The analysis of the FAS is the primary analysis. The FAS for Cohort 1 is based on a modified intent to treat (mITT) approach. With this approach, confirmation of eligibility in patients may occur after receiving study drug. This specifically applies to Inclusion Criterion number 2c (must be confirmed via a central laboratory), Exclusion Criterion number 1 (may be confirmed via a central or local laboratory), and Exclusion Criterion number 2 (may be confirmed via a central or local laboratory). Based on the above, the FAS includes all patients who receive at least one dose of ravulizumab, have at least one post-baseline efficacy assessment, and meet all of the following criteria (these are the same criteria that if not satisfied result in discontinuation of the patient and potential replacement): (1) patients who satisfy Inclusion Criterion number 2c, (2) patients who satisfy Exclusion Criterion number 1, and (3) patients who satisfy Exclusion Criterion number 2. The FAS for Cohort 2 includes all patients who receive at least one dose of ravulizumab and have at least one post-baseline efficacy assessment. The FAS is determined prior to database lock and prior to the database snapshots for the analyses performed at the end of the 26-week Initial Evaluation Period.

The primary efficacy endpoint is Complete TMA Response during the 26-week Initial Evaluation Period. The primary analysis consists in estimating the proportion of complete TMA responders among ravulizumab treated patients. This is performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ravulizumab treated patients. The CI is based on exact confidence limits using the Clopper-Pearson method. This analysis is only performed for Cohort 1.

For the secondary efficacy endpoint of time to Complete TMA Response, a Kaplan-Meier cumulative distribution curve is generated along with a 2-sided 95% CI. The corresponding summary table presents the cumulative distribution function (CDF) estimate, the number of patients at risk, the number of patients responding, and the number of patients censored at each post-baseline time point. The table also presents first quartile, median and third quartile, along with corresponding 2-sided 95% CI, of time to complete response. This analysis is only performed for Cohort 1.

Complete TMA response is also summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point. A similar approach is used to summarize the number and proportion of patients with an increase from baseline in hemoglobin ≥ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. This analysis is only performed for Cohort 1.

Kidney function (dialysis requirement status, eGFR, CKD stage), as well as hematologic parameters (platelets, LDH, hemoglobin), is summarized at baseline and each post-baseline time point. These analyses are performed for both Cohort 1 and Cohort 2. Descriptive statistics for continuous variables (eGFR, platelets, LDH, hemoglobin) are used to summarize the observed value, as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may be fit to test whether changes differ from zero at each time point. Dialysis requirement status and CKD stage are summarized over time. Dialysis requirement status is summarized among patients receiving dialysis within five days prior to ravulizumab treatment initiation by presenting the number and proportion of those patients receiving and not receiving dialysis at each time point. A 2-sided 95% CI for the proportion receiving dialysis is provided. CKD stage is summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 is considered the worst category, while Stage 1 is considered the best category. A 2-sided 95% CI for the proportion is provided for each category.

Quality of life is assessed in patients ≥ 5 years of age by the pediatric FACIT-Fatigue Questionnaire (patient-reported for patients who were ≥ 8 years of age at the time of enrollment; caregiver-reported or caregiver assistance for patients who were 5 to < 8 years of age at the time of enrollment). This measure is summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value, as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the test's baseline value as covariates may be fit to test whether changes differ from zero at each time

point. These analyses are performed for both Cohort 1 and Cohort 2. Analyses are separate for patients who were 5 to < 8 years of age at the time of enrollment (caregiver-reported or caregiver assistance) and patients who were ≥ 8 years of age at the time of enrollment (patient-reported).

Safety analyses are performed on the Safety Set defined as all patients who received at least 1 dose of ravulizumab for both Cohort 1 and Cohort 2. The incidence of treatment emergent adverse events (TEAEs) and SAEs are summarized by system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to treatment. Observed values and changes from baseline (last assessment prior to ravulizumab) in ECGs, vital signs, and laboratory assessments, as well as presence of ADA, are summarized. Shifts from baseline in laboratory assessments are summarized for all study visits. These analyses are performed for both Cohort 1 and Cohort 2.

Meningococcal infections are an important identified risk in this study.

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (*e.g.*, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Situations in which an untoward medical occurrence did not occur (*e.g.*, hospitalization for elective surgery if planned before the start of the study, admissions for social reasons or convenience), and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

The severity of AEs is graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher. A grading (severity) scale is provided for each AE term. Each CTCAE term is a Lowest Level Term (LLT) per the Medical Dictionary for Regulatory Activities (MedDRA®). Each LLT is coded to a MedDRA preferred term (PT). Grade refers to the severity of the AE. The CTCAE assigns a grade of 1 through 5, with unique clinical descriptions of severity for each AE (Table 4).

Table 4: Adverse Event Severity Grading Scale

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Any change in the severity of an AE is documented based on specific guidelines in the eCRF Completion Guidelines. Severity and seriousness are differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for a serious adverse event (SAE).

An Investigator must provide a causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) for all AEs (both serious and nonserious) based upon the Investigator's medical judgment and the observed symptoms associated with the event (Table 5). This assessment is recorded on the eCRF and any additional forms as appropriate.

Table 5: Causality Assessment Descriptions

Assessment	Description
Not Related/Unrelated	Suggests that there is no causal association between the investigational product and the reported event.
Unlikely Related	Suggests that the clinical picture is highly consistent with a cause other than the investigational product but attribution cannot be made with absolute certainty and a relationship between the investigational product and AE cannot be excluded with complete confidence.
Possibly Related	Suggests that treatment with the investigational product may have caused or contributed to the AE (*e.g.*, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the investigational product, but could also have been produced by other factors).

Assessment	Description
Probably Related	Suggests that a reasonable temporal sequence of the event with the investigational product administration exists and the likely causal association of the event with the investigational product. This is based upon the known pharmacological action of the investigational product, known or previously reported adverse reactions to the investigational product or class of drugs, or judgment based on the Investigator's clinical experience.
Definitely Related	Temporal relationship to the investigational product, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, reappearance on rechallenge.

A serious adverse event (SAE) is any untoward medical occurrence that: results in death, is life-threatening (*i.e.*, patient was at risk of death at the time of the event), requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events that may not result in death, be immediately life-threatening or require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure.

All SAEs are recorded regardless of the Investigator's assessment of causality. No time limit exists on reporting SAEs that are thought to be causally related to the study drug. Investigators are at liberty to report SAEs irrespective of causality at any time.

For all SAEs, the Investigator must provide the following: appropriate and requested follow-up information, causality of the SAE(s), treatment of/intervention for the SAE(s), uutcome of the SAE(s), and supporting medical records and laboratory/diagnostic information.

Pregnancy data are collected during this study for all patients and female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal

exposure. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication. Complications of pregnancy and abnormal outcomes of pregnancy, however, are AEs and may meet the criteria for an SAE (*e.g.*, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Sparse PK and PD (serum free C5) samples are collected over the course of the study. Individual serum concentration data for all patients from the FAS and who have evaluable PK data are used to derive the PK parameters for ravulizumab. These analyses are performed for both Cohort 1 and Cohort 2. Graphs of mean serum concentration-time profiles are constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times are used for all calculations. Descriptive statistics are calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

PD analyses are performed for all patients from the Cohort 1 FAS and Cohort 2 FAS who have evaluable PD data. The PD effects of ravulizumab are evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 serum concentrations over time, as appropriate. Descriptive statistics are calculated for the PD data at each sampling time, as appropriate. Assessments of PK/PD relationships may be explored using data from this study or in combination with data from other studies.

Exploratory analyses may be conducted for both Cohort 1 and Cohort 2 to evaluate changes from baseline in biomarkers that may include, but are not limited to, markers of complement dysregulation (*e.g.*, Factor Ba), vascular inflammation (*e.g.*, sTNFR1), endothelial activation/damage (*e.g.*, sVCAM-1, thrombomodulin) coagulation (*e.g.*, D-dimer), and renal injury (*e.g.*, cystatin C). Additional analysis may include evaluation of ravulizumab excretion in urine, cRBC hemolysis, total C5, and autoantibodies to complement proteins (*e.g.*, anti-factor H).

Exploratory genetics may be performed for both Cohort 1 and Cohort 2 to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of

ravulizumab. Patients (or legal guardian) may decline from providing a sample for exploratory genetics and still participate in the study.

Extra-renal signs or symptoms of aHUS are summarized at baseline and each post-baseline assessment by presenting the number and proportion of patients with a specific symptom present. This analysis is performed for both Cohort 1 and Cohort 2.

EXAMPLE 2: Interim Data for Phase 3, Open-Label, Multicenter Study of Ravulizumab in Complement Inhibitor-Naïve Children and Adolescent Patients with aHUS

The following is a summary of interim data from a single arm, open label, estimation study of ravulizumab in children and adolescents with aHUS that was conducted substantially according to the protocol described above in Example 1. It includes results through the end of the 26-week Initial Evaluation Period or until study discontinuation for the first 16 patients enrolled in the study, all of whom are in Cohort 1. The study design is depicted in FIG. 1.

The objective of the study is to assess the efficacy of ravulizumab in complement inhibitor treatment-naïve pediatric patients with aHUS to inhibit complement-mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis and renal impairment. The primary endpoint is complete TMA response within the initial evaluation period (26 weeks).

A. Data Sets Analyzed

Four patients in each of four age groups were included, *i.e.*, (A) birth to < 2 years, (B) 2 to < 6 years, (C) 6 to < 12 years and (D) 12 to < 18 years. Sixteen subjects were enrolled and received at least one dose (included in safety set), two enrolled and were replaced (deemed ineligible post-first dose and discontinued), and fourteen were in the full analysis set, and one subject discontinued on Day 21 due to adverse events. There was 100% compliance with the study treatment. A patient disposition summary is set forth in FIG. 2 and further described in Table 6. The baseline demographics (Table 7) and baseline disease characteristics (Table 8) are set forth below.

Table 6: Disposition of Patients– Initial Evaluation Period (All Enrolled Patients)

	ravulizumab n (%)
Enrolled	16 (100.0)

	ravulizumab n (%)
Treated	16 (100.0)
Completed the Initial Evaluation Period	13 (81.3)
Completed study	0
Discontinued from treatment	3 (18.8)
Adverse event	1 (6.3)
Non-compliance with study drug	0
Physician decision	0
Pregnancy	0
Protocol violation	1 (6.3)
Subject decision	0
Lack of efficacy	0
Other [a]	1 (6.3)
Withdrawn from study	3 (18.8)
Adverse event	1 (6.3)
Death	0
Lost to follow-up	0
Non-compliance with study drug	0
Physician decision	0
Pregnancy	0
Protocol violation	1 (6.3)
Study terminated by Sponsor	0
Withdrawal by subject	0
Lack of efficacy	0
Deemed ineligible post-treatment	1 (6.3)
Other	0

[a] This patient was withdrawn from study drug since the patient was deemed ineligible based on the central laboratory results received after the first dose.

Table 7: Baseline Demographics

Variable	Overall (N=14)
Age at Time of First Infusion (years)	
Mean (SD)	6.1 (4.52)
Median (min, max)	5.2 (0.9, 17.3)
Age at Time of First Infusion (years) category, n (%):	
Birth to < 2 years	2 (14.3)

2 to<6 years	7 (50.0)
6 to<12 years	4 (28.6)
12 to<18 years	1 (7.1)
Sex. n(%): Males	5 (35.7
Sex. n(%): Females	9 (64.3)
Ethnicity, n (%): Hispanic or Latino	2 (14.3)
Ethnicity, n (%): Not Hispanic or Latino	12 (85.7)
Race, n(%):	
American Indian or Alaskan Native	1 (7.1)
Asian	4 (28.6)
Black or African American	2 (14.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)
White	7 (50.0)
Unknown	1 (7.1)
Japanese Descent, n (%)	
Yes	1 (7.1)
No	13 (92.9)
Height at Baseline (cm)	
Mean (SD)	108.5 (24.70)
Median (min, max)	108.5 (64, 138.1)
Weight at Time of First Infusion (kg), Mean (SD)	
Mean	19.8 (9.94)
Median (min, max)	16.2 (8.4, 35.75)
Weight at Time of First Infusion (kg) category, n (5)	
>=5 to <10 kg	2 (14.3)
>=10 to <20 kg	7 (50.0)
>=20 to <30 kg	2 (14.3)
>=30 to <40 kg	3 (21.4)

Table 8: Baseline Disease Characteristics

Variable	Overall (N=14)
Age(years) at time of first aHUS symptoms, Mean (SD)	4.94 (3.081)
Pre-treatment Extra-Renal signs or symptoms of aHUS, n(%)	10 (71.4)
Kidney Transplant Prior to Entering the study, n(%)	1 (7.1)
CKD stage at baseline, n(%)	
1	0 (0.0)
2	2 (14.3)
3a	1 (7.1)
3b	0 (0.0)
4	6 (42.9)
5	5 (35.7)
Dialysis Within 5 Days of First Dose, n(%)	5 (35.7)

The first 16 patients enrolled and treated in Cohort 1 are included in the Safety Set (Table 9). Two patients were excluded from the full analysis set. Both of these patients were treated based on verification of inclusion and exclusion criteria through local laboratory results and then later discontinued due to failure to meet certain eligibility criteria once all Screening/Day 1 central laboratory results were available. All 14 patients in the full analysis set were included in the per protocol set.

Table 9: Analysis Data Sets (All Enrolled Patients)

Variable	**ravulizumab n (%)**
Number of enrolled patients	16 (100.0)
Number of patients in the FAS	14 (87.5)
Number of patients excluded from the FAS	2 (12.5)
Number of patients in the PP Set	14 (87.5)
Number of patients excluded from the PP Set	2 (12.5)
Number of patients in the Safety Set	16 (100.0)
Number of patients excluded from the Safety Set	0
Number of patients in the PK/PD Analysis Set	14 (87.5)
Number of patients excluded from the PK Analysis Set	2 (12.5)

Abbreviations: FAS = Full Analysis Set; PD = pharmacodynamics; PK = pharmacokinetics;

PP = Per Protocol.

For the 14 patients in the full analysis set, the mean age at the time of first aHUS symptoms was 4.94 years (

Table). At baseline (within 5 days of the first dose of study drug), 5 (35.7%) of the 14 patients in the FAS had received kidney dialysis related to kidney failure caused by aHUS. One (7.1%) patient in the full analysis set had a kidney transplant related to aHUS prior to entering the. The majority of patients (11 of 16 patients) evaluated at baseline were CKD Stage 4 or 5, with 5 patients (35.7%) being Stage 5.

Table 10: Disease Characteristics (Full Analysis Set)

Characteristic	**ravulizumab (N = 14)**
Age (years) at time of first aHUS symptoms	
Mean (SD)	4.94 (3.081)
Median (min, max)	4.10 (0.8, 11.2)
Dialysis at baseline, n (%)	5 (35.7)
Any kidney transplant prior to entering the study[a], n (%)	1 (7.1)
Related to aHUS[b]	1 (100.0)
Baseline platelets (10^9/L) blood [normal range 229 to 533 10^9/L]	
Mean (SD)	60.50 (33.281)
Median (min, max)	64.00 (14, 125)
Baseline LDH (U/L) serum [normal range 165 to395 U/L]	
Mean (SD)	2324.11 (1361.515)
Median (min, max)	2077.00 (772, 4985)
Baseline hemoglobin (g/L) blood [normal range 107 to131 g/L]	
Mean (SD)	74.82 (19.516)
Median (min, max)	74.25 (32, 106)
Baseline eGFR (mL/min/1.73 m^2) [normal range $\geq$ 60 mL/min/1.73 m^2]	
Mean (SD)	28.4 (23.11)
Median (min, max)	22.0 (10, 84)
Baseline CKD stage, n (%)	
1	0
2	2 (14.3)
3A	1 (7.1)
3B	0
4	6 (42.9)
5	5 (35.7)

Abbreviations: aHUS = atypical hemolytic uremic syndrome; chronic kidney disease; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; LLN = lower limit of normal; max = maximum; min = minimum.

The majority (10/14; 71.4%) of patients had pretreatment extra-renal signs or symptoms of aHUS at baseline (Table).

Table 11: Pretreatment Extra-renal Signs or Symptoms of aHUS (Full Analysis Set)

Organ System **Sign or Symptom**	**ravulizumab** **(N = 14)** **n (%)**
Any pretreatment extra-renal signs or symptoms of aHUS	10 (71.4)
Cardiovascular	7 (50.0)
Hypertension	5 (35.7)
Sinus tachycardia	1 (7.1)
Pericardial effusion	1 (7.1)
Other	1 (7.1)
Pulmonary	1 (7.1)
Pulmonary hemorrhage	1 (7.1)
Pleural effusion	1 (7.1)
Central nervous system	5 (35.7)
Lethargy	3 (21.4)
Irritability	2 (14.3)
Headache	1 (7.1)
Seizures	1 (7.1)
Other	1 (7.1)
Gastrointestinal	8 (57.1)
Nausea	4 (28.6)
Vomiting	5 (35.7)
Abdominal pain	4 (28.6)
Elevated transaminases (ALT/AST)	4 (28.6)
Pancreatitis	1 (7.1)
Other	4 (28.6)
Skin	7 (50.0)
Petechiae	5 (35.7)
Other	4 (28.6)
Skeletal muscle	1 (7.1)
Myalgias	1 (7.1)
Other	1 (7.1)

Note: Extra-renal signs or symptoms of aHUS were evaluated by the Investigator using clinical laboratory measurements (*e.g.*, troponin I, amylase, and lipase), vital signs (*e.g.*, heart rate, respiratory rate, pulse oximetry), and an organ system review. In summarizing n (%), if a patient had multiple reports for a particular organ system/sign or symptom, he/she was counted only

once for that organ system/sign or symptom. Patients could have been counted in more than 1 organ system/sign or symptom category. Abbreviations: aHUS = atypical hemolytic uremic syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

All 14 patients in the full analysis set had a hospitalization and/or an emergency room visit due to aHUS prior to start of Screening as shown in Table 12. Prior to Screening, 6 (42.9%) patients had received ICU level care during hospitalizations due to aHUS with the mean (SD) duration of the ICU stay of 10.0 (18.63 days). At the time of the first dose of study drug, 13/14 (92.9%) patients were hospitalized due to aHUS.

Table 12: Emergency Room Visits and Hospitalization Due to aHUS Prior to Start of Screening (Full Analysis Set)

	ravulizumab (N = 14) n (%)
Any emergency room visits or hospitalizations, n (%)[a]	14 (100.0)
Visit type, n (%)[b]	
Emergency room visit	3 (21.4)
Hospitalization	13 (92.9)
ICU level of care, n (%)[b]	
Yes	6 (42.9)
No	8 (57.1)
Number of days of ICU stay	
n[c]	8
Mean (SD)	10.0 (18.63)
Median	4.0
Min, max	1, 56

Note: Patients may have been counted in both emergency room visit and hospitalization.
[a] Percentages were based on the total number of patients.
[b] Percentages were based on the total number of patients who had any emergency room visits or hospitalizations due to aHUS prior to the start of Screening.
[c] Patient could have had more than one ICU stay.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; ICU = intensive care unit; max = maximum; min = minimum.

All 16 patients had a history of prior medication use. The most commonly reported (≥ 15% of patients) groupings of prior medications included pneumococcal vaccines (87.5%), Hib vaccines (75%), meningococcal vaccines (50.0%), sulfonamides (43.8%), solutions affecting the electrolyte balance (37.5%), combined bacterial and viral vaccines (31.3%), benzodiazepine derivatives (31.3%), blood substitutes and plasma protein fractions (31.3%), electrolyte solutions

(31.3%), other general anesthetics (31.3%), anilides (25.0%), dihydropyridine derivatives (25.0%), H_2-receptor antagonists (25.0%), proton pump inhibitors (25.0%), alpha and beta blocking agents (18.8%), glucocorticoids (18.8%), opioid anesthetics (18.8%), other antianemic preparations (18.8%), potassium (18.8%), substituted alkylamines (18.8%), third-generation cephalosporins (18.8%), and other quaternary ammonium compounds (18.8%).

Prior to the study, 87.5% of the patients underwent a nonpharmacologic therapy or medical procedure within 28 days of screening. A total of 31.3% of the patients had pre-treatment plasma exchange/plasma infusion (PE/PI) related to the current TMA and 37.5% of the patients had kidney dialysis within 56 days prior to the first dose of study drug.

All of the patients took at least one concomitant medication. The most commonly reported ($\geq$ 15% of patients) groupings of concomitant medications were penicillins with extended spectrum (75.0%), anilides (68.8%), dihydropyridine derivatives (68.8%), meningococcal vaccines (68.8%), solutions affecting the electrolyte balances (62.5%), osmotically acting laxatives (56.3%), serotonin antagonists (50.0%), benzodiazepine derivatives (43.8%), electrolyte solutions (43.8%), enemas (43.8%), other general anesthetics (43.8%), plain ACE inhibitors (37.5%), glucocorticoids (37.5%), hydrazinophthalazine derivatives (37.5%), selective immunosuppressants (37.5%), plain sulfonamides (37.5%), first-generation cephalosporins (31.3%), H_2-receptor antagonists (31.3%), heparin group (31.3%), other antianemic preparations (31.3%), proton pump inhibitors (31.3%), third-generation cephalosporins (31.3%), vitamin D and analogues (31.3%), alpha and beta blocking agents (25.0%), anesthetics for topical use (25.0%), oral iron bivalent preparations (25.0%), mucolytics (25.0%), natural opium alkaloids (25.0%), phenylpiperidine derivatives (25.0%), pneumococcal vaccines (25.0%), selective beta-2-adrenoreceptor agonists (25.0%), amides (18.8%), plain angiotension II antagonists (18.8%), antibiotics (18.8%), beta-lactamase sensitive penicillins (18.8%), drugs for treatment of hyperkalemia and hyperphosphatemia (18.8%), fluoroquinolones (18.8%), influenza vaccines (18.8%), solutions for parenteral nutrition (18.8%), and magnesium (18.8%).

During the study, 93.8% of patients received nonpharmacologic therapies or medical procedures. None of the patients received PE/PI.

For the 14 patients in the full analysis set, the mean (SD) treatment duration was 24.51 (6.196) weeks and all patients received all of the planned infusions during the Initial Evaluation Period. The one patient who discontinued study drug was considered 100% compliant because she had no missed doses prior to the date of discontinuation. Infusion interruption due to an adverse event was reported for one patient.

B. Efficacy Results

With respect to efficacy, the primary efficacy endpoint of complete TMA response showed a proportion of response of 71.4% (10/14) with a 95% CI = (0.419, 0.916) during the 26-week Initial Evaluation Period as shown in FIG. 3 and Table 13. The criteria for Complete TMA Response are (1) normalization of platelet count, (2) Normalization of LDH and (3) ≥ 25% improvement in serum creatinine from baseline. Components of complete TMA response, as well as other secondary efficacy endpoints, also showed consistent results to cTMA response as shown in FIG. 4.

Table 13: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (Full Analysis Set)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	14	10	0.714 (0.419, 0.916)
Components of Complete TMA Response			
Platelet count normalization	14	13	0.929 (0.661, 0.998)
LDH normalization	14	12	0.857 (0.572, 0.982)
25% improvement in serum creatinine from Baseline	14	11	0.786 (0.492, 0.953)
Hematologic normalization	14	12	0.857 (0.572, 0.982)

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method. Abbreviations: CI = confidence intervals; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Patients must have met all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Hematologic normalization includes normalization of platelet count and normalization of LDH. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. When a patient was on dialysis at

baseline, then the first valid creatinine value to be used as the baseline value was the first assessment ≥ 6 days post-dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

With the exception of one patient who withdrew from the study after 2 doses of ravulizumab, all 13 patients achieved platelet count normalization during the Initial Evaluation Period as shown in Table 13. Twelve patients achieved LDH normalization and 11 patients achieved renal function improvement (defined as 25% reduction in serum creatinine from baseline) during the Initial Evaluation Period.

Among four patients who did not achieve Complete TMA Response, two patients achieved LDH and platelet count normalization and one patient achieved platelet count normalization and renal function improvement during the Initial Evaluation Period. The one patient who did not have improvement in any of the Complete TMA response components withdrew from the study due to an adverse event after receiving 2 doses of study drug.

A separate sensitivity analysis was performed using a modified version of Complete TMA Response. The modification applied strictly to the patients on dialysis at baseline. For the modified Complete TMA Response analysis, Complete TMA Response was observed a majority of these patients (71.4% [95% CI: 41.9%, 91.6%) in the FAS and PP Set.

The median time to Complete TMA Response during the Initial Evaluation Period was 30 days and occurred as early as 15 days following the first dose of ravulizumab as shown in FIG. 3. As shown in FIG. 5, the latest response was observed at Day 88 and all cTMA responses were sustained to Day 183. Patients who did not have a response were censored at the date of last visit or study discontinuation. One patient was censored at Day 21, one at Day 181 and two at Day 183.

The 10 patients who achieved the Complete TMA Response status had all done so by Day 85 as shown in Table 14 and FIG. 6. Nine of these responders had sustained their response status from the first time point when they achieved Complete TMA Response through the end of the 26-week Initial Evaluation Period. One patient achieved a Complete TMA Response at Day 15 and continued to meet the response criteria through the end of the 26-week Initial Evaluation Period, except at 1 visit time point (Day 71).

Table 14: Complete TMA Response Status Over Time With a Confirmatory Result (Full Analysis Set)

Visit		Overall (N = 14)
	n/m	Proportion (95% CI)[a]
Day 8	0/13	0.000 (0.000, 0.247)
Day 15	2/13	0.154 (0.019, 0.454)
Day 22	3/13	0.231 (0.050, 0.538)
Day 29	7/13	0.538 (0.251, 0.808)
Day 43	7/13	0.538 (0.251, 0.808)
Day 57	9/13	0.692 (0.386, 0.909)
Day 71	8/13	0.615 (0.316, 0.861)
Day 85	10/13	0.769 (0.462, 0.950)
Day 99	10/13	0.769 (0.462, 0.950)
Day 113	10/13	0.769 (0.462, 0.950)
Day 127	10/13	0.769 (0.462, 0.950)
Day 141	10/13	0.769 (0.462, 0.950)
Day 155	10/13	0.769 (0.462, 0.950)
Day 169	10/13	0.769 (0.462, 0.950)
Day 183	10/13	0.769 (0.462, 0.950)

[a] 95% CIs for the proportion are based on exact confidence limits using the Clopper-Pearson method. Abbreviations: CI = confidence interval; m = number of patients with a possible confirmatory result available at each visit; TMA = thrombotic microangiopathy.

With the exception of 1 patient who withdrew from the study after 2 doses of ravulizumab, all remaining 13 patients in the FAS achieved platelet count normalization as shown in FIG. 6. Platelet count normalization was achieved after the first dose of study drug (*i.e.*, by Day 15) for 12 patients; 9 patients at Day 8 and 3 patients at Day 15. The latest response was observed at Day 71 (n = 1). When platelet count normalization was achieved, it was sustained by all patients, with the exception of one patient who did not meet this criterion at a single time point and then platelet count normalization resumed for the remainder of the Initial Evaluation Period.

For the 12 patients who achieved LDH normalization, this was achieved by Day 15 for 4 patients as shown in FIG. 6. The latest response was observed at Day 99 (n = 1). When LDH normalization was achieved, it was sustained by all patients, with the exception of 2 patients who did not meet this criterion at a single time point (1 patient at Day 183; 1 patient transiently at Day 71 and then LDH count normalization resumed for the remainder of the Initial Evaluation Period).

For the 11 patients in the full analysis set that achieved renal function improvement, this improvement was achieved after the first dose of study drug (*i.e.*, by Day 15) for 6 patients; 5 patients by Day 8 and 1 patient by Day 15 as shown in FIG. 6. The latest response was observed at Day 57 (n = 1). All of the patients that met the criteria for the renal function improvement component sustained this response during the Initial Evaluation Period).

Hematologic normalization included normalization of platelet count and normalization of LDH. During the Initial Evaluation Period, hematologic normalization was observed in 12 of 14 patients (85.7% [95% CI: 57.2%, 98.2%]) as shown in Table 15 and FIG. 6.

Overall, patients in the full analysis set showed improvement in all of the hematologic TMA parameters (platelets, LDH and hemoglobin) during the Initial Evaluation Period with improvements in platelets and LDH observed starting on Day 8 and improvement in hemoglobin starting on Day 22.

The mean (SD) change from baseline in platelet count was 238.08 (154.402) at Day 8 and this mean increase was sustained over the duration of the Initial Evaluation Period (see FIG. 7).

The mean (SD) change from baseline in LDH was -1330.61 (952.371) at Day 8, and increased to -2111.88 (1350.886) at Day 29, and this mean decrease was sustained over the duration of the Initial Evaluation Period (see FIG. 8).

The mean (SD) change from baseline in hemoglobin was 10.79 (16.120) at Day 15, and increased to 36.13 (21.597) at Day 43, and this mean increase was sustained over the duration of the Initial Evaluation Period (see FIG. 9).

During the Initial Evaluation Period, 12 of the 14 patients in the full analysis set (85.7% [95% CI: 57.2%, 98.2%]) had an increase in hemoglobin of ≥ 20 g/L compared to baseline with a confirmatory result (*e.g.*, a hemoglobin response). Of the 13 patients that completed the 26 weeks of ravulizumab treatment, 12 patients had a hemoglobin response as of Day 99 as shown in Table 15.

Table 15: Hemoglobin Response With a Confirmatory Result (Full Analysis Set)

		Overall (N = 14)	
Parameter	Visit	n/m	Proportion (95% CI)[a]
Hemoglobin ≥ 20 g/L increase from baseline	Day 8	0/13	0.000 (0.000, 0.247)

Parameter	Visit	Overall (N = 14)	
		n/m	Proportion (95% CI)[a]
	Day 15	2/13	0.154 (0.019, 0.454)
	Day 22	6/13	0.462 (0.192, 0.749)
	Day 29	6/13	0.462 (0.192, 0.749)
	Day 43	9/13	0.692 (0.386, 0.909)
	Day 57	11/13	0.846 (0.546, 0.981)
	Day 71	11/13	0.846 (0.546, 0.981)
	Day 85	11/13	0.846 (0.546, 0.981)
	Day 99	12/13	0.923 (0.640, 0.998)
	Day 113	12/13	0.923 (0.640, 0.998)
	Day 127	12/13	0.923 (0.640, 0.998)
	Day 141	12/13	0.923 (0.640, 0.998)
	Day 155	12/13	0.923 (0.640, 0.998)
	Day 169	12/13	0.923 (0.640, 0.998)
	Day 183	12/13	0.923 (0.640, 0.998)

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method. Abbreviation: CI = confidence interval; m = number of patients with a possible confirmatory result available at each visit.

Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could have included results from Screening and the Day 1 visit). A patient was included in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed. Hemoglobin values obtained from the day of a blood transfusion of either whole blood or packed red blood cells through 7 days after the transfusion were excluded from all analyses.

FIG. 10 shows the dialysis status over time for the patients. Day 1 is the treatment start date. Five days prior to the treatment start date was used as the start. As shown in FIG. 10, four of five patients on dialysis at baseline were weaned off dialysis after 29 days or less of exposure to ravulizumab. No new patients initiated dialysis after starting treatment.

FIG. 11 depicts estimated glomerular filtration rate (EGFR) change from baseline, including the mean change and 95% confidence interval. Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from Screening and the Day 1 visit). For eGFR, 10 mL/min/1.73 m^2 was imputed for patients requiring dialysis for acute kidney injury. A mixed model for repeated measures (MMRM) was used. It included the fixed, categorical effect of visit and fixed,

continuous effect of the baseline value as covariates. A Toeplitz covariance structure was used to model the within patient errors. Observed values: mean ± 95% CI. Model based values: mean ± 95% CI.

Renal function, as assessed by mean (SD) eGFR, improved from 28.4 (23.11) mL/min/1.73m^2 at baseline to 108.0 (63.21) mL/min/1.73m^2 at the end of the Initial Evaluation Period. Results from the mixed model for repeated measures (MMRM) statistical analysis of the change in eGFR from baseline demonstrated improvements within 29 days of the start of ravulizumab treatment (see FIG. 11). One patient had a history of kidney transplant; this patient also had an improvement in eGFR during the Initial Evaluation Period compared to baseline (22.0 to 29.0 mL/min/1.73m2).

The majority of patients (11 of 14 patients) evaluated at baseline were chronic kidney disease (CKD) Stage 4 or 5, with 5 (35.7%) patients being Stage 5 as shown in Table 16. With the exception of 2 patients, all of these patients improved their CKD stage (*e.g.*, shifted to a lower CKD stages from baseline through the end of the Initial Evaluation Period (Day 183); the shift was substantial as 9 patients improved by 2 or more stages.

Table **16: CKD Stage Shift from Baseline to End of Initial Evaluation Period (26 Weeks** [Day 183]) (Full Analysis Set)

		Post-Baseline CKD Stage at Day 183 (N = 13)[a]					
Baseline CKD Stage	Baseline n (%)	1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	0	0	0	0	0	0	0
2	2 (14.3)	**1 (7.7)**	0	0	0	0	0
3A	1 (7.1)	**1 (7.7)**	**0**	0	0	0	0
3B	0	**0**	**0**	**0**	**0**	0	0
4	6 (42.9)	**3 (23.1)**	**1 (7.7)**	**1 (7.7)**	**0**	1 (7.7)	0
5	5 (35.7)	**3 (23.1)**	**1 (7.7)**	**0**	**0**	**0**	1 (7.7)
Total	14 (100.0)	8 (61.5)	2 (15.4)	1 (7.7)	0	1 (7.7)	1 (7.7)

[a] The percentages for the post-baseline CKD Stage at Day 183 are based on the 13 patients with available data.

Bold values in Table 16 indicate improvement compared to baseline and underlined values indicate worsening compared to baseline. Baseline was derived based on the last

available eGFR before starting treatment. Patients with both baseline and at least one value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR 15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).

At the end of the Initial Evaluation Period, 11 (84.6%) of 13 patients had improvement in CKD Stage compared to baseline as shown in Table 17. Three of these patients had improvement by 5 stages, 4 patients had improvement by 4 stages, 3 patients had improvement by 2 stages, and 1 patient improved by 1 stage.

Two patients had no improvement in the CKD Stage score during the Initial Evaluation Period. One of these patients had a history of kidney transplant prior to the study. None of the patients worsened in CKD Stage during the Initial Evaluation Period.

Table 17: Chronic Kidney Disease Stage Shift by Visit (Full Analysis Set)

Visit	Status[a]	Statistic	Overall (N = 14)
Day 1 83	Improved[b]	n/m	11/13
		Proportion (95% CI)[(d)]	0.846 (0.546, 0.981)
	Worsened[c]	n/m	0/8
		Proportion (95% CI)[(d)]	0.000 (0.000, 0.369)
	Stayed the Same	n/m	2/13
		Proportion (95% CI)[(d)]	0.154 (0.019, 0.454)

Note: CKD Stage 5 is considered the worst category, while Stage 1 is considered the best category. Baseline was derived based on the last available eGFR before starting treatment.
[a] Compared to CKD stage at baseline.
[b] Excluded those with Stage 1 at baseline as they cannot improve.
[c] Excluded those with Stage 5 at baseline as they cannot worsen.
[d] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
Abbreviations: CI = confidence interval; CKD = chronic kidney disease; m = number of patients available at each visit.

For the 8 treated patients who were > 5 years of age, Quality of Life (QoL) was assessed using the pediatric FACIT-Fatigue Questionnaire. Baseline was from the Day 1 value. Pediatric FACIT-Fatigue questionnaire was used. The pediatric FACIT-fatigue questionnaire at baseline

and each post-infusion timepoint was scored using standard scoring algorithms. A mixed model for repeated measures was used that included the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates. An unstructured covariance structure was used to model the within patient errors. FACIT score ranged from 0-52, with a higher score indicating less Fatigue. Observed values: mean ± 95% confidence interval (CI). Model based values: mean ± 95% CI.

During the Initial Evaluation Period, these 8 patients had a mean (SD) improvement in the pediatric FACIT-Fatigue score of 18.91 (14.988) compared to baseline as shown in FIG. 12. Three (37.5%) of 8 patients had a 3-point improvement in FACIT-Fatigue total score from baseline at Day 8, 7 (87.5%) patients had a 3-point improvement from baseline at Day 29, and all 8 patients had a 3-point improvement from baseline by Day 71.

C. Efficacy Conclusions

Ten of the 14 (71.4%) patients in the FAS (95% CI: 41.9%, 91.6%) achieved the primary efficacy endpoint, Complete TMA Response during the 26 week Initial Evaluation Period. Thirteen of 14 patients in the FAS achieved platelet count normalization during the Initial Evaluation Period. Twelve patients achieved LDH normalization and 11 patients achieved renal function improvement (defined as 25% reduction in serum creatinine from baseline) during the Initial Evaluation Period.

Results for secondary endpoints were as follows. The median time to Complete TMA Response was 30 days and the earliest response occurred by 15 days following the first dose of ravulizumab. For the 10 patients who achieved Complete TMA Response status, these responses were sustained through the end of the 26 week Initial Evaluation Period.

Hematologic normalization, defined as normalization of both LDH and platelets, was observed in 12 of 14 patients (85.7% [95% CI: 57.2%, 98.2%]).

Twelve of the 14 patients in the full analysis set (85.7% [95% CI: 57.2%, 98.2%]) had an increase in hemoglobin of $\geq$ 20 g/L compared to baseline with a confirmatory result.

Dialysis was discontinued in 4 of 5 patients who had been receiving dialysis at baseline. All 4 of these patients discontinued dialysis within the first 29 days of exposure to ravulizumab. No patients initiated dialysis after starting treatment with ravulizumab.

Renal function, as assessed by eGFR, improved from a mean of 28.4 mL/min/1.73m^2 at baseline to 108.0 mL/min/1.73m^2 at the end of the Initial Evaluation Period. Most patients had improvement of at least 1 CKD Stage compared to baseline.

Three (37.5%) of 8 patients (*e.g.*, those > 5 years of age) had at least a 3 point improvement in FACIT-Fatigue total score from baseline at Day 8, 7 (87.5%) patients had at least a 3 point improvement from baseline at Day 29, and all 8 patients had at least a 3 point improvement from baseline by Day 71.

D. Pharmacokinetic and Pharmacodynamic Results

All patients in the full analysis set were included in the PK/PD) Analysis Set. The mean (SD) ravulizumab serum concentration by dosing interval (*e.g.*, q4w and q8w) versus time profile (linear scale) is presented in FIG. 13.

Pharmacokinetic parameters for ravulizumab are summarized by dosing interval in Table 18 and Table 19 for the loading and last maintenance doses, respectively. Following the first loading dose mean (SD) C_{max} was 656.4 (250.3) and 599.8 (103.8) µg/mL for the q4w and q8w dosing interval groups, respectively, and C_{trough} was 240.7 (125.4) and 185.6 (30.7) µg/mL, respectively. Following the last maintenance dose mean (SD) C_{max} was 1466.6 (554.4) and 1863.3 (284.6) µg/mL for the q4w and q8w dosing interval groups, respectively, and C_{trough} was 682.9 (315.1) and 549.3 (187.4) µg/mL, respectively. The exposures in patients weighing < 20 kg (q4w) and ≥ 20 kg (q8w) were similar.

Table 1: ravulizumab PK Parameters (C_{max} and C_{trough}) Following the First (Loading) Dose of ravulizumab by Dosing Interval (q4w and q8w) (PK/PD Analysis Set)

Parameter	Statistics	q4w (< 20 kg)	q8w (≥ 20 kg)
C_{max} (µg/mL)	n	8	4
	Mean (SD)	656.4 (250.3)	599.8 (103.8)
	CV%	38.1	17.3
	Median (min, max)	594.0 (270, 1020)	555.5 (534, 754)
C_{trough} (µg/mL)	n	9	5
	Mean (SD)	240.7 (125.4)	185.6 (30.705)
	CV%	52.1	16.5
	Median (min, max)	227.0 (57.9, 432)	181.0 (142, 217)

Abbreviations: C_{max} = maximum serum concentration; C_{trough} = trough serum concentration; CV = coefficient of variation; max = maximum; min = minimum; q4w =once every 4 weeks; q8w = once every 8 weeks; SD = standard deviation

Table 2: ravulizumab PK Parameters (C_{max} and C_{trough}) Following the Final Maintenance Dose of ravulizumab by Dosing Interval (Q4W and Q8W) (PK/PD Analysis Set)

Parameter	Statistics	q4w (< 20 kg)	q8w (≥ 20 kg)
C_{max} (µg/mL)	n	7	6
	Mean (SD)	1466.6 (554.4)	1863.3 (284.6)
	CV%	37.8	15.3
	Median (min, max)	1510.0 (760, 2240)	1890.0 (1490, 2280)
C_{trough} (µg/mL)	n	7	6
	Mean (SD)	682.9 (315.1)	549.3 (187.4)
	CV%	46.1	34.1
	Median (min, max)	732.0 (193, 1090)	556.0 (280, 790)

Abbreviations: C_{max} = maximum serum concentration; C_{trough} = trough serum concentration; CV = coefficient of variation; max = maximum; min = minimum; q4w =once every 4 weeks; q8w = once every 8 weeks; SD = standard deviation.

Final maintenance dose was administered on Day 155 for the < 20 kg group and on Day 127 for the ≥ 20 kg group.

Noncompartmental PK parameters following the last maintenance dose of ravulizumab are presented by dosing interval in Table 20.

Table 20: Summary of ravulizumab Noncompartmental Analysis of PK Parameters Following the Last Maintenance Dose of ravulizumab by Dosing Interval(Q4W and Q8W) (PK/PD Analysis Set)

PK Parameter (Unit)	q4w (< 20 kg)	q8w (≥ 20 kg)
	Mean ± SD (%CV)	Mean ± SD (%CV)
n	7[a]	6
t_{max} (h)[b]	2.4 ± 0.22 (9.2)	3.745 ± 0.47 (12.6)
C_{max} (µg/mL)[b]	1466.6 ± 554.4 (37.8)	1863.3 ± 284.6 (15.3)
C_{trough} (µg/mL)	682.9 ± 315.1 (46.1)	549.3 ± 187.4 (34.1)
AUC_τ (h·µg/mL)	ND[c]	1309000.0 ± 252265.7 (19.3)
CL (mL/h)	ND[c]	1.2 ± 0.3 (27.7)
V_z (mL)	ND[c]	1548.3 ± 213.7 (13.8)

[a] Patient 0199-701 who was switched from q4w to q8w dosing regimen on Visit Day 127 based on body weight in assignment; Patient 0411-702 who discontinued after Day 15.
[b] t_{max} values are presented as median (minimum, maximum).
[c] These PK parameters could be not derived due to limited data points after C_{max}.
Abbreviations: AUC_τ = area under the serum concentration versus time curve over the dosing interval; C_{max} = maximum observed serum concentration; C_{trough} = concentrations at the end of the dosing interval; CL = total clearance; CV = coefficient of variation; ND = not determined; q4w = once every 4 weeks; q8w = once every 8 weeks; SD = standard deviation; t_{max} = time to maximum observed serum concentration; V_z = volume of distribution at steady state

Steady state was achieved following weight-based q4w and q8w maintenance dosing of ravulizumab as shown in Table 21.

Table 21: Assessment of ravulizumab PK Steady State Attainment by Dosing Interval (Q4W and Q8W) (PK/PD Analysis Set)

Steady State Attainment	Dosing Interval Group	Slope	Lower 95% CI	Upper 95% CI	Steady State Reached?
Days 43, 71, 99, 127, 155, 183	q4w (< 20 kg)	0.00303	-0.00042279	0.00649	Yes
Days 15, 71, 127, 183	q8w (≥ 20 kg)	0.00028792	-0.00007662	0.00065245	Yes
Days 71, 127, 183	All Patients	0.00126	-0.00267	0.00519	Yes

Abbreviations: CI = confidence interval; q4w = once every 4 weeks; q8w = once every 8 weeks.

FIG. 14 presents box plots of serum free C5 concentrations versus time profiles by dosing interval. Following weight-based dosing, ravulizumab treatment resulted in immediate and complete terminal complement inhibition (free C5 < 0.5 µg/mL) and sustained throughout the

entire treatment period for all patients at all times with the exception of a single patient from the ≥ 5 to < 10 kg body weight group at Day 15.

A prespecified initial analysis of PK/PD data in 9 patients (CPR-0019.00) was conducted to assess the suitability of the pediatric dosing. The modeling and simulation results supported all pediatric dosing with the exception of the loading dose in patients weighing ≥ 5 to < 10 kg. Consequently, the loading dose was increased from 300 mg to 600 mg (with no change to the maintenance dosing of 300 mg q4w) in this body weight group.

The mean (95% CI) total serum C5 concentration versus time profile is presented by weight based dosing regimen in FIG. 15. The rate and magnitude of change in serum total C5 was similar between groups.

E. Pharmacokinetic and Pharmacodynamic Conclusions

Following ravulizumab weight-based dosing, steady-state was achieved for both dosing intervals and across all pediatric patients.

Immediate and complete terminal complement inhibition was achieved (defined as free C5 < 0.5) and sustained throughout the entire treatment period for all patients at all times with the exception of a single patient at Day 15.

Based on an initial PK/PD analysis as described in the protocol, conducted to assess the suitability of the pediatric dosing, the loading dose in patients from ≥ 5 to < 10 kg body weight has been increased to 600 mg from 300 mg; the dose regimen in all other pediatric weight groups is appropriate.

F. Safety

Exposure to ravulizumab, including follow-up duration, treatment duration, and number of infusions per patient, is summarized in Table . Except for 3 patients who were withdrawn from the study prior to Day 183, all patients received all planned infusions according to the protocol-specified visit schedule and a full dose at each visit during the Initial Evaluation Period. A change to the dose regimen based on patient's body weight was made for 1 patient, whose weight increased to 20.4 kg on Day 113 (Dose Regimen Decision Day).

The median duration of treatment was 26.14 weeks (range: 1 to 26.6 weeks), and all patients were compliant with treatment. Two patients in the weight range of ≥ 5 to < 10 kg

received a loading dose of 300 mg, rather than 600 mg, as the patients were enrolled before an Amendment to the protocol was effective.

Table 22: Treatment Exposure and Follow-up Duration: Initial Evaluation Period (Safety Set)

Parameter	Birth to < 6 years (N = 9)	6 to < 18 years (N = 7)	Overall (N = 16)
Follow-up duration[a] (weeks)			
N	9	7	16
Mean (SD)	23.63 (7.742)	19.06 (12.001)	21.63 (9.750)
Median	26.29	26.00	26.14
Min, max	3, 26.5714	1, 26.2857	1, 26.5714
Q1, Q3	25.86, 26.29	2.00, 26.14	25.86, 26.29
Treatment duration[b] (weeks)			
n	9	7	16
Mean (SD)	23.64 (7.745)	19.06 (11.998)	21.64 (9.752)
Median	26.30	26.00	26.10
Min, max	3, 26.6	1, 26.3	1, 26.6
Q1, Q3	25.90, 26.30	2.00, 26.10	25.90, 26.30
Number of infusions			
1	0 (0.0)	2 (28.6)	2 (12.5)
2	1 (11.1)	0 (0.0)	1 (6.3)
4	0 (0.0)	5 (71.4)	5 (31.3)
6	1 (11.1)	0 (0.0)	1 (6.3)
7	7 (77.8)	0 (0.0)	7 (43.8)
Compliance, n (%)			
≥ 100%	9 (100.0)	7 (100.0)	16 (100.0)

[a] Follow-up duration is defined as the number of weeks from date of first dose to completion of study/ last available study visit/ study discontinuation + 1 day.

[b] Treatment duration is defined as ([the date of last dose + 56 days] – [the date of first dose]) or ([study discontinuation date] – [the date of first dose]), if study discontinuation date is earlier than (the date of last dose + 56 days). The result is presented in weeks.

Abbreviations: max = maximum; min = minimum; Q1 = 25th percentile; Q3 = 75th percentile. q4w = once every 4 weeks.

Percentages are based on the number of patients with non-missing data in each group. Patients received a weight-based loading dose of ravulizumab on Day 1, followed by weight-based maintenance treatment on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, for a total of 26 weeks of treatment. Weight-based dosing is based on the patient's body weight recorded on Dose Regimen Decision

Days. Dosing on Day 183 represents the start of the Extension Period and is not included in these calculations.

Exposure to ravulizumab, including follow-up duration, treatment duration, and number of infusions per patient, is summarized in Table . Except for 3 patients who were withdrawn from the study prior to Day 183, all patients received all planned infusions according to the protocol-specified visit schedule and a full dose at each visit during the Initial Evaluation Period. A change to the dose regimen based on patient's body weight was made for 1 patient, whose weight increased to 20.4 kg on Day 113 (Dose Regimen Decision Day).

The median duration of treatment was 26.14 weeks (range: 1 to 26.6 weeks), and all patients were compliant with treatment. Two patients in the weight range of ≥ 5 to < 10 kg received a loading dose of 300 mg, rather than 600 mg, as the patients were enrolled before an amendment to the protocol was effective.

During the Initial Evaluation Period, 15 (93.8%) of patients experienced at least 1 adverse event (162 events) as indicated in Table 23. Eight (50%) patients reported adverse events that were assessed by the investigator to be related to study drug.

The majority of patients experienced adverse events that were Grade 1 or Grade 2 in severity. Three (18.8%) patients experienced adverse events of Grade 3 severity. One patient in the 6 to < 18 years age group experienced an adverse event of Grade 4 severity (neutrophil count decreased).

Eight (50%) patients experienced a serious adverse event during the Initial Evaluation Period. One patient (< 6 years age group) withdrew from the study due to SAEs (hypertensive crisis and anemia) during the Initial Evaluation Period.

Three patients experienced non-serious AEs during infusion of study drug (hypertension in 2 patients and dizziness in 1 patient). Hypertension in 1 patient (Day 15) was of Grade 2 severity and treatment was interrupted for 10 minutes. The infusion was then restarted and the full dose was completed. The AE was resolving as of the data cutoff date of this report. The other 2 AEs were of Grade 1 severity, did not require interruption of infusion, and resolved during the Initial Evaluation Period.

No death was reported. No meningococcal infection was reported.

Table 23: Overall Treatment-Emergent Adverse Events During the Initial Evaluation Period (Safety Set)

	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
Adverse Event Categories	n (%)	E	n (%)	E	n (%)	E
Any AE	8 (88.9)	70	7 (100.0)	92	15 (93.8)	162
Any SAE	3 (33.3)	6	5 (71.4)	7	8 (50.0)	13
Deaths	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs resulting in study drug discontinuations	1 (11.1)	2	0 (0.0)	0	1 (6.3)	2
SAEs resulting in study drug discontinuations	1 (11.1)	2	0 (0.0)	0	1 (6.3)	2
AEs resulting in study withdrawal	1 (11.1)	2	0 (0.0)	0	1 (6.3)	2
SAEs resulting in study withdrawal	1 (11.1)	2	0 (0.0)	0	1 (6.3)	2
Relationship to study drug[a]						
Related AEs	4 (44.4)	8	4 (57.1)	14	8 (50.0)	22
Not related AEs	8 (88.9)	62	7 (100.0)	78	15 (93.8)	140
Severity						
Grade 1	7 (77.8)	46	6 (85.7)	74	13 (81.3)	120
Grade 2	6 (66.7)	19	5 (71.4)	14	11 (68.8)	33
Grade 3	2 (22.2)	5	1 (14.3)	3	3 (18.8)	8
Grade 4	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Grade 5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

[a] Related AEs include AEs classified as possibly, probably, or definitely related. Not related AEs include AEs classified as not related or unlikely related.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = total number of events; SAE = serious adverse event.

The most frequently reported AE was pyrexia (5 [31.3%] patients), which was of Grade 1 or Grade 2 severity in all 5 patients) and did not occur during study drug administration (see Table 24). Other events reported by 3 (18.8%) or more patients were pyrexia, constipation, vomiting, hypertension, headache, diarrhea and nasopharyngitis.

Table 24: Treatment-Emergent Adverse Events Experienced by 2 or More Patients Overall During the Initial Evaluation Period, by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
	n (%)	E	n (%)	E	n (%)	E
Any TEAE	8 (88.9)	70	7 (100.0)	92	15 (93.8)	162
Gastrointestinal disorders						
Constipation	3 (33.3)	5	1 (14.3)	1	4 (25.0)	6
Vomiting	2 (22.2)	6	2 (28.6)	11	4 (25.0)	17
Diarrhoea	2 (22.2)	3	1 (14.3)	1	3 (18.8)	4
Abdominal pain	0 (0.0)	0	2 (28.6)	4	2 (12.5)	4
Nausea	0 (0.0)	0	2 (28.6)	3	2 (12.5)	3
Infections and infestations						
Nasopharyngitis	2 (22.2)	3	1 (14.3)	1	3 (18.8)	4
Tonsillitis	2 (22.2)	2	0 (0.0)	0	2 (12.5)	2
Upper respiratory tract infection	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Vascular disorders						
Hypertension	2 (22.2)	2	2 (28.6)	3	4 (25.0)	5
Hypotension	0 (0.0)	0	2 (28.6)	2	2 (12.5)	2
General disorders and administration site conditions						
Pyrexia	2 (22.2)	8	3 (42.9)	7	5 (31.3)	15
Investigations						
Vitamin D decreased	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Blood and lymphatic system disorders						

System Organ Class Preferred Term	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
	n (%)	E	n (%)	E	n (%)	E
Anaemia	1 (11.1)	2	1 (14.3)	1	2 (12.5)	3
Lymphadenopathy	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Metabolism and nutrition disorders						
Iron deficiency	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Musculoskeletal and connective tissue disorders						
Myalgia	1 (11.1)	1	1 (14.3)	2	2 (12.5)	3
Nervous system disorders						
Headache	0 (0.0)	0	4 (57.1)	10	4 (25.0)	10
Injury, poisoning and procedural complications						
Contusion	0 (0.0)	0	2 (28.6)	4	2 (12.5)	4

Abbreviations: AE = adverse event; PT = Preferred Term; SOC = System Organ Class.

During the Initial Evaluation Period, 8 (50%) patients reported AEs assessed as related to study drug by the Investigator. None of the related AE preferred terms occurred in more than 1 patient.

During the Initial Evaluation Period, the majority of patients experienced AEs that were Grade 1 (4 [25%] patients) or Grade 2 (8 [50%] patients]) in severity. Three (18.8%) patients experienced Grade 3 events that were reported as SAEs.

One patient had a Grade 4 AE of neutrophil count decreased, but this AE did not require specific treatment or interruption or discontinuation of study drug. This patient also had a Grade 3 AE of pleural effusion, which resolved within 9 days of onset.

During the Initial Evaluation Period, 8 (50.0%) patients experienced SAEs as shown in Table 25. SAEs were reported most frequently in the system organ class of infections and infestations (4 [25.0%] patients), followed by the SOC of gastrointestinal disorders (3 [18.8%] patients) and vascular disorders (2 [12.5%] patients). Apart from abdominal pain,

which was reported by 2 (12.5%) patients, other SAEs were reported in no more than 1 patient. An overview of SAEs is provided in Table .

Table 25: Treatment-Emergent SAEs During the Initial Evaluation Period, by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
	n (%)	E	n (%)	E	n (%)	E
Any SAE	3 (33.3)	6	5 (71.4)	7	8 (50.0)	13
Infections and infestations	2 (22.2)	3	2 (28.6)	2	4 (25.0)	5
Cytomegalovirus enteritis	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Escherichia bacteraemia	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Escherichia pyelonephritis	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Gastroenteritis rotavirus	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Viral infection	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Gastrointestinal disorders	1 (11.1)	1	2 (28.6)	2	3 (18.8)	3
Abdominal pain	0 (0.0)	0	2 (28.6)	2	2 (12.5)	2
Pancreatitis	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Vascular disorders	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Hypertension	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Hypertensive crisis	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Blood and lymphatic system disorders	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
Anaemia	1 (11.1)	1	0 (0.0)	0	1 (6.3)	1
General disorders and administration site conditions	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Pyrexia	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1
Pulmonary haemorrhage	0 (0.0)	0	1 (14.3)	1	1 (6.3)	1

Abbreviations: PT = Preferred Term; SOC = System Organ Class.

Table 26: Overview of All Treatment-Emergent SAEs (Safety Set)

Patient ID	Serious Adverse Events (Preferred Term)	Onset Day/Resolution Day	Led to Discontinuation (Yes/No)	Relatedness to RAVULIZUMAB
Birth to < 6 years				
A	Escherichia pyelonephritis	20/24	No	Possibly related

Patient ID	Serious Adverse Events (Preferred Term)	Onset Day/Resolution Day	Led to Discontinuation (Yes/No)	Relatedness to RAVULIZUMAB
Birth to < 6 years				
	Escherichia bacteraemia	20/24	No	Possibly related
	Pancreatitis	129/132	No	Unlikely related
B	Viral infection	9/10	No	Unlikely related
C	Anaemia	20/37	Yes	Possibly related
	Hypertensive crisis	9/37	Yes	Not related
6 to < 18 years				
D	Cytomegalovirus enteritis	8/Ongoing	No	Not related
E	Abdominal pain	29/30	No	Not related
F[a]	Abdominal pain	35/41	Not applicable	Not related
G	Pulmonary haemorrhage	38/39	No	Unlikely related
H	Pyrexia	3/10	No	Possibly related
	Hypertension	3/12	No	Unlikely related
	Gastroenteritis rotavirus	85/88	No	Unlikely related

[a.] Note: This patient was withdrawn from the study on Day 14 because post-treatment the patient was deemed to be ineligible for participation.

Anemia and hypertensive crisis in 1 patient resulted in discontinuation of study drug and withdrawal from the study.

All SAEs resolved during the Initial Evaluation Period, except for cytomegalovirus enteritis, which was reported as ongoing at data cut off.

During the Initial Evaluation Period, 1 patient (1.8 years of age, 9 kg body weight) experienced AEs (hypertensive crisis and anemia) that led to discontinuation of study drug and withdrawal from the study. The patient had a history of hypertension and developed hypertensive crisis on Day 9. Anemia (verbatim: worsening anemia) occurred on Day 20. Both events were SAEs of Grade 3 severity. The patient was withdrawn from the study on Day 21 and was started on eculizumab 600 mg on the same day. The AEs resolved on Day 37. Anemia was assessed to be possibly related to study drug by the Investigator and hypertensive crisis was assessed as not related to study drug.

During the Initial Evaluation Period, 1 patient (0.9 years of age) experienced non-serious Grade 2 hypertension that resulted in interruption of the infusion. The patient's systolic BP at Screening, Baseline, and Day 15 (pre-dose) was 90 mmHg. On Day 15, during the infusion, the BP value was not reported. The infusion was interrupted for 10 minutes due to hypertension. The infusion was then restarted, and the full dose was completed. The patient started receiving antihypertensive drugs. The patient's systolic BP ranged between 85 mmHg to 100 mmHg during the subsequent visits. The adverse event was reported as resolving as of the data cutoff date of this report. The diastolic BP was within the normal range throughout the Initial Evaluation Period except on 2 occasions, when the values were reported as 70 mm Hg (Day 54) and 55 mm Hg (Day 85).

Meningococcal infections were considered AEs of special interest (AESIs) for this study During the Initial Evaluation Period, no meningococcal infections were reported. No deaths were reported during the Initial Evaluation Period.G. Discussion and Overall Conclusion

This is an interim analysis of data from 16 complement inhibitor-naïve pediatric patients (2 patients aged < 2 years, 7 patients aged 2 to < 6 years, 5 patients aged 6 to < 12 years, and 2 patients 12 to < 18 years) with aHUS who received ravulizumab during a 26-week treatment period. Two patients were withdrawn prematurely after 1 dose of study drug because they were confirmed to be ineligible based on central laboratory results, thus the FAS consists of 14 patients.

These 14 pediatric patients were extremely ill at baseline: 13/14 (92.9%) were hospitalized when they received their first dose of study drug, 11 (78.6%) had advanced kidney disease (CKD Stage 4 or 5), and 10 (71.4%) had extra-renal signs or symptoms. Five (35.7%) patients were on dialysis at baseline, and 1 (7.1%) had a kidney transplant prior to the study.

The primary endpoint, Complete TMA Response at Week 26, was achieved by 10 of 14 patients (71.4%; 95% CI: 41.9%, 91.6%). This compares favorably to the pivotal eculizumab study (C10-003) in pediatric patients, in which this endpoint was reached by 14 of 22 patients (64%; 95% CI: 41%, 83%). For the 10 patients who achieved Complete TMA Response, this endpoint was achieved rapidly (median 30 days) and was sustained over time. These results demonstrate the adequacy of the dose regimen used in this study, as well as the clinical benefits

of the immediate, complete, and sustained complement inhibition provided by ravulizumab treatment.

Most of the patients were between the ages of 2 and 11 years, with 2 patients under 2 years of age. Results from an interim PK/PD analysis showed that the loading dose in the smallest patients (≥ 5 to < 10 kg) was insufficient. One of these 2 patients was withdrawn on Day 21 due to SAEs of hypertensive crisis and anemia; the investigator immediately started this patient on high-dose eculizumab. The protocol has since been amended with a larger loading dose in this weight group.

All 13 (93%) of the patients who completed the Initial Evaluation Period achieved platelet count normalization by Week 26. In addition, 12 patients (86%) achieved LDH normalization and 11 patients (79%) achieved renal function improvement (defined as 25% improvement in serum creatinine from baseline). Improvement in renal function was also evident in shifts to lower CKD stage severity in all but 2 patients. The mean (SD) increase in EGFR from baseline was 84 (60) mL/min/1.73 m2. Immediate, complete and sustained suppression of free C5 was observed throughout the dosing interval. Furthermore, 4 of the 5 patients who were on dialysis at baseline where able to discontinue dialysis within several weeks of initiating ravulizumab, and no patients needed to initiate dialysis while on study. These functional improvements were reflected in clinically meaningful improvements in QoL, as demonstrated by higher FACIT-Fatigue scores over time.

There were no safety findings of concern during the Initial Evaluation Period among the 16 patients in the Safety Set. No deaths, meningococcal infections, or treatment-emergent immunogenicity were observed. The most frequent SAE was abdominal pain (2 patients). The weight-based dose regimen of ravulizumab appeared to be well-tolerated in pediatric patients with aHUS who were naïve to complement inhibitor treatment.

This analysis of data from the Initial Evaluation Period for the first 16 patients enrolled demonstrates that ravulizumab provided immediate, complete and sustained inhibition of terminal complement in this pediatric aHUS population. Complete TMA Response was achieved by Week 26 in 71.4% of patients, with consistent results observed for response components, as well as other secondary efficacy endpoints. Decreased disease burden was also evident in improved QoL scores and reduced need for dialysis and improved QoL scores.

Ravulizumab was generally well tolerated in these complement inhibitor treatment naïve patients. In sum, this interim analysis shows that in children treated for aHUS, weight based ravulizumab administered every 4 to8 weeks resulted in improved haematological and renal endpoints with no unexpected safety concerns. The favorable benefit/risk profile of ravulizumab in this study supports its use for the treatment pediatric patient with aHUS.

SEQUENCE SUMMARY

SEQ ID NO:1 GYIFSNYWIQ
SEQ ID NO:2 EILPGSGSTEYTENFKD
SEQ ID NO:3 YFFGSSPNWYFDV
SEQ ID NO:4 GASENIYGALN
SEQ ID NO:5 GATNLAD
SEQ ID NO:6 QNVLNTPLT
SEQ ID NO:7 QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS
SEQ ID NO:8 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIK
SEQ ID NO:9 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK
SEQ ID NO:10 QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST

YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK
SEQ ID NO:11 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
SEQ ID NO:12 QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SS
SEQ ID NO:13 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN VFSCSVLHEA LHSHYTQKSL SLSLGK
SEQ ID NO:14 QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVLH EALHSHYTQK SLSLSLGK
SEQ ID NO:15 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VTSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL YITREPEVTC VVVDVSHEDP EVQFNWYVDG MEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK
SEQ ID NO:16 QVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVTSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD

TLYITREPEV TCVVVDVSHE DPEVQFNWYV DGMEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP APIEKTISKT KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
SEQ ID NO:17 GASENIYHALN
SEQ ID NO:18 EILPGSGHTEYTENFKD
SEQ ID NO:19 GHIFSNYWIQ
SEQ ID NO:20 QVQLVQSGAE VKKPGASVKV SCKASGHIFS NYWIQWVRQA PGQGLEWMGE ILPGSGHTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK
SEQ ID NO:21 SYAIS
SEQ ID NO:22 GIGPFFGTANYAQKFQG
SEQ ID NO:23 DTPYFDY
SEQ ID NO:24 SGDSIPNYYVY
SEQ ID NO:25 DDSNRPS
SEQ ID NO:26 QSFDSSLNAEV
SEQ ID NO:27 QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISVWRQA PGQGLEWMGG IGPFFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDT PYFDYWGQGT LVTVSS
SEQ ID NO:28 DIELTQPPSV SVAPGQTARI SCSGDSIPNY YVYWYQQKPG QAPVLVIYDD SNRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQSF DSSLNAEVFG GGTKLTVL
SEQ ID NO:29 NYIS
SEQ ID NO:30 IIDPDDSYTEYSPSFQG
SEQ ID NO:31

YEYGGFDI
SEQ ID NO:32 SGDNIGNSYVH
SEQ ID NO:33 KDNDRPS
SEQ ID NO:34 GTYDIESYV
SEQ ID NO:35 EVQLVQSGAE VKKPGESLKI SCKGSGYSFT NYISWVRQMP GKGLEWMGII DPDDSYTEYS PSFQGQVTIS ADKSISTAYL QWSSLKASDT AMYYCARYEY GGFDIWGQGT LVTVSS
SEQ ID NO:36 SYELTQPPSV SVAPGQTARI SCSGDNIGNS YVHWYQQKPG QAPVLVIYKD NDRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCGTY DIESYVFGGG TKLTVL
SEQ ID NO:37 SSYYVA
SEQ ID NO:38 AIYTGSGATYKASWAKG
SEQ ID NO:39 DGGYDYPTHAMHY
SEQ ID NO:40 QASQNIGSSLA
SEQ ID NO:41 GASKTHS
SEQ ID NO:42 QSTKVGSSYGNH
SEQ ID NO:43 QVQLVESGGG LVQPGGSLRL SCAASGFTSH SSYYVAWVRQ APGKGLEWVG AIYTGSGATY KASWAKGRFT ISKDTSKNQV VLTMTNMDPV DTATYYCASD GGYDYPTHAM HYWGQGTLVT VSS
SEQ ID NO:44 DVVMTQSPSS LSASVGDRVT ITCQASQNIG SSLAWYQQKP GQAPRLLIYG ASKTHSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYCQS TKVGSSYGNH FGGGTKVEIK
SEQ ID NO:45 QVQLVESGGG LVQPGRSLRL SCAASGFTVH SSYYMAWVRQ APGKGLEWVG AIFTGSGAEY KAEWAKGRVT ISKDTSKNQV VLTMTNMDPV DTATYYCASD AGYDYPTHAM HYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL RRGPKVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVLHEALHA HYTRKELSLS

P
SEQ ID NO:46 DIQMTQSPSS LSASVGDRVT ITCRASQGIS SSLAWYQQKP GKAPKLLIYG ASETESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN TKVGSSYGNT FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC

CLAIMS

1. A method of treating a human pediatric patient with Atypical Hemolytic Uremic Syndrome (aHUS), the method comprising administering to the patient an effective amount of an anti-C5 antibody or antigen binding fragment thereof, comprising CDR1, CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, and CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs: 4, 5 and 6, respectively, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered:

(a) once on Day 1 at a loading dose of:

i. 600 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 900 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg,

v. 2400 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3000 mg to a patient weighing ≥ 100 kg; and

(b) on Day 15 at a maintenance dose of:

i. 300 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg,

v. 3000 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3600 mg to a patient weighing ≥ 100 kg;

wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter.

2. A method of treating a human pediatric patient with Atypical Hemolytic Uremic Syndrome (aHUS), the method comprising administering to the patient an effective amount of an anti-C5 antibody or antigen binding fragment thereof, comprising CDR1,

CDR2 and CDR3 heavy chain sequences as set forth in SEQ ID NOs:19, 18 and 3, respectively, CDR1, CDR2 and CDR3 light chain sequences as set forth in SEQ ID NOs:4, 5 and 6, respectively, and a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn), wherein the variant human Fc CH3 constant region comprises Met429Leu and Asn435Ser substitutions at residues corresponding to methionine 428 and asparagine 434, each according to the EU numbering convention, wherein the anti-C5 antibody or antigen binding fragment thereof, is administered:

(a) once on Day 1 at a loading dose of:

i. 600 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 900 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg,

v. 2400 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3000 mg to a patient weighing ≥ 100 kg; and

(b) on Day 15 at a maintenance dose of:

i. 300 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg,

v. 3000 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3600 mg to a patient weighing ≥ 100 kg;

wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter.

3. The method of Claim 1 or 2, wherein the anti-C5 antibody comprises a heavy chain variable region set forth in SEQ ID NO:12 and a light chain variable region set forth in SEQ ID NO:8.

4. The method of any one of the preceding claims, wherein the anti-C5 antibody further comprises a heavy chain constant region set forth in SEQ ID NO:13.

5. The method of any one of the preceding claims, wherein the antibody comprises a heavy chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:14 and a light chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:11.

6. The method of any one of the preceding claims, wherein the anti-C5 antibody binds to human C5 at pH 7.4 and 25C with an affinity dissociation constant (K_D) that is in the range 0.1 nM to 1 nM.

7. The method of any one of the preceding claims, wherein the anti-C5 antibody binds to human C5 at pH 6.0 and 25C with a $K_D \geq 10$ nM.

8. The method of any one of the preceding claims, wherein the anti-C5 antibody is administered to a patient weighing ≥ 5 to < 10 kg:
   (a) once on Day 1 at a loading dose of 600 mg; and
   (b) once on Day 15 at a maintenance dose of 300 mg and every four weeks thereafter.

9. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 10 to < 20 kg:
   (a) once on Day 1 at a loading dose of 600 mg; and
   (b) once on Day 15 at a maintenance dose of 600 mg and every four weeks thereafter.

10. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 20 to < 30 kg:
   (a) once on Day 1 at a loading dose of 900 mg; and
   (b) once on Day 15 at a maintenance dose of 2100 mg and every eight weeks thereafter.

11. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 30 to < 40 kg:
   (a) once on Day 1 at a loading dose of 1200 mg; and
   (b) once on Day 15 at a maintenance dose of 2700 mg and every eight weeks thereafter.

12. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 40 to < 60 kg:
    (a) once on Day 1 at a loading dose of 2400 mg; and
    (b) once on Day 15 at a maintenance dose of 3000 mg and every eight weeks thereafter.

13. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 60 to < 100 kg:
    (a) once on Day 1 at a loading dose of 2700 mg; and
    (b) once on Day 15 at a maintenance dose of 3300 mg and every eight weeks thereafter.

14. The method of any one of Claims 1-7, wherein the anti-C5 antibody is administered to a patient weighing ≥ 100 kg:
    (a) once on Day 1 at a loading dose of 3000 mg; and
    (b) once on Day 15 at a maintenance dose of 3600 mg and every eight weeks thereafter.

15. The method of any one of the preceding claims, wherein the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 100 μg/mL or greater.

16. The method of any one of the preceding claims, wherein the treatment maintains a serum trough concentration of the anti-C5 antibody or antigen binding fragment thereof of 200 μg/mL or greater.

17. The method of any one of the preceding claims, wherein the treatment maintains a free C5 concentration of 0.309 to 0.5 μg/mL or lower.

18. The method of any one of the preceding claims, wherein the anti-C5 antibody is administered at a dose of 300 mg or 600 mg every four weeks after the treatment for up to two years.

19. The method of any one of the preceding claims, wherein the anti-C5 antibody is administered at a dose of 2100 mg, 2700 mg, 3000 mg, 3300 mg or 3600 mg every eight weeks after the treatment for up to two years.

20. The method of any one of the preceding claims, wherein the anti-C5 antibody is formulated for intravenous administration.

21. The method of any one of the preceding claims, wherein the patient has not previously been treated with a complement inhibitor.

22. The method of any one of the preceding claims, wherein the patient is < 18 years of age.

23. The method of any one of the preceding claims, wherein the treatment is an administration cycle comprising a total of 26 weeks of treatment.

24. The method of any one of the preceding claims, wherein the treatment results in terminal complement inhibition.

25. The method of any one of the preceding claims, wherein the treatment results in a complete thrombotic microangiopathy (TMA) response.

26. The method of any one of the preceding claims, wherein the treatment results in a ≥ 25% reduction in serum creatinine levels compared to baseline.

27. The method of any one of the preceding claims, wherein the treatment results in an increase in platelet count compared to baseline.

28. The method of any one of the preceding claims, wherein the treatment results in a reduction of hemolysis compared to baseline as assessed by lactate dehydrogenase (LDH) levels.

29. The method of Claim 1 or 2, wherein the treatment produces a reduction or cessation of at least one therapeutic marker selected from the group consisting of: severe hypertension, proteinuria, uremia, lethargy, fatigue, irritability, thrombocytopenia, microangiopathic hemolytic anemia and renal function impairment, compared to baseline.

30. The method of any one of the preceding claims, wherein the treatment produces a shift toward normal levels of a marker selected from the group consisting of: Factor Ba, soluble tumor necrosis factor receptor 1 (sTNFR1), soluble vascular adhesion molecule 1 (sVCAM1), thrombomodulin, D-dimer and cystatin C, compared to baseline.

31. The method of any one of the preceding claims, wherein the treatment produces a reduction in the need for blood transfusions compared to baseline.

32. The method of any one of the preceding claims, wherein the treatment produces a reduction in major adverse vascular events (MAVEs) compared to baseline.

33. The method of any one of the preceding claims, wherein the treatment produces a change from baseline in quality of life, assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 or the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale compared to baseline.

34. A kit for treating Atypical Hemolytic Uremic Syndrome (aHUS) in a human pediatric patient, the kit comprising:

(a) a dose of an anti-C5 antibody or antigen binding fragment thereof, comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:12, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:8; and

(b) instructions for using the anti-C5 antibody or antigen binding fragment thereof in the method of Claim 1 or 2.

35. The kit of Claim 34, wherein the anti-C5 antibody, or antigen binding fragment thereof, is administered to a patient weighing ≥ 5 to < 10 kg:

(a) once on Day 1 at a loading dose of 600 mg; and

(b) once on Day 15 at a maintenance dose of 300 mg and every four weeks thereafter.

36. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 10 to < 20 kg:

(a) once on Day 1 at a loading dose of 600 mg; and

(b) once on Day 15 at a maintenance dose of 600 mg and every four weeks thereafter.

37. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 20 to < 30 kg:

(a) once on Day 1 at a loading dose of 900 mg; and

(b) once on Day 15 at a maintenance dose of 2100 mg and every eight weeks thereafter.

38. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 30 to < 40 kg:

(a) once on Day 1 at a loading dose of 1200 mg; and

(b) once on Day 15 at a maintenance dose of 2700 mg and every eight weeks thereafter.

39. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 40 to < 60 kg:

(a) once on Day 1 at a loading dose of 2400 mg; and

(b) once on Day 15 at a maintenance dose of 3000 mg and every eight weeks thereafter.

40. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 60 to < 100 kg:

(a) once on Day 1 at a loading dose of 2700 mg; and

(b) once on Day 15 at a maintenance dose of 3300 mg and every eight weeks thereafter.

41. The kit of Claim 34, wherein the anti-C5 antibody or antigen binding fragment thereof is administered to a patient weighing ≥ 100 kg:

(a) once on Day 1 at a loading dose of 3000 mg; and

(b) once on Day 15 at a maintenance dose of 3600 mg and every eight weeks thereafter.

42. An anti-C5 antibody or antigen binding fragment thereof comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:12, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:8, wherein the anti-C5 antibody or antigen binding fragment thereof is administered:

(a) once on Day 1 at a loading dose of:

i. 600 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 900 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 1200 mg to a patient weighing ≥ 30 to < 40 kg,

v. 2400 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 2700 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3000 mg to a patient weighing ≥ 100 kg; and

(b) on Day 15 at a maintenance dose of:

i. 300 mg to a patient weighing ≥ 5 to < 10 kg,

ii. 600 mg to a patient weighing ≥ 10 to < 20 kg,

iii. 2100 mg to a patient weighing ≥ 20 to < 30 kg,

iv. 2700 mg to a patient weighing ≥ 30 to < 40 kg,

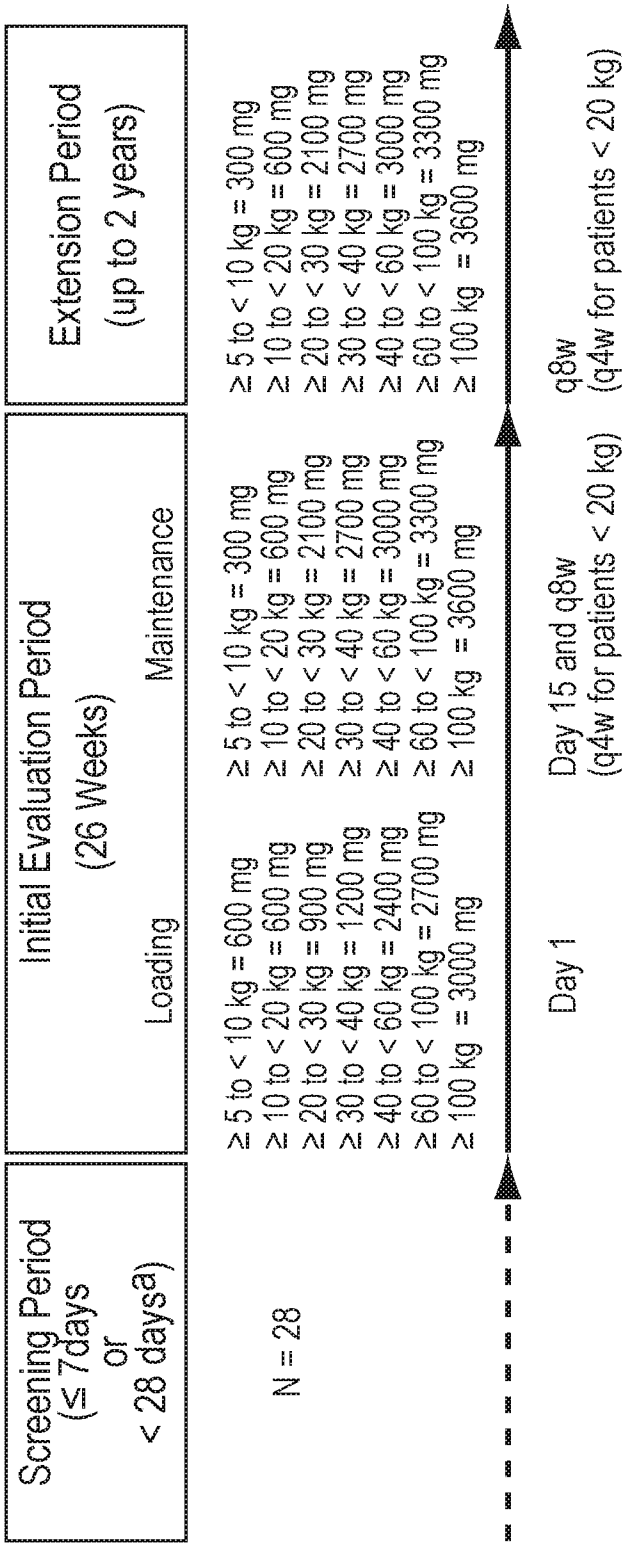
v. 3000 mg to a patient weighing ≥ 40 to < 60 kg,

vi. 3300 mg to a patient weighing ≥ 60 to < 100 kg, or

vii. 3600 mg to a patient weighing ≥ 100 kg;

wherein patients weighing < 20 kg receive additional maintenance doses every four weeks thereafter, and patients weighing ≥ 20 kg receive additional maintenance doses every eight weeks thereafter.

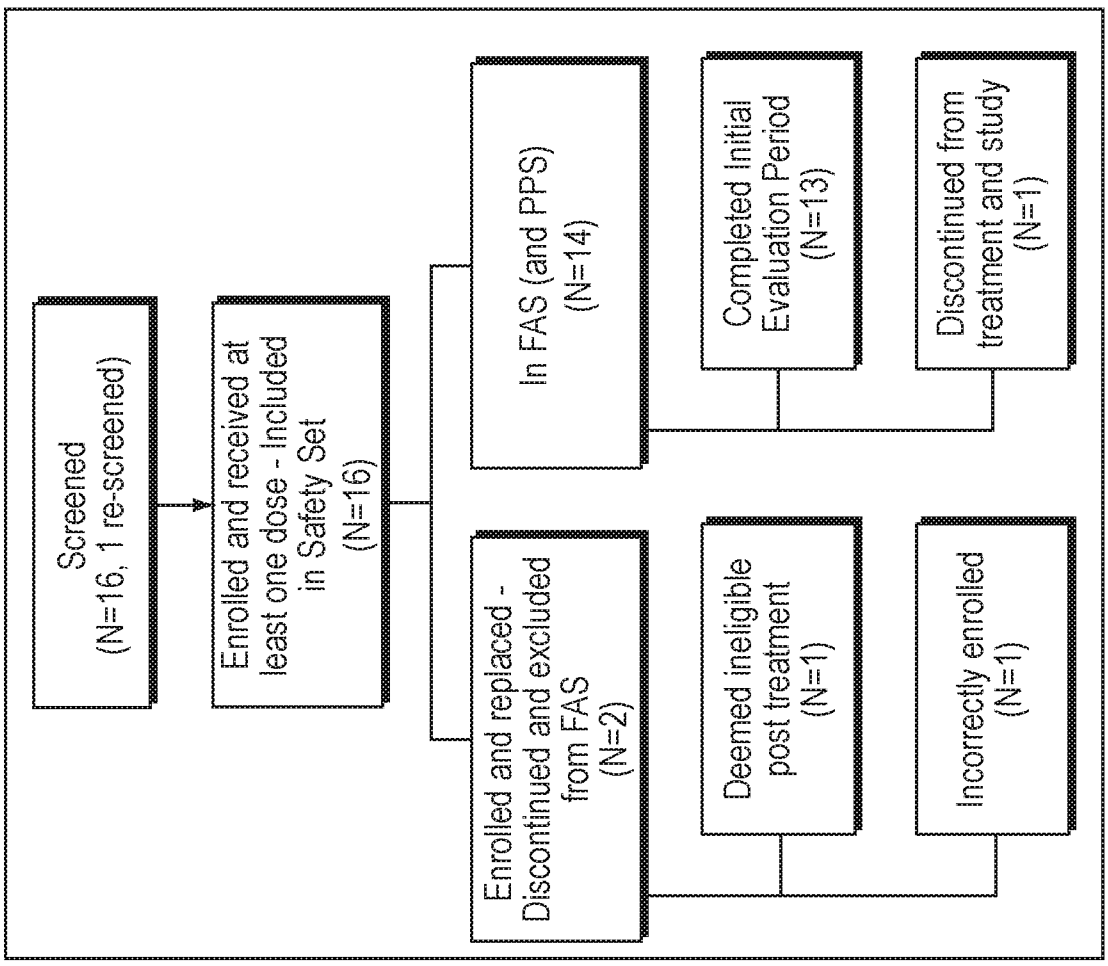
43. The antibody of Claim 42, wherein the antibody is determined to be safe, tolerable, efficacious and sufficiently non-immunogenic after multiple IV doses in aHUS patients.



Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks

[a]The Screening Period is up to 7 days for complement inhibitor treatment-naïve patients (ie, Cohort 1) and up to 28 days for eculizumab-experienced adolescent patients (ie, Cohort 2).

FIG. 1



- Study continuing to enroll
  - 4 additional naïve patients enrolled
  - Potential need for 2 more naïve patients in birth to <2 years group
  - 10 "switch" patients enrolled
    - 7 in 12 to <18 group
    - 3 Japanese patients <12 years

FIG. 2

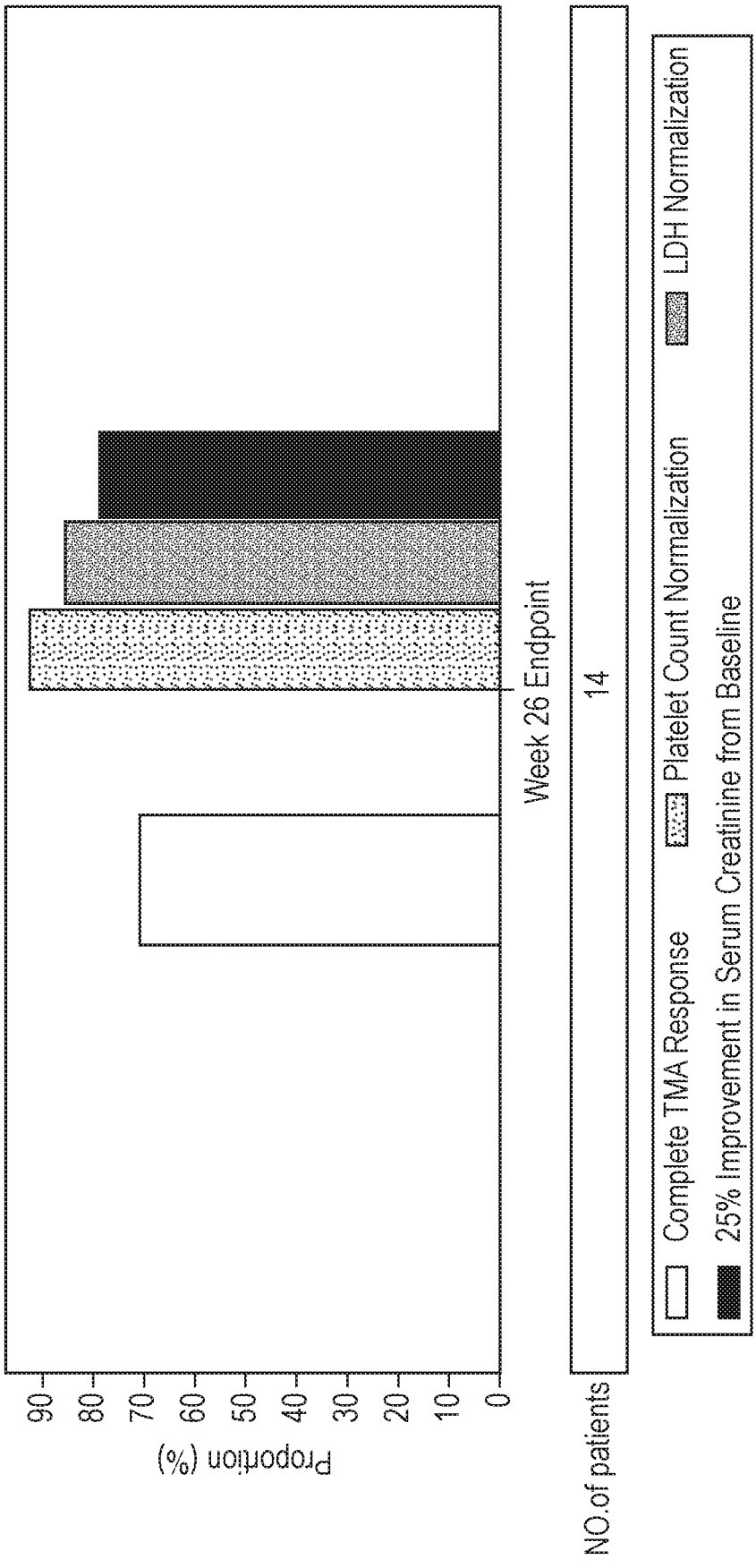

Proportion (%)
0
10
20
30
40
50
60
70
80
90
Week 26 Endpoint
NO.of patients
14
Complete TMA Response
Platelet Count Normalization
LDH Normalization
25% Improvement in Serum Creatinine from Baseline

FIG. 3

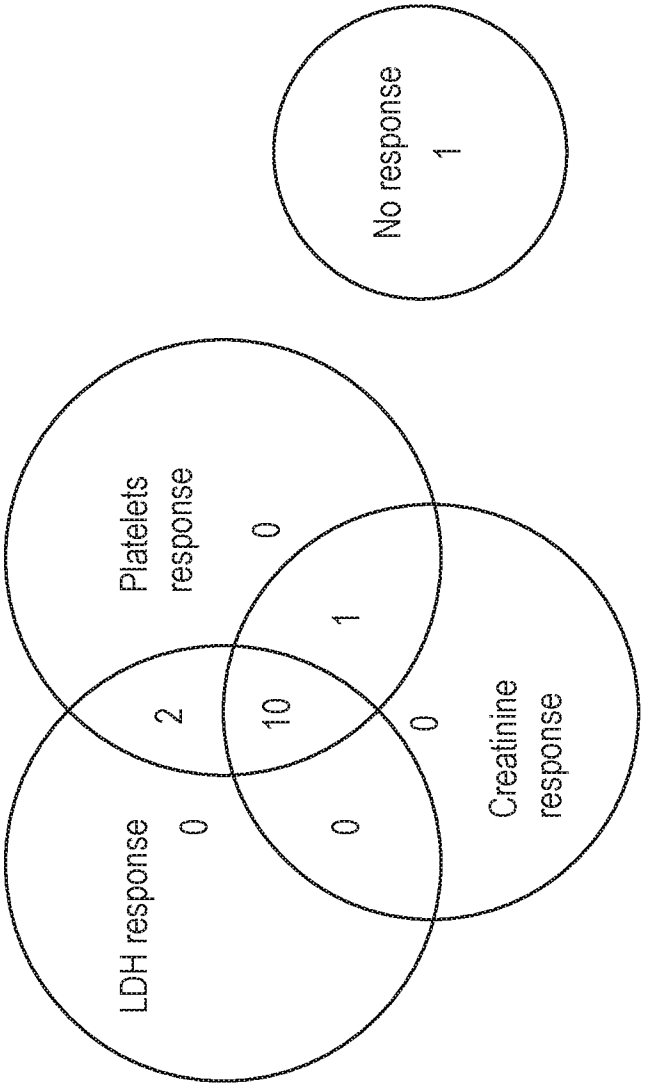

No response
1
Platelets
response
0
1
2
10
0
LDH response
0
0
Creatinine
response

FIG. 4

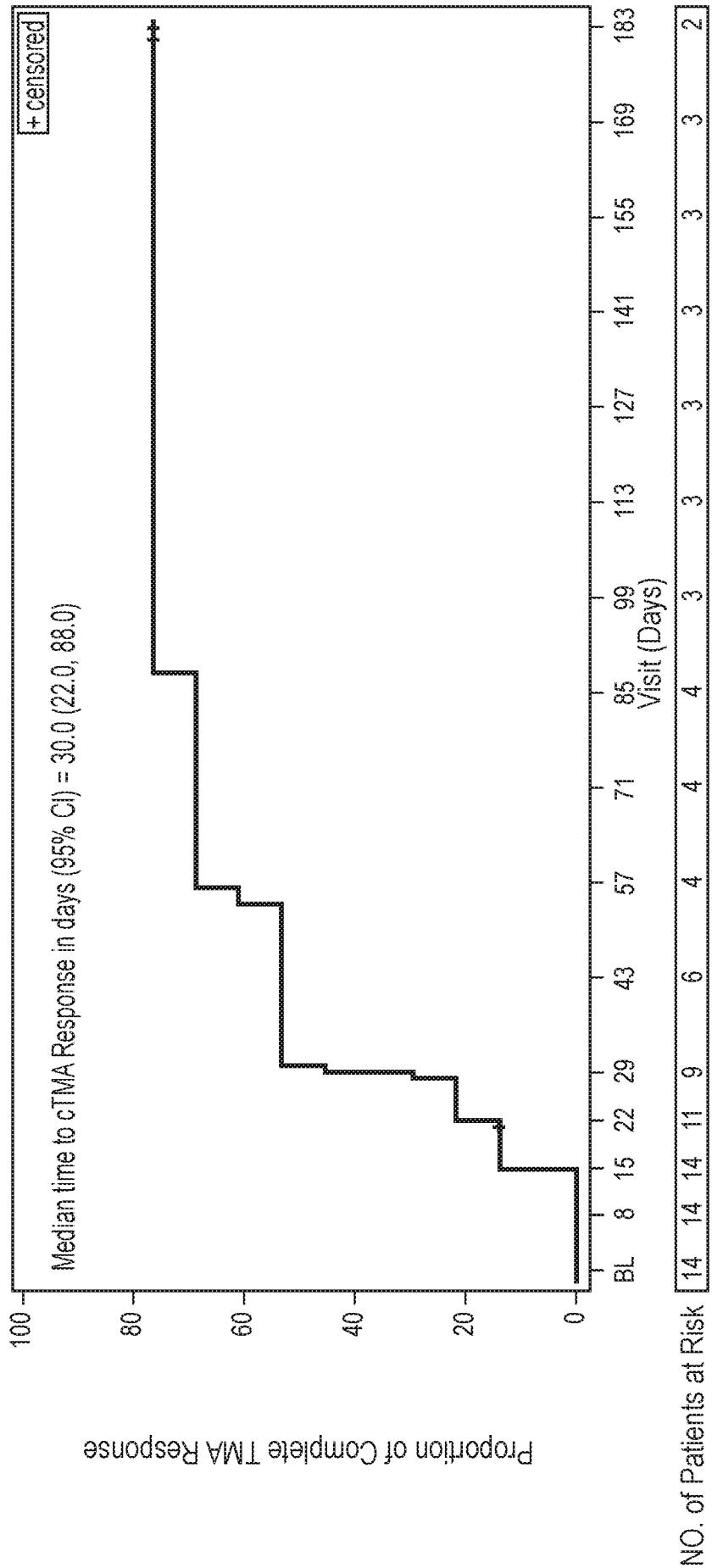

+ censored
Median time to cTMA Response in days (95% CI) = 30.0 (22.0, 88.0)
Proportion of Complete TMA Response
100
80
60
40
20
0
BL 8 15 22 29 43 57 71 85 99 113 127 141 155 169 183
Visit (Days)
NO. of Patients at Risk
14 14 14 11 9 6 4 4 4 3 3 3 3 3 3 2

FIG. 5

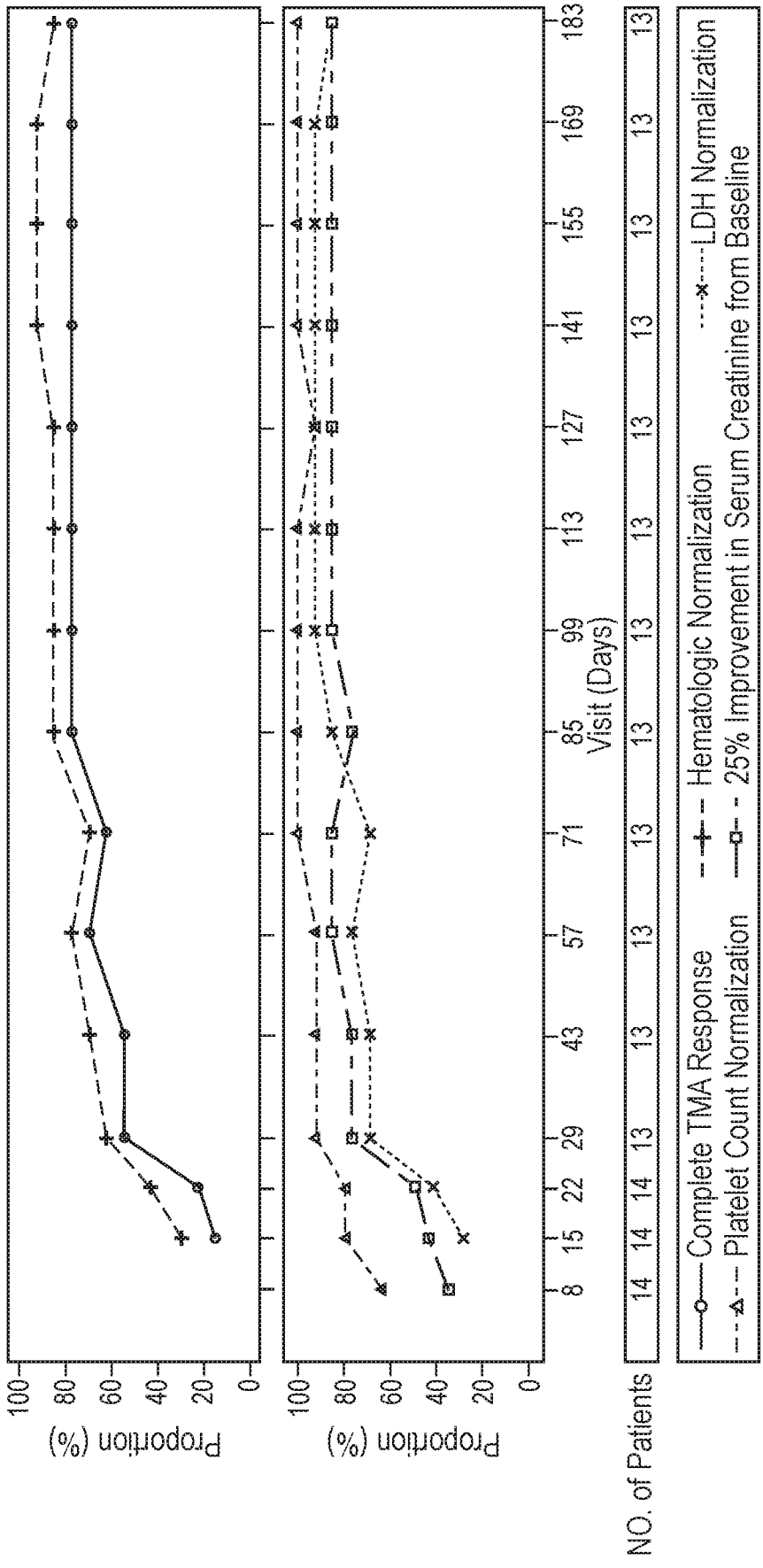

Proportion (%)
100
80
60
40
20
0
Visit (Days)
8 15 22 29 43 57 71 85 99 113 127 141 155 169 183
NO. of Patients
14 14 14 13 13 13 13 13 13 13 13 13 13 13 13
Complete TMA Response
Hematologic Normalization
LDH Normalization
Platelet Count Normalization
25% Improvement in Serum Creatinine from Baseline

FIG. 6

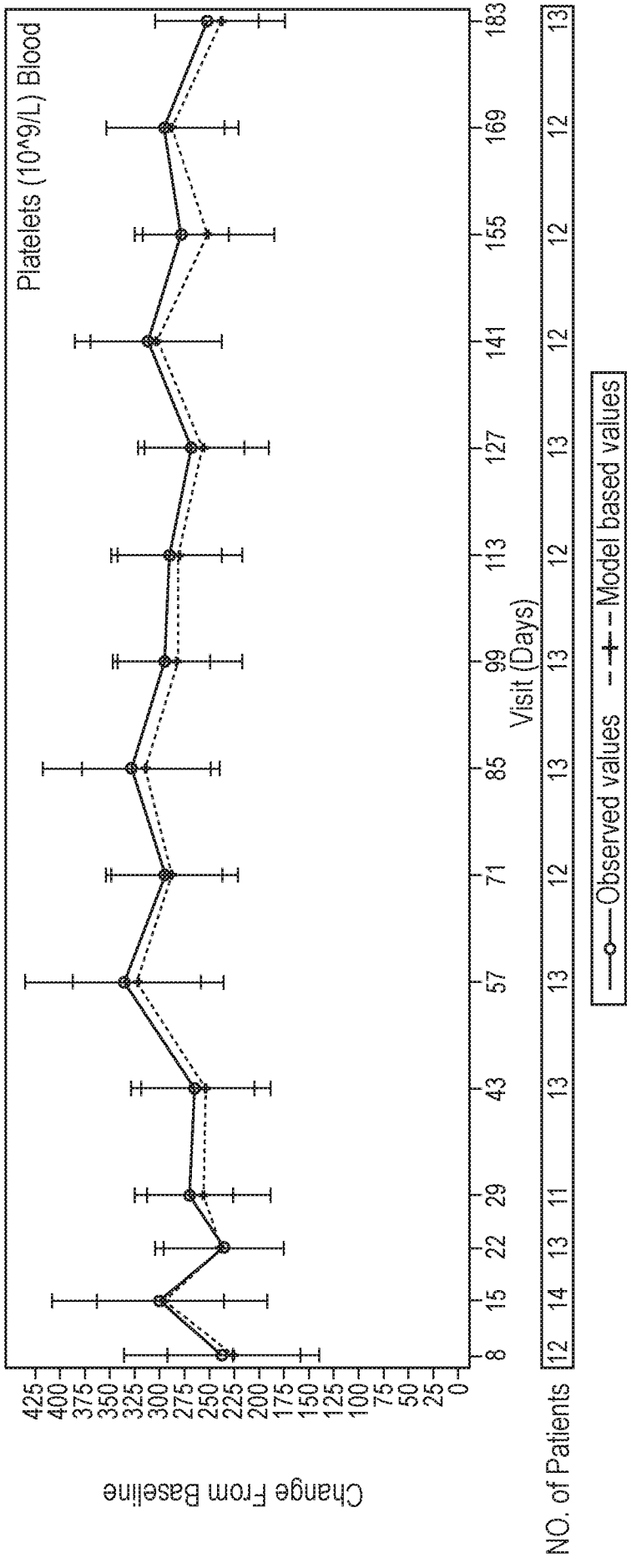

Platelets (10^9/L) Blood
Change From Baseline
425
400
375
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
Visit (Days)
8
15
22
29
43
57
71
85
99
113
127
141
155
169
183
NO. of Patients
12 14 13 11 13 13 12 13 13 12 13 12 12 12 13
Observed values
Model based values

FIG. 7

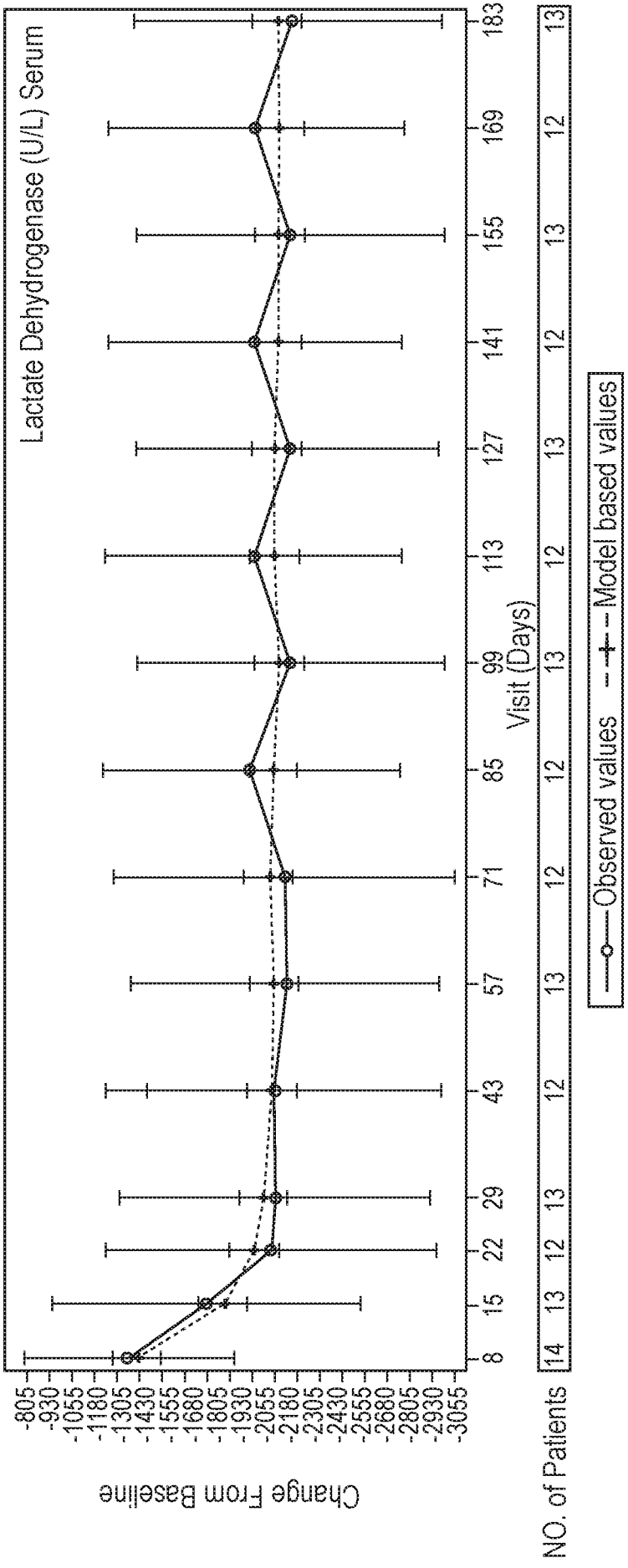

Lactate Dehydrogenase (U/L) Serum
Change From Baseline
-805
-930
-1055
-1180
-1305
-1430
-1555
-1680
-1805
-1930
-2055
-2180
-2305
-2430
-2555
-2680
-2805
-2930
-3055
8
15
22
29
43
57
71
85
99
113
127
141
155
169
183
Visit (Days)
NO. of Patients
14 13 12 13 12 12 13 12 13 12 13 12 13
Observed values
Model based values

FIG. 8

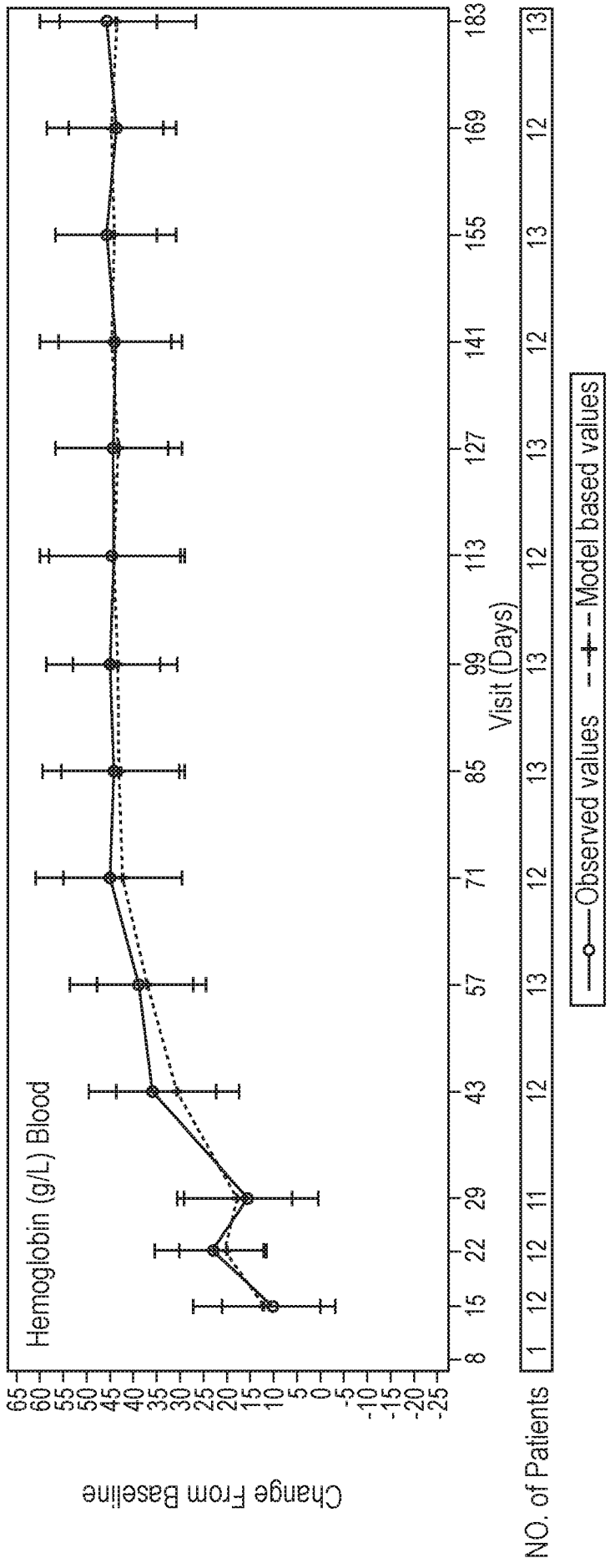

Hemoglobin (g/L) Blood
Change From Baseline
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
8
15
22
29
43
57
71
85
99
113
127
141
155
169
183
Visit (Days)
NO. of Patients
1 12 12 11 12 13 12 13 13 12 13 12 13 12 13
Observed values
Model based values

FIG. 9

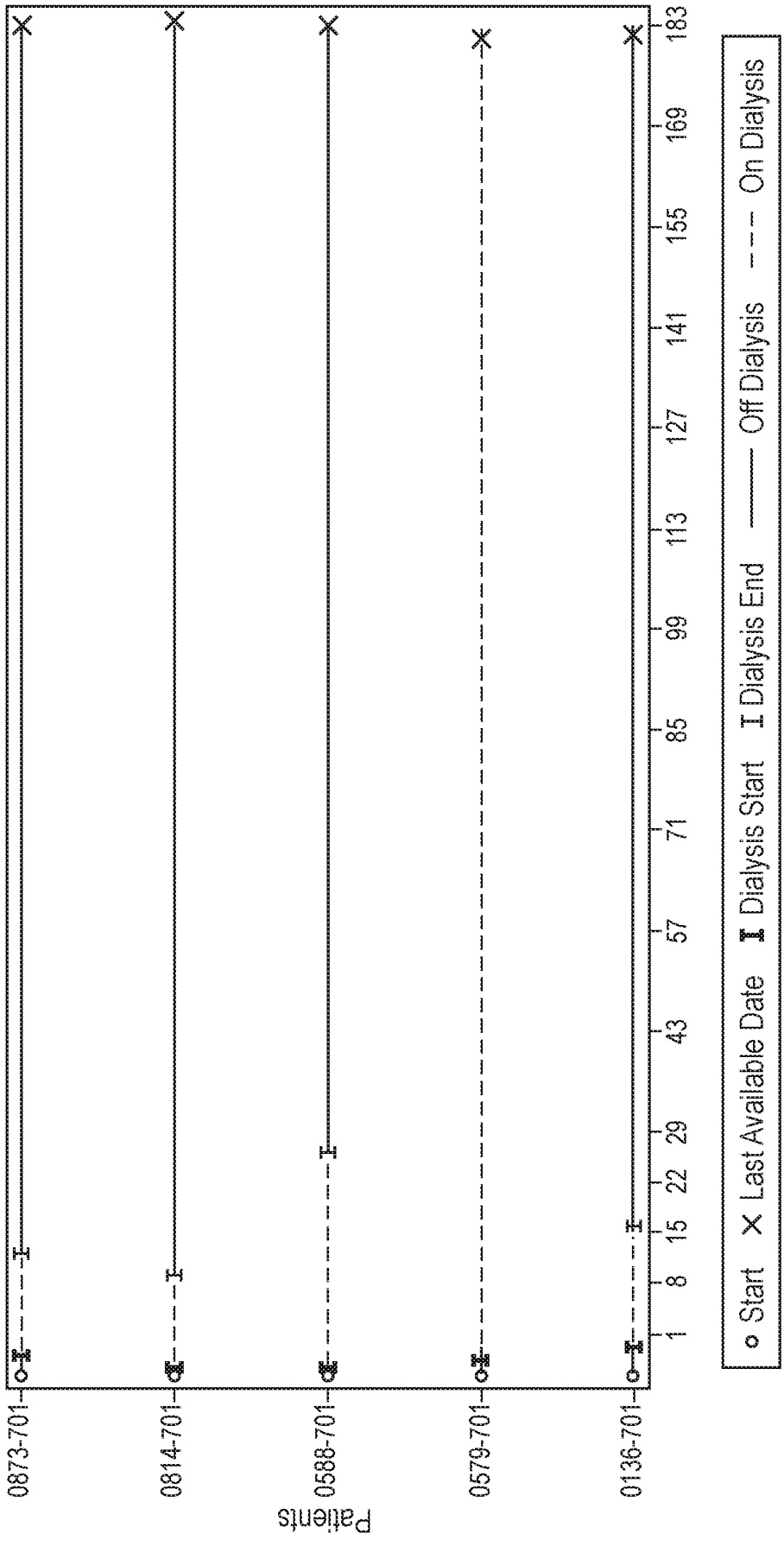

0873-701
0814-701
0588-701
0579-701
0136-701
Patients
1
8
15
22
29
43
57
71
85
99
113
127
141
155
169
183
Start
Last Available Date
Dialysis Start
Dialysis End
Off Dialysis
On Dialysis

FIG. 10

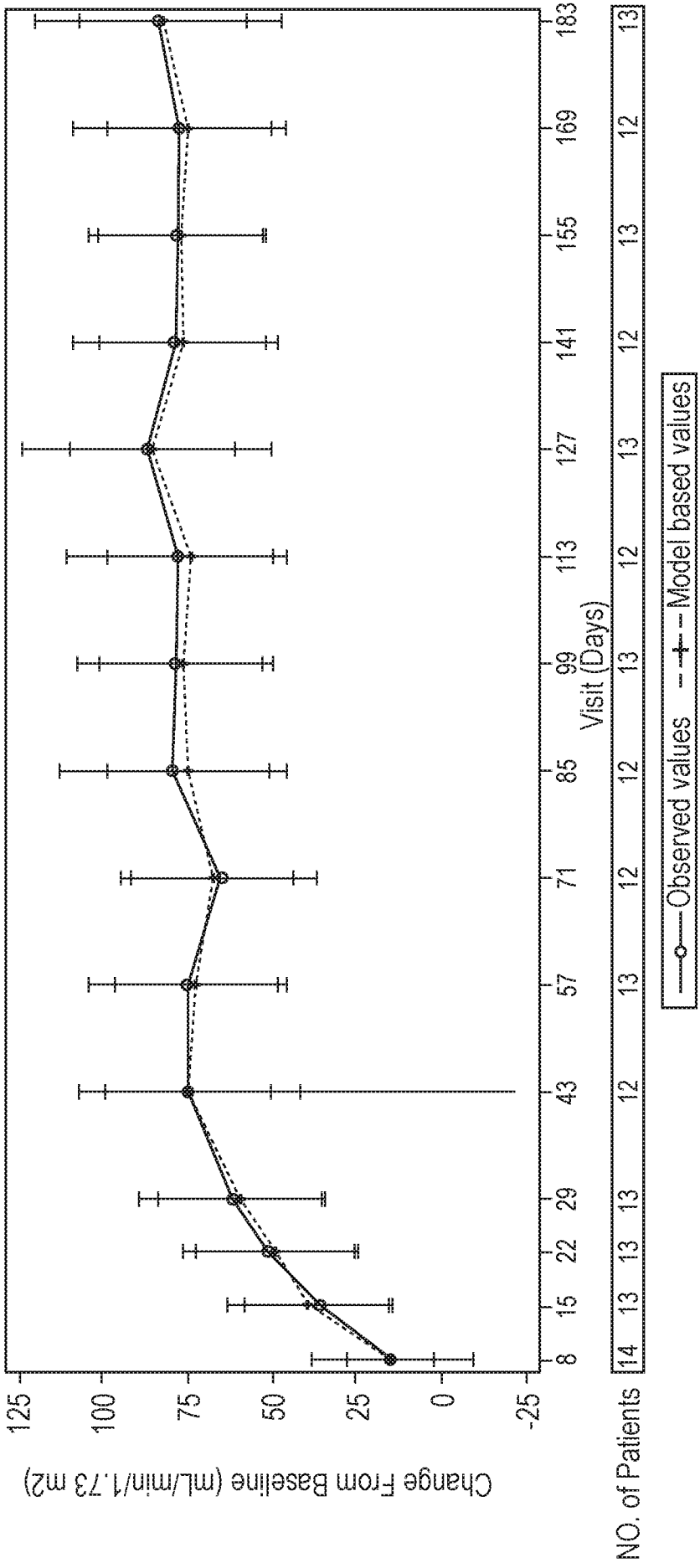

Change From Baseline (mL/min/1.73 m2)
125
100
75
50
25
0
-25
Visit (Days)
8 15 22 29 43 57 71 85 99 113 127 141 155 169 183
NO. of Patients
14 13 13 13 12 13 12 12 13 12 13 12 13 12 13
Observed values
Model based values

FIG. 11

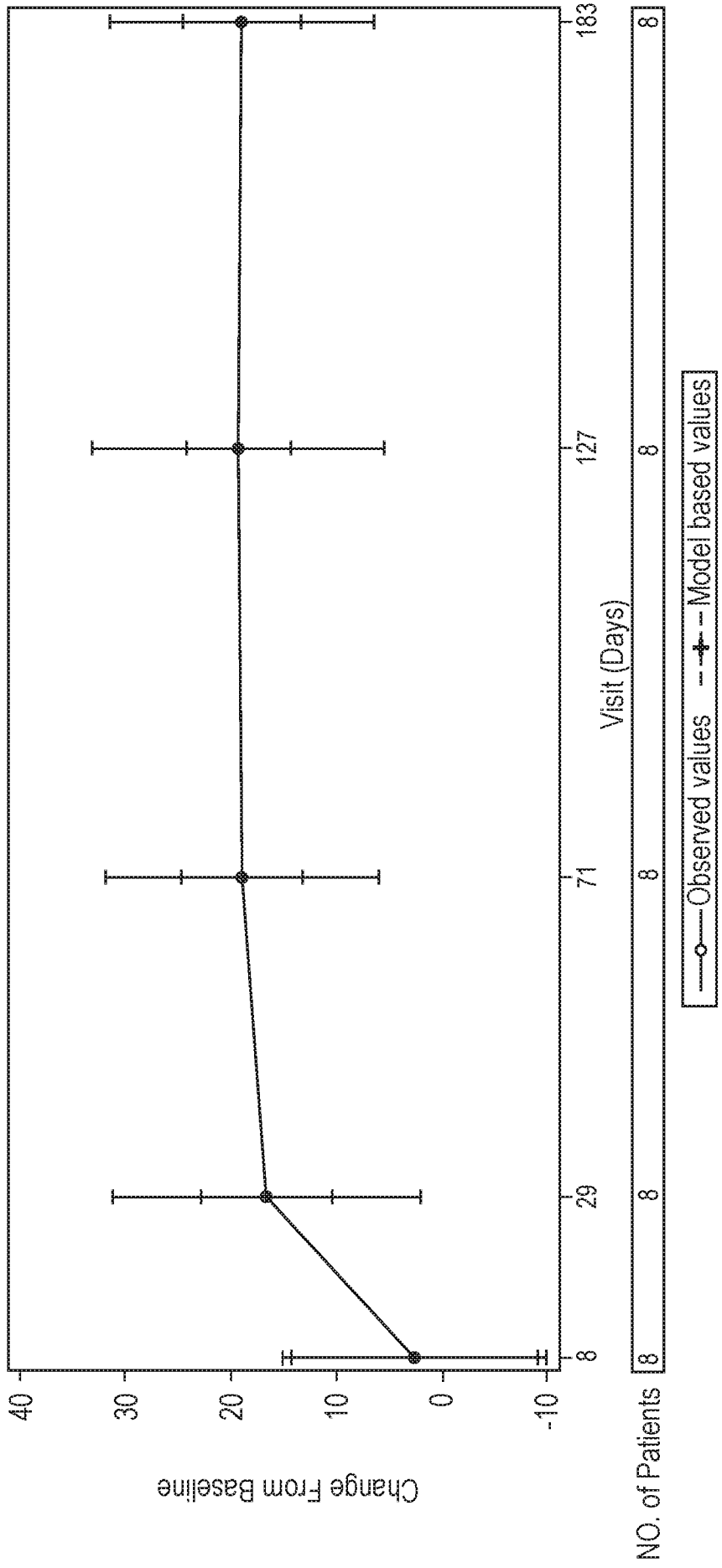

Change From Baseline
40
30
20
10
0
-10
8
29
71
127
183
Visit (Days)
NO. of Patients
8
8
8
8
8
Observed values
Model based values

FIG. 12

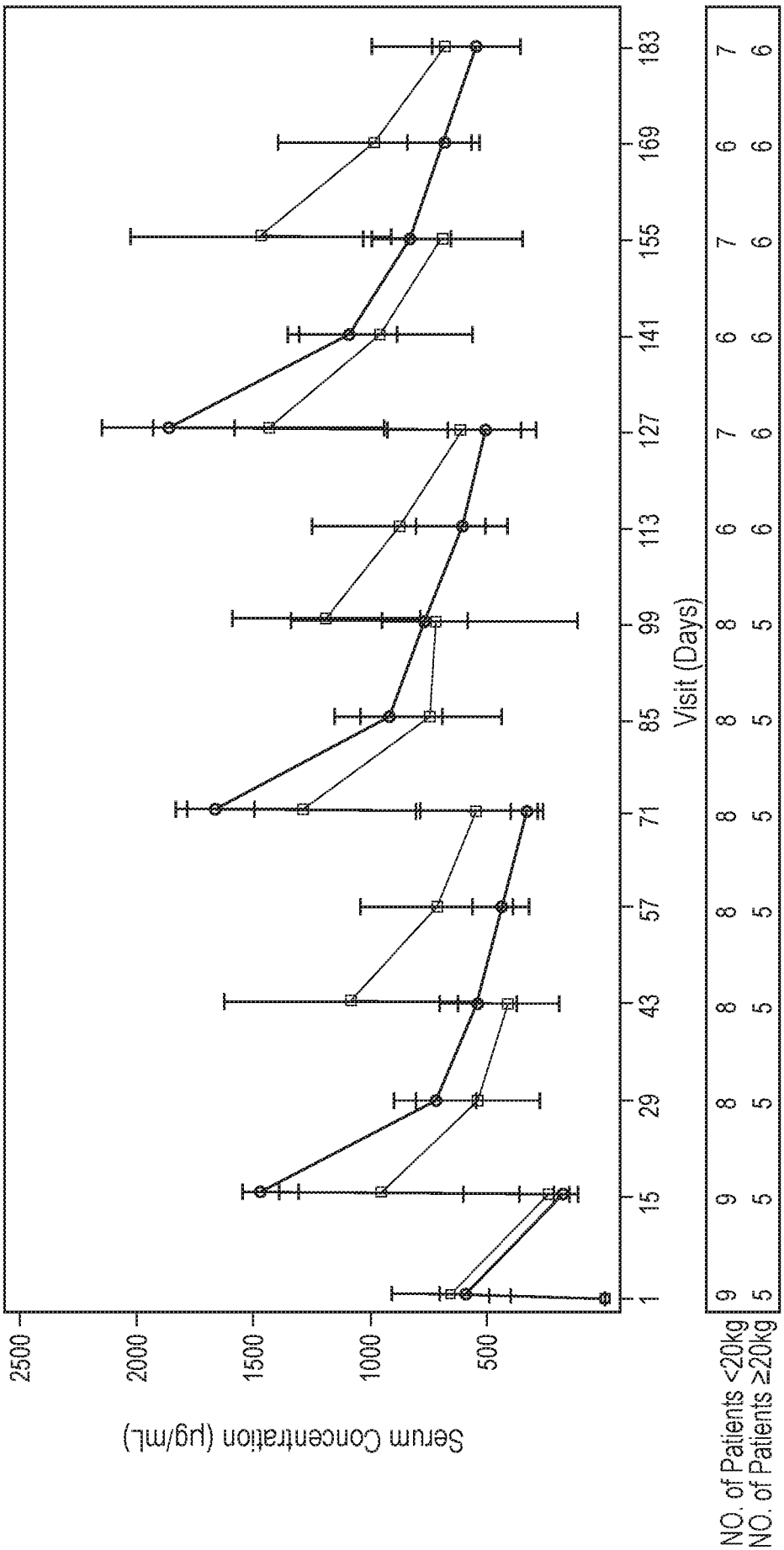

Serum Concentration (μg/mL)
2500
2000
1500
1000
500
1
15
29
43
57
71
85
99
113
127
141
155
169
183
Visit (Days)
NO. of Patients <20kg
NO. of Patients ≥20kg
9 9 8 8 8 8 8 8 8 8 8 7 7 6
5 5 5 5 5 5 5 6 6 6 6 6 6 6

FIG. 13

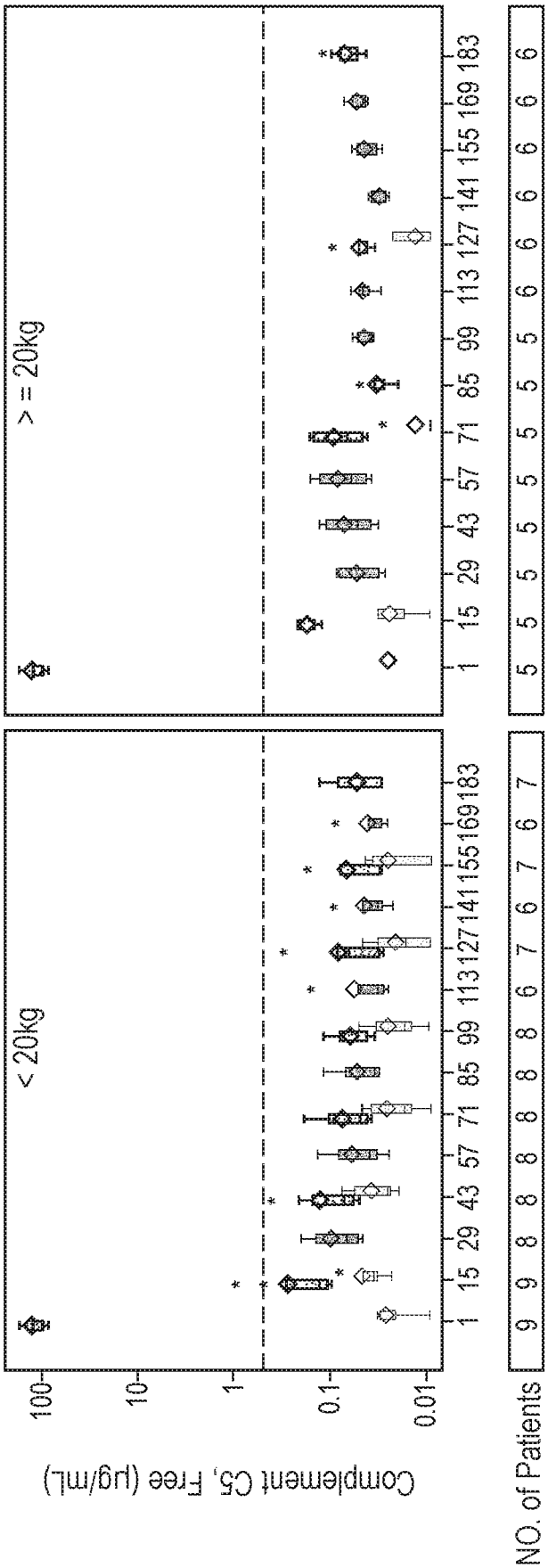

< 20kg
>= 20kg
Complement C5, Free (µg/mL)
100
10
1
0.1
0.01
1 15 29 43 57 71 85 99 113 127 141 155 169 183
NO. of Patients
9 9 8 8 8 8 8 8 6 7 6 7 6 7
5 5 5 5 5 5 5 5 6 6 6 6 6 6
Visit (Days)
Anytime
EOI
Pre-dose

FIG. 14

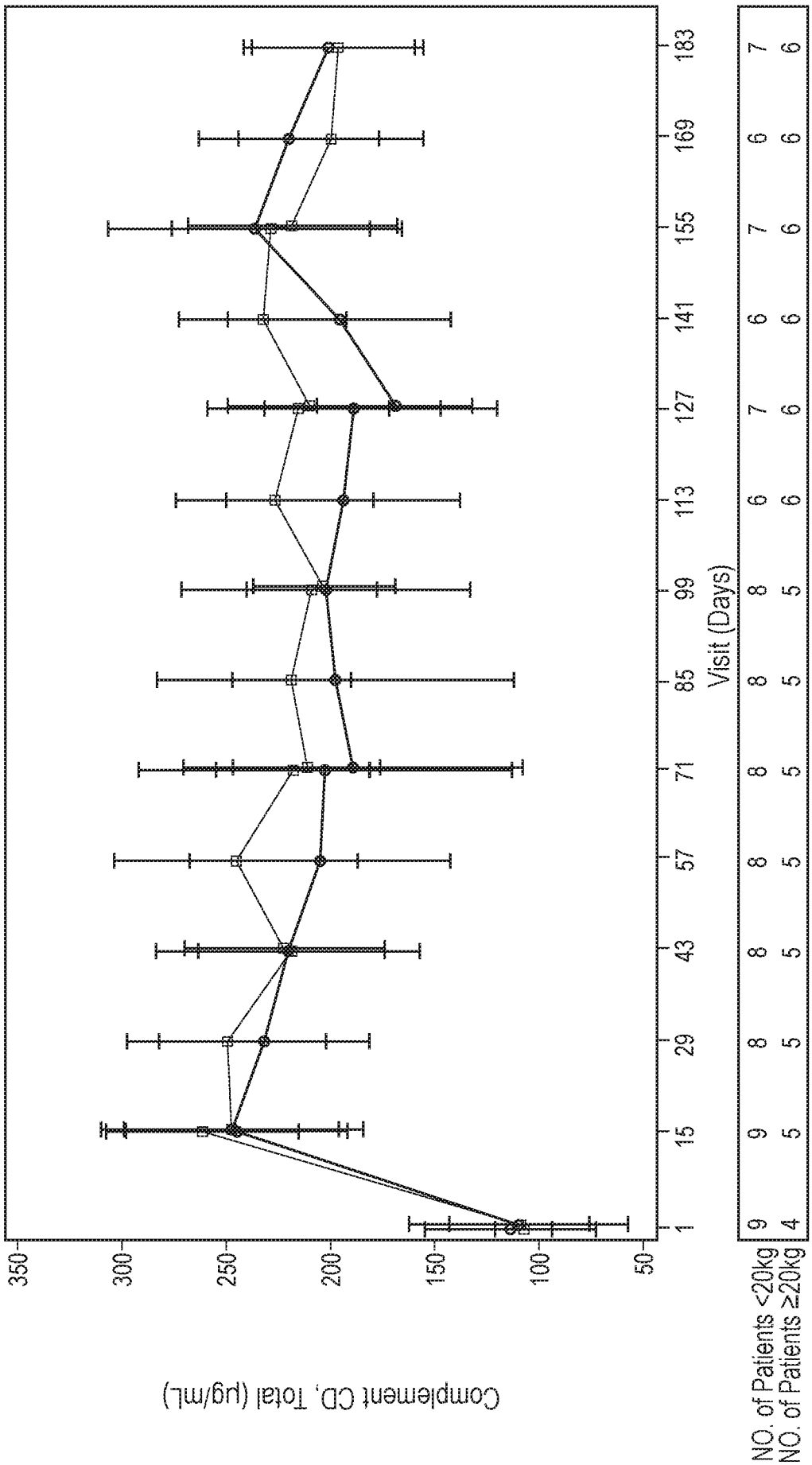

Complement CD, Total (µg/mL)
350
300
250
200
150
100
50
1
15
29
43
57
71
85
99
113
127
141
155
169
183
Visit (Days)
NO. of Patients <20kg
NO. of Patients ≥20kg
9 9 8 8 8 8 8 8 6 6 6 6 6 6 7
4 5 5 5 5 5 5 5 6 6 6 6 6 6 6

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/034297

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P7/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/123636 A1 (ALEXION PHARMA INC [US]) 20 July 2017 (2017-07-20) page 24, line 7 - line 16 -----	1-43
A	Anonymous: "Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients With Atypical Hemolytic Uremic Syndrome (aHUS)", , 25 October 2016 (2016-10-25), pages 1-6, XP055619305, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT02949128?term=alxn1210&rank=8 [retrieved on 2019-09-06] ----- -/--	1-43

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2019	25/09/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marinoni J-C

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Anonymous: "Study of ALXN1210 in Children and Adolescents With Atypical Hemolytic Uremic Syndrome (aHUS)", , 27 April 2017 (2017-04-27), pages 1-9, XP055619309, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT03131219?term=alxn1210&rank=5 [retrieved on 2019-09-06]	1-43
A	AU 2018 201 961 A1 (ALEXION PHARMA INC) 12 April 2018 (2018-04-12) page 9, line 31 - page 10, line 2 examples 2-4	1-43
A	WO 2017/044811 A1 (ANDRIEN BRUCE [US]; HUNTER JEFFREY [US]; MALANSON HUNTER [US]) 16 March 2017 (2017-03-16) paragraph [0076.0077]; table 1	1-43
A	WO 2016/209956 A1 (ALEXION PHARMA INC [US]) 29 December 2016 (2016-12-29) table 1	1-43
A	WO 2016/160756 A2 (ALEXION PHARMACEUTICLAS INC [US]) 6 October 2016 (2016-10-06) page 6, line 2 - page 7, line 6	1-43
A	SHERIDAN DOUGLAS ET AL: "Design and preclinical characterization of ALXN1210: A next generation anti-C5 monoclonal antibody with improved pharmacokinetics and duration of action", IMMUNOBIOLOGY, vol. 221, no. 10, 2016, page 1158, XP029684394, ISSN: 0171-2985, DOI: 10.1016/J.IMBIO.2016.06.078	1-43
A	DOUGLAS SHERIDAN ET AL: "Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action", PLOS ONE, vol. 13, no. 4, 12 April 2018 (2018-04-12) , page e0195909, XP055611308, DOI: 10.1371/journal.pone.0195909	1-43
X,P	WO 2019/084438 A1 (ALEXION PHARMA INC [US]) 2 May 2019 (2019-05-02) the whole document	1-7, 12-43

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/034297

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017123636 A1	20-07-2017	EP 3402816 A1	21-11-2018
		US 2019023775 A1	24-01-2019
		WO 2017123636 A1	20-07-2017
AU 2018201961 A1	12-04-2018	AU 2015227544 A1	08-10-2015
		AU 2017202426 A1	04-05-2017
		AU 2018201961 A1	12-04-2018
WO 2017044811 A1	16-03-2017	EP 3328885 A1	06-06-2018
		JP 2018528218 A	27-09-2018
		US 2017073399 A1	16-03-2017
		WO 2017044811 A1	16-03-2017
WO 2016209956 A1	29-12-2016	EP 3313437 A1	02-05-2018
		JP 2018520139 A	26-07-2018
		US 2018142010 A1	24-05-2018
		WO 2016209956 A1	29-12-2016
WO 2016160756 A2	06-10-2016	EP 3277715 A2	07-02-2018
		JP 2018511609 A	26-04-2018
		US 2019135903 A1	09-05-2019
		WO 2016160756 A2	06-10-2016
WO 2019084438 A1	02-05-2019	NONE	