Supplementary material of the article:

The inhibition of complement system in formal and emerging indications: Results from parallel one-stage pairwise and network meta-analyses of clinical trials and real-life data studies

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Table S1: The included studies after searches with respect to (a) their relevant information from study participants grouped by diseases, (b) the risk of bias in clinical trials, and (c) the risk of bias in real-life NRSI.

Figure S1: Forest and inconsistency plot for (a) hemolysis in PNH, (b) TMA in aHUS, and (c) AKI in aHUS.

Panel S1. Full search strategy and search results.

Table S1. The included studies after searches with respect to:
(a) Their relevant information from study participants grouped by diseases,

Information from clinical trial (R/NR)[€] / NRSI study in:	Study participant characteristics:
PNH	Age (range in yr), AA/MDS (%), disease duration (range in yr), previous/concomitant treatments (%):
(a) Eculizumab parent studies (1/2) & (b) common extension study (0/1)	18–85, 30.3, 0–39, 36.0
(c) AEGIS (0/1) plus extension follow-up	26–70, 45.0, NA, 48.0
(d) 301 (1/0) plus extension follow-up	30–61, NA, 3–4, NA
(e) 302 (1/0) plus extension follow-up	34–62, 37.4, 3–21, NA
(f) International PNH registry & (g) country PNH registries[$]	3–99, 21.0, 1–47, 28.0
aHUS	Age (range in yr), disease duration (range in mo), previous/concomitant treatments (%), KRT need (%):
(h) C08-002 (0/1) plus extension follow-up	17–68, 0–236, 100.0, 35.0
(i) C08-003 (0/1) plus extension follow-up	13–63, 1–286, 100.0, 10.0
(j) C10-003 & (k) C10-004 (0/2)	0–80, 0–313, 100.0, 41.0
(l) C09-001r (0/1) & common extension study for eculizumab parent studies (0/1)	0–80, 0–313, 100.0, 39.0
(m) 311 (0/1)	18–79, NA, 100.0, 45.0
(n) Global aHUS registry & (o) country aHUS registries[$]	0–82, 0–612, 100.0, 47.0
gMG	Age (range in yr), disease duration (range in yr), previous/concomitant treatments (%):
(p) Eculizumab pilot study (1/0)	30–72, 1–30, 50.0
(q) REGAIN (1/0) & ECU-MG-302 (0/1)	20–57, 1–18, 96.0
aAMR	Age (range in yr), allo-reactivity findings (%), post-TX time (range in yr), previous/concomitant treatments (%):
(r) Berinert pilot study (0/1)[£]	44–58, 100.0, 0–16, 100.0
(s) Cinryze pilot study (1/0) & post-hoc analysis[£]	36–61, 44.0, 70–366, 78.0
(t) 07-007208 (0/1)[£]	37–61, 100.0, 0.0, 69.0
(u) Berinert exploratory study (1/0) & post-hoc analyses[£]	32–62, 40.0, 0.0, 100.0
(v) C10-001 (1/0)[£]	29–57, 100.0, 0.0, 100.0
(w) C10-002 (0/1) plus extension follow-up[£]	24–70, 100.0, 0.0, 0.0
DGF	Age (range in yr), risk for DGF (%), previous/concomitant treatments (%):
(x) Eculizumab for reperfusion (1/0) plus extension follow-up	31–51, 30.0, 100.0
(y) C1INHDGF (1/0) plus extension follow-up	48–67, 42.0, 100.0
(z) 10-1600 & 13-0920 (2/0)	51–68, 100.0, 100.0
(aa) PROTECT (1/0) plus extension follow-up	18–55, 100.0, 100.0

(b) the risk of bias in clinical trials,

Trials	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Pilot PNH (a)	H	H	H	H	H	H	U
TRIUMPH (a)	L	L	L	U	U	U	U
SHEPHERD (a)	H	H	H	H	U	U	U
PNH eculizumab parent studies common extension (b)	H	H	H	H	L	L	U
AEGIS (c)	H	H	H	H	H	H	U
301 (d)	L	L	U	U	U	U	U
302 (e)	L	L	U	U	U	U	U
C08-002 (h)	H	H	H	H	U	U	U
C08-003 (i)	H	H	H	H	U	U	U
C10-003 (j)	H	H	H	H	H	H	U
C10-004 (k)	H	H	H	H	H	H	U
C09-001r & C11-003 (l)	H	H	H	H	H	H	H
311 (m)	H	H	H	H	U	U	U
pilot rgMG (p)	L	L	L	U	U	U	H
REGAIN & extension (q)	L	L	L	U	H	H	U
Berinert pilot (r)	H	H	H	H	H	H	U
Cinryze pilot (s)	L	L	L	U	U	U	U
07-007208 (t)	H	H	H	H	H	H	U
Berinert exploratory study (u)	L	L	L	U	U	U	U
C10-001 (v)	L	L	L	U	U	U	U
C10-002 (w)	H	H	H	H	H	H	U
Eculizumab for reperfusion (x)	L	L	U	U	H	U	U
C1INHDGF (y)	L	L	L	U	U	U	U
10-1600 (z)	L	L	L	U	U	L	U
13-0920 (z)	L	L	L	U	U	L	U
PROTECT (aa)	L	L	L	L	U	U	U

(c) The risk of bias in real-life NRSI.

Real-life NRSI	Confounding	Participants selection	Interventions	Deviations	Missing data	Outcomes measurement	Selection of the reported result
International PNH registry (a)	S	M	S	S	C	M	S
Country PNH registries (a)	S	C	S	C	C	S	S
Global aHUS registry (a)	S	M	S	S	C	M	S
Country aHUS registries (b)	S	C	S	C	C	S	S

(a) The PNH eculizumab parent studies were the following: 12-week, single arm, open-label, phase 2 pilot study and its 1-year extension follow-up study (1, 2), 26-week, randomized, double-blind, placebo-controlled, phase 3 TRIUMPH study (NCT00122330) (3), and 52-week, single arm, open-label, phase 3 SHEPHERD study (NCT00130000) (4).
(b) 102-week, single arm, open-label, phase 3 common pilot-TRIUMPH-SHEPHERD extension study (5–7).
(c) 12-week, single arm, open-label, phase 2 pivotal AEGIS study (8) and its 2-year extension follow-up study (9).
(d) 26-week, randomized, open-label, active-controlled, phase 3 ALXN 1210-PNH-301 study (NCT02946463) and its 2-year extension follow-up study (10).
(e) 26-week, randomized, open-label, active-controlled, phase 3 ALXN 1210-PNH-302 study (NCT03056040) and its 2-year extension follow-up study (11).
(f) The International PNH registry (NCT01374360) was a global, prospective, non-interventional, observational study (12–16).
(g) The following country PNH registries were non-interventional, observational studies involving prospective (Japan (17) and Korea (18–21)) and retrospective (France (22, 23), Spain (24–26), Taiwan (27), and UK (28)) data collection.
(h) 26-week, single arm, open-label, phase 2 C08-002 study of Eculizumab (NCT00844545, NCT00844844) and its 2-year extension follow-up study (29–31).
(i) 26-week, single arm, open-label, phase 2 C08-003 study of Eculizumab (NCT00838513, NCT00844428) and its 2-year extension follow-up study (29–31).
(j) 26-week, single arm, open-label, phase 2 C10-003 study of Eculizumab (NCT01193348) (32).
(k) 26-week, single arm, open-label, phase 2 C10-004 study of Eculizumab (NCT01194973) (33).
(l) Retrospective, observational, C09-001r study of Eculizumab (NCT01770951) and the long-term prospective, observational, C11-003 follow-up study for all participants in Eculizumab parent studies C08-002, C08-003, C10-003, C10-004, and C09-001r (NCT01522170) (34, 35).
(m) 26-week, single arm, open-label, phase 3 ALXN 1210-aHUS-311 study (NCT02949128) (36).
(n) The Global aHUS registry (NCT01522183) was a global, prospective, non-interventional, observational study (37–40).
(o) The following country aHUS registries were non-interventional, observational studies involving prospective (Japan (41–43), Australia (44), and Brazil (45)), prospective/retrospective (Turkey (46–48)) and retrospective (France (49–55), Spain (56–58), and UK and Ireland (59, 60)) data collection.
(p) 37-week, crossover, randomized, double-blind, placebo-controlled, phase 2 pilot study of Eculizumab in rgMG (61).
(q) 24-week, randomized, double-blind, placebo-controlled, phase 3 REGAIN study (NCT01997229) (62) and its 2-year extension ECU-MG-302 study (NCT02301624) (63).
(r) 24-week, single arm, open-label, phase 2 pilot study of Berinert for treatment of acute AMR (64).
(s) 2-week, randomized, double-blind, placebo-controlled, phase 2 pilot study of Cinryze for treatment of acute AMR (NCT01147302) and its 6-month post-hoc analysis (65).
(t) 12-week, single arm, open-label, phase 2 07-007208 study of Eculizumab for prevention of AMR (NCT00670774) (66).
(u) 24-week, randomized, double-blind, placebo-controlled, phase 1/2 exploratory study of Berinert for prevention of AMR (NCT01134510) (67) and its 2-year and 3-year post hoc analyses (68, 69).
(v) 9-week, randomized, open-label, standard of care-controlled, phase 2 C10-001 study of Eculizumab for prevention of AMR (NCT01399593) (70).
(w) 9-week, single arm, open-label, phase 2 C10-002 study of Eculizumab for prevention of AMR (NCT01567085) and its 1-year and 3-year extension follow-up studies (71).

(x) 4-week, randomized, open-label, placebo-controlled, phase 2 study of Eculizumab for prevention of reperfusion injury (NCT01756508) and its 1-year and 3-year extension follow-up studies (72).
(y) 4-week, randomized, double-blind, placebo-controlled, phase 1/2 C1INHDGF study of Berinert for prevention of DGF (NCT02134314) (73) and its 1-year extension follow-up study.
(z) 24-week, randomized, double-blind, placebo-controlled phase 2 10-1600 pilot study of Eculizumab for prevention of DGF (NCT01403389), and 24-week, randomized, double-blind, placebo-controlled phase 2 13-0920 study of Eculizumab for prevention of DGF (NCT01919346) (74).
(aa) 26-week, randomized, double-blind, placebo-controlled, phase 2/3 PROTECT study (NCT02145182) and its 1-year extension follow-up study (75).

€For each study and in the case of more than one study, random allocation in a given study and the number of randomized and non-randomized trials in each group of studies are specified. $Until 83% and 75% out of data in country PNH registries (29–41) and country aHUS registries (54–73) were already considered, respectively, into the data of the International PNH registry (24–28) and the Global aHUS registry (50–53). £Two studies assessed complement inhibitors for uses as treatment (76, 77), and not for prevention of aAMR (78–83). ¥Number of individuals undergoing the interventions or exposed to comparisons. @The judgement for each of risk of bias domain in the Cochrane Collaboration tool is presented as (L), (U) or (H) to indicate low, unclear, or high risk of bias, respectively. @The judgement for each of risk of bias domain in the ROBINS-I tool is presented as (L), (M), (S), (C), or (N) to indicate low, moderate, serious, critical, or no information on risk of bias, respectively.

Abbreviations: AA, aplastic anemia; AEGIS, AEGIS registration study of Eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria; aHUS, atypical hemolytic uremic syndrome; AMR, antibody-mediated rejection; C1INHDGF, C1INH (Berinert) for DGF study; DGF, delayed graft function; ECU-MG-302, extension study of ECU-MG-301 to evaluate safety and efficacy of Eculizumab in refractory generalized myasthenia gravis; ICA-GBS, Inhibition of Complement Activation in Guillain-Barré syndrome; JET-GBS, Japanese Eculizumab Trial for Guillain-Barré syndrome; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; PROTECT, Study of Eculizumab for the prevention of delayed graft function after kidney transplantation; REGAIN, safety and efficacy of eculizumab in REfractory GenerAlIzed MyastheNia Gravis; rgMG, refractory generalized myasthenia gravis; ROBINS-I, Risk Of Bias In Non-randomized Studies - of Interventions; SHEPHERD, Safety in HEmolytic PnH patients treated with Eculizumab: a multi-center open-label Research Design; TRIUMPH, Transfusion Reduction efficacy and safety clinical Investigation, a randomized, multicenter, double-blind, placebo-controlled, Using eculizuMab in Paroxysmal nocturnal Hemoglobinuria.

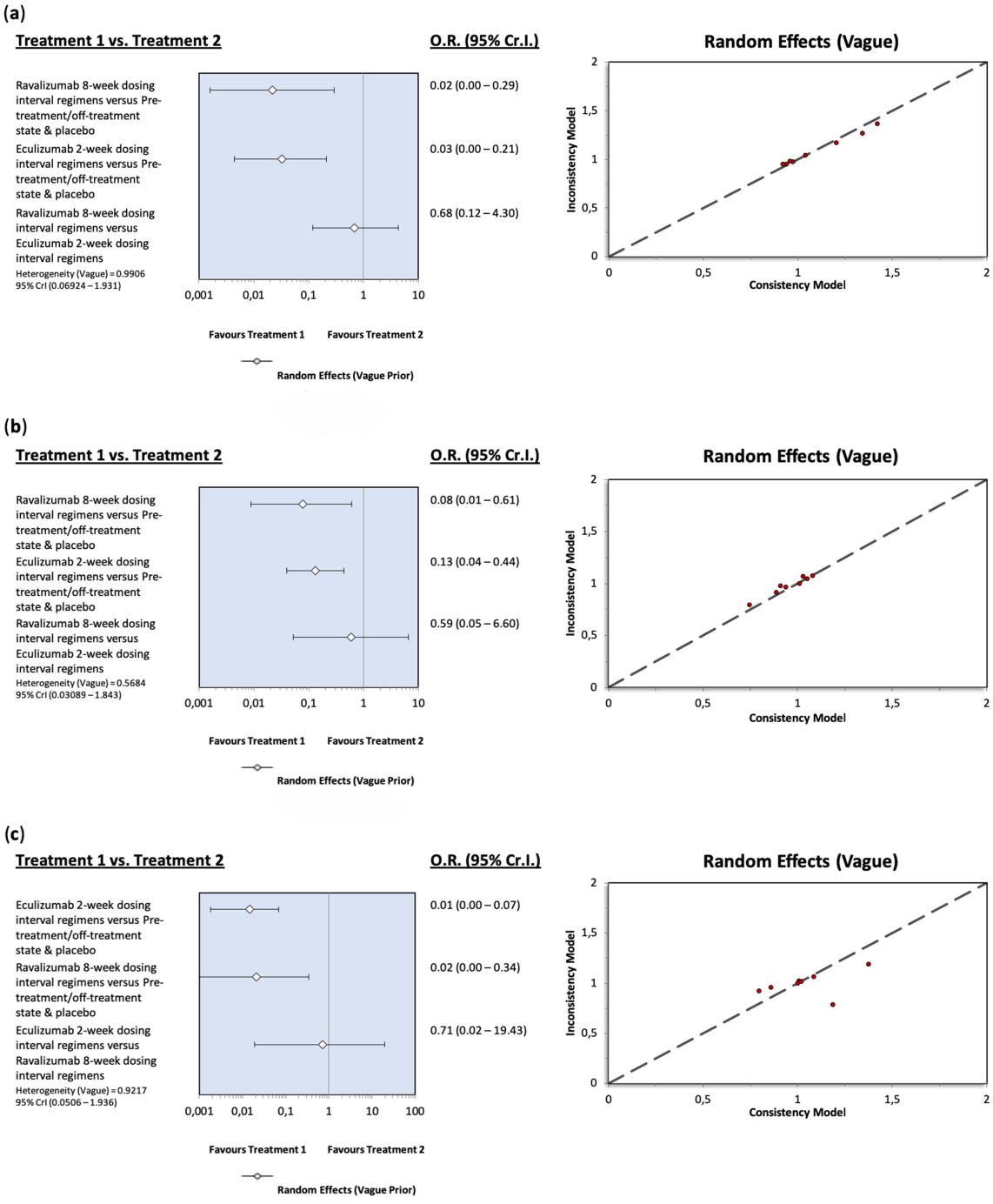

Figure S1. Forest and inconsistency plot for (a) hemolysis in PNH and (b) TMA and (c) AKI in aHUS. aHUS; atypical hemolytic uremic syndrome; AKI; acute kidney injury; PNH, paroxysmal nocturnal hemoglobinuria; TMA, thrombotic microangiopathy

Panel S1. Full search strategy and search results.

Formulae	Citations
PubMed	
((((("hemoglobinuria, paroxysmal"[MeSH Terms]) OR "atypical hemolytic uremic syndrome"[MeSH Terms]) OR "myasthenia gravis"[MeSH Terms]) OR "graft rejection"[MeSH Terms]) OR "delayed graft function"[MeSH Terms]	79553
(((((("paroxysmal nocturnal hemoglobinuria"[Text Word]) OR "atypical hemolytic uremic syndrome"[Text Word]) OR "myasthenia gravis"[Text Word]) OR "antibody mediated rejection"[Text Word]) OR "ischemia reperfusion injury"[Text Word]) OR "delayed graft function"[Text Word]	48752
("eculizumab"[Supplementary Concept]) OR "ravulizumab"[Supplementary Concept]	930
("eculizumab"[Text Word]) OR "soliris"[Text Word]	1663
(("ravulizumab"[Text Word]) OR "ultomiris"[Text Word]) OR "alxn1210"[Text Word]	19
"complement c1 inhibitor protein"[MeSH Terms]	1091
("serping1 protein, human"[Supplementary Concept]) OR "conestat alpha"[Supplementary Concept]	365
((((("c1 esterase inhibitor"[Text Word]) OR "berinert"[Text Word]) OR "cinryze"[Text Word]) OR "haegarda"[Text Word]) OR "ruconest"[Text Word]	1041
Ovid Medline(R)	
exp hemoglobinuria, paroxysmal/ or exp atypical hemolytic uremic syndrome/ or exp myasthenia gravis/ or exp graft rejection/ or exp delayed graft function/ OvidMEDLINE(R) ALL 1946 to September 30, 2019	79540
(paroxysmal adj nocturnal adj hemoglobinuria).tw. or (atypical adj hemolytic adj uremic adj syndrome).tw. or (myasthenia adj gravis).tw. or (antibody adj mediated adj rejection).tw. or (ischemia adj reperfusion adj injury).tw. or (delayed adj graft adj function).tw. Journals@Ovid Subscribed Ovid journals by Sacyl Ovid MEDLINE(R) ALL 1946 to September 30, 2019	113695
(Eculizumab or soliris).tw. Journals@Ovid Subscribed Ovid journals by Sacyl Ovid MEDLINE(R) ALL 1946 to September 30, 2019	4552
(ravulizumab or ultomiris or alxn1210).tw. Journals@Ovid Subscribed Ovid journals by Sacyl Ovid MEDLINE(R) ALL 1946 to September 30, 2019	41
exp complement c1 inhibitor protein/ OvidMEDLINE(R) ALL 1946 to March 31, 2020	1089
(c1 adj esterase adj inhibitor).tw. or berinert.tw. or cinryze.tw. or haegarda.tw. or ruconest.tw. Journals@Ovid Subscribed Ovid journals by Sacyl Ovid MEDLINE(R) ALL 1946 to September 30, 2019	3181
Elsevier's Scopus	
(KEY ("paroxysmal nocturnal hemoglobinuria") OR KEY ("hemolytic uremic syndrome") OR KEY ("myasthenia gravis") OR KEY ("acute graft rejection") OR KEY ("antibody mediated rejection") OR KEY ("delayed graft function")) AND NOT INDEX (medline)	8891
(TITLE-ABS-KEY ("paroxysmal nocturnal hemoglobinuria") OR TITLE-ABS-KEY ("atypical hemolytic uremic syndrome") OR TITLE-ABS-KEY ("myasthenia gravis")	13143

OR TITLE-ABS-KEY ("antibody mediated rejection") OR TITLE-ABS-KEY ("ischemia reperfusion injury") OR TITLE-ABS-KEY ("delayed graft function")) AND NOT INDEX (medline)	
(KEY (eculizumab) OR KEY (ravulizumab)) AND NOT INDEX (medline)	729
(TITLE-ABS-KEY (eculizumab) OR TITLE-ABS-KEY (soliris)) AND NOT INDEX (medline)	788
(TITLE-ABS-KEY (ravulizumab) OR TITLE-ABS-KEY (ultomiris) OR TITLE-ABS-KEY (alxn1210)) AND NOT INDEX (medline)	5
KEY ("complement component C1s inhibitor") AND NOT INDEX (medline)	672
(KEY ("SERPING1 protein,human") OR KEY (haegarda)) AND NOT INDEX (medline)	14
(TITLE-ABS-KEY ("c1 esterase inhibitor") OR TITLE-ABS-KEY (berinert) OR TITLE-ABS-KEY (cinryze) OR TITLE-ABS-KEY (haegarda) OR TITLE-ABS-KEY (ruconest)) AND NOT INDEX (medline)	337
Web of Science	
TOPIC: ("paroxysmal nocturnal hemoglobinuria") OR TOPIC: ("atypical hemolytic uremic syndrome") OR TOPIC: ("myasthenia gravis") OR TOPIC: ("antibody mediated rejection") OR TOPIC: ("ischemia reperfusion injury") OR TOPIC: ("delayed graft function") Web of Science Core Collection Current Contents Connect Derwent Innovations Index KCI-Korean Journal Database Medline Russian Science Citation Index SciELO Citation Index	101709
TOPIC: (eculizumab) OR TOPIC: (soliris) Web of Science Core Collection Current Contents Connect Derwent Innovations Index KCI-Korean Journal Database Medline Russian Science Citation Index SciELO Citation Index	3428
TOPIC: (ravulizumab) OR TOPIC: (ultomiris) OR TOPIC: (alxn1210) Web of Science Core Collection Current Contents Connect Derwent Innovations Index KCI-Korean Journal Database Medline Russian Science Citation Index SciELO Citation Index	41
TOPIC: ("c1 esterase inhibitor") OR TOPIC: (berinert) OR TOPIC: (cinryze) OR TOPIC: (haegarda) OR TOPIC: (ruconest) Web of Science Core Collection Current Contents Connect Derwent Innovations Index KCI-Korean Journal Database Medline Russian Science Citation Index SciELO Citation Index	1929
The Cochrane Central Register of Controlled Trials (CENTRAL)	

MeSH descriptor: [Hemoglobinuria, Paroxysmal] explode all trees or MeSH descriptor: [Atypical Hemolytic Uremic Syndrome] explode all trees or MeSH descriptor: [Myasthenia Gravis] explode all trees or MeSH descriptor: [Graft Rejection] explode all trees or MeSH descriptor: [Delayed Graft Function] explode all trees	2320
("paroxysmal nocturnal hemoglobinuria"):ti,ab,kw OR ("atypical hemolytic uremic syndrome"):ti,ab,kw OR ("myasthenia gravis"):ti,ab,kw OR ("antibody mediated rejection"):ti,ab,kw OR ("ischemia reperfusion injury"):ti,ab,kw OR ("delayed graft function"):ti,ab,kw	2060
(eculizumab):ti,ab,kw OR (soliris):ti,ab,kw	206
(ravulizumab):ti,ab,kw OR (ultomiris):ti,ab,kw OR (alxn1210):ti,ab,kw	27
MeSH descriptor: [Complement C1 Inhibitor Protein] in all MeSH products	73
("c1 esterase inhibitor"):ti,ab,kw OR (berinert):ti,ab,kw OR (cinryze):ti,ab,kw OR (haegarda):ti,ab,kw OR (ruconest):ti,ab,kw	164
ClinicalTrials.gov, the EU Clinical Trials Register, the United Kingdoms' ISRCTN registry	
paroxysmal nocturnal hemoglobinuria Also searched for Paroxysmal Hemoglobinuria, PIGA Gene, and Marchiafava Micheli Syndrome in ClinicalTrials.gov	82
atypical hemolytic uremic syndrome	26
myasthenia gravis	97
antibody mediated rejection	59
ischemia reperfusion injury	293
delayed graft function	71
eculizumab Also searched for Soliris in ClinicalTrials.gov	93
ravulizumab Also searched for ALXN 1210 in ClinicalTrials.gov	12
c1 esterase inhibitor Also searched C1 Inhibitor, C1 Inactivator, Complement C1s, Cinryze, Berinert, and SERPING1 in ClinicalTrials.gov	72
DART Europe E-Theses	
paroxysmal nocturnal hemoglobinuria	17
atypical hemolytic uremic syndrome	300
myasthenia gravis	240
antibody mediated rejection	138
ischemia reperfusion injury	1340
delayed graft function	119
eculizumab	16
ravulizumab	0
c1 esterase inhibitor	26
berinert	2
ruconest	3
Open Access Theses and Dissertations (OATD)	
paroxysmal nocturnal hemoglobinuria	10
atypical hemolytic uremic syndrome	6
myasthenia gravis	107
antibody mediated rejection	37
ischemia reperfusion injury	256
delayed graft function	46
eculizumab	9
ravulizumab	0
c1 esterase inhibitor	27

Berinert	0
ruconest	1
Oral communications and posters presented in relevant medical society meetings	
Free manual search American Association of Immunologists Annual Meeting 2006 to 2019 European Congress of Immunology 2006, 2009, 2012, 2015, and 2018 American Society of Hematology Annual Meeting 2001 to 2019 World Congress of the International Society of Hematology 2002, 2005, 2007, 2008, 2010, 2012, 2014, 2016, and 2018 American Academy of Neurology Annual Meeting 2002 to 2019 World Congress of Neurology 2001, 2005, 2009, 2011, 2013, 2015, 2017, and 2019 American Society of Nephrology (ASN) Kidney Week 2003 to 2019 International Society of Nephrology (ISN) World Congress of Nephrology 2001, 2003, 2005, 2007, 2009, 2011, 2013, 2015, 2017, and 2019 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress 2003 to 2019 American Transplant Congress 2002-2005, 2007-2013, and 2015-2019 World Transplant Congress 2006 and 2014	42

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