# Supplementary Table 1. Classification of the importance of the outcomes

|  |  |  |
| --- | --- | --- |
| **Classification** | **Outcome** | **Average score** |
| **CRITICAL (7 to 9)**  Outcome critical for decision making | Response time to treatment | 8,7 |
| Response to treatment | 9 |
| Recurrence | 8,7 |
| Clinical remission | 9 |
| Relapse | 8,7 |
| Exacerbation | 8,7 |
| Refractory aTTP | 8,7 |
| Quality of life | 8,3 |
| Mortality | 9 |
| Number of days of plasma exchange | 8,0 |
| Volume of plasma exchange | 7,3 |
| Number of days of hospitalization | 8,0 |
| Number of days in intensive care unit | 8,0 |
| Any adverse event | 7,0 |
| Serious adverse events | 8,3 |
| Serious adverse events related to the drug | 8,7 |
| Any adverse event related to the drug | 8,0 |
| Discontinuation or interruption of treatment due to an adverse event | 8,7 |
| Adverse events of interest (bleeding) | 9 |

# Supplementary Table 2. Complete search strategies

|  |  |
| --- | --- |
| **Electronic search report No. 1** | |
| **Type of search** | New |
| **Database** | Ovid MEDLINE(R) ALL 1946 to February 25, 2022 |
| **Platform** | OVID |
| **Date of search** | 01/03/2022 |
| **Range of search dates** | Without restriction |
| **Language restrictions** | Without restriction |
| **Other limits** | Clinical trials |
| **Search strategy (results)** | 1. exp Purpura, Thrombotic Thrombocytopenic/ (4,877) 2. (Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (5,010) 3. (Thrombotic adj3 Thrombopenic adj3 Purpura).ab,ti. (47) 4. (Acquired adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (311) 5. (Autoimmune adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (53) 6. (Immune adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (135) 7. (Immune-mediated adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (75) 8. ((Acquired or autoimmune or immune-mediated or immune) adj3 TTP).ab,ti. (359) 9. aTTP.ab,ti. (671) 10. iTTP.ab,ti. (103) 11. TTP.ab,ti. (8,795) 12. cTTP.ab,ti. (35) 13. Chronic TTP.ab,ti. (9) 14. Thrombotic Microangiopathies.ab,ti. (590) 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (13,232) 16. Caplacizumab.ab,ti. (145) 17. Caplacizumab-yhdp.ab,ti. (2) 18. ALX-0081.ab,ti. (11) 19. "ALX 0081".ab,ti. (11) 20. Cablivi.ab,ti. (9) 21. exp Single-Domain Antibodies/ (1,631) 22. exp ADAMTS13 Protein/ (2,065) 23. Factor VIII concentrate.ab,ti. (683) 24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (4,385) 25. exp Plasma Exchange/ (6,872) 26. "Plasma Exchange\*".ab,ti. (9,391) 27. (Plasma adj3 exchange\*).ab,ti. (10,423) 28. PEX.ab,ti. (1,453) 29. (therap\* adj3 plasma adj3 Exchange\*).ab,ti. (2,557) 30. TPE.ab,ti. (3,846) 31. exp Rituximab/ (17,017) 32. Rituximab.ab,ti. (23,693) 33. Current treatment.ab,ti. (20,292) 34. Conventional treatment.ab,ti. (12,760) 35. "Glucocorticoid\*".ab,ti. (73,347) 36. "Steroid\*".ab,ti. (248,412) 37. exp Glucocorticoids/ (201,395) 38. "Corticosteroid\*".ab,ti. (112,207) 39. "Immunosuppress\*".ab,ti. (162,823) 40. (Immunosuppress\* adj3 therap\*).ab,ti. (25,653) 41. exp "Standard of Care"/ (4,859) 42. "Care Standard\*".ab,ti. (1,430) 43. "Standard\* of Care".ab,ti. (58,953) 44. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (770,347) 45. 15 and 24 (1,418) 46. 44 and 45 (46) |
| **References identified** | 46 |
| **Electronic search report No. 2** | |
| **Type of search** | New |
| **Database** | Embase |
| **Platform** | Elsevier |
| **Date of search** | 01/03/2022 |
| **Range of search dates** | Without restriction |
| **Language restrictions** | Without restriction |
| **Other limits** | ('clinical trial'/de OR 'clinical trial topic'/de OR 'controlled clinical trial'/de OR 'phase 1 clinical trial topic'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial topic'/de OR 'phase 3 clinical trial topic'/de OR ‘randomized controlled trial'/de OR 'randomized controlled trial topic'/de)  [article]/lim  [humans]/lim  [embase]/lim |
| **Search strategy (results)** | #1. 'thrombotic thrombocytopenic purpura'/exp (18,700)  #2. (thrombotic NEAR/3 thrombocytopenic NEAR/3 purpura):ab,ti (7,469)  #3. (thrombotic NEAR/3 thrombopenic NEAR/3 purpura):ab,ti (50)  #4. (acquired NEAR/3 thrombotic NEAR/3 thrombocytopenic NEAR/3 purpura):ab,ti (619)  #5. (autoimmune NEAR/3 thrombotic NEAR/3 thrombocytopenic NEAR/3 purpura):ab,ti (112)  #6. (immune NEAR/3 thrombotic NEAR/3 thrombocytopenic NEAR/3 purpura):ab,ti (277)  #7. ('immune mediated' NEAR/3 thrombotic NEAR/3 thrombocytopenic NEAR/3 purpura):ab,ti (143)  #8. ((acquired OR autoimmune OR 'immune mediated' OR immune) NEAR/3 ttp):ab,ti (819)  #9. attp:ab,ti (886)  #10. ittp:ab,ti (225)  #11. ttp:ab,ti (16,645)  #12. cttp:ab,ti (90)  #13. 'chronic ttp':ab,ti (13)  #14. 'thrombotic microangiopathies':ab,ti (938)  #15. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR#9 OR #10 OR #11 OR #12 OR #13 OR #14 (31,872)  #16. 'caplacizumab' (480)  #17. caplacizumab:ab,ti (254)  #18. 'caplacizumab yhdp':ab,ti (1)  #19. 'alx 0081':ab,ti (20)  #20. 'alx 0081':ab,ti (20)  #21. cablivi:ab,ti (9)  #22. 'nanobody'/exp (2,989)  #23. 'von willebrand factor cleaving proteinase'/exp (5,611)  #24. 'factor viii concentrate':ab,ti ( 913)  #25. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 ( 9,692)  #26. 'plasma exchange'/exp (8,932)  #27. 'plasma exchange\*':ab,ti (16,283)  #28. (plasma NEAR/3 exchange\*):ab,ti (17,496)  #29. pex:ab,ti (2,425)  #30. (therap\* NEAR/3 plasma NEAR/3 exchange\*):ab,ti (4,757)  #31. tpe:ab,ti (5,006)  #32. 'rituximab'/exp (93,602)  #33. rituximab:ab,ti (53,570)  #34. 'current treatment':ab,ti (30,563)  #35. 'conventional treatment':ab,ti (18,695)  #36. 'glucocorticoid\*':ab,ti (98,195)  #37. 'steroid\*':ab,ti (362,346)  #38. 'glucocorticoid'/de (96,983)  #39. 'corticosteroid\*':ab,ti (173,770)  #40. 'immunosuppress\*':ab,ti (252,599)  #41. ('immunosuppress\*' NEAR/3 therap\*):ab,ti (42,046)  #42. 'care standard\*':ab,ti (2,097)  #43. 'standard\* of care':ab,ti (80,930)  #44. #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 (1,036,694)  #45. #15 AND #25 (3,765)  #46. #44 AND #45 (2,065)  #47. #44 AND #45 AND [article]/lim AND [humans]/lim AND [embase]/lim (733)  #48. #47 AND ('clinical trial'/de OR 'clinical trial topic'/de OR 'controlled clinical trial'/de OR 'phase 1 clinical trial topic'/de OR 'phase 2 clinical trial'/de OR 'phase 2 clinical trial topic'/de OR 'phase 3 clinical trial topic'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de) (34) |
| **References identified** | 34 |
| **Electronic search report No. 3** | |
| **Type of search** | New |
| **Database** | Cochrane Central Register of Controlled Trials <January 2022> |
| **Platform** | OVID |
| **Date of search** | 01/03/2022 |
| **Range of search dates** | Without restriction |
| **Language restrictions** | Without restriction |
| **Other limits** | None |
| **Search strategy (results)** | 1. exp Purpura, Thrombotic Thrombocytopenic/ (39) 2. (Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti (176) 3. (Thrombotic adj3 Thrombopenic adj3 Purpura).ab,ti. (2) 4. (Acquired adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (81) 5. (Autoimmune adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (3) 6. (Immune adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (7) 7. (Immune-mediated adj3 Thrombotic adj3 Thrombocytopenic adj3 Purpura).ab,ti. (7) 8. ((Acquired or autoimmune or immune-mediated or immune) adj3 TTP).ab,ti. (41) 9. aTTP.ab,ti. (59) 10. iTTP.ab,ti. (8) 11. TTP.ab,ti. (2,058) 12. cTTP.ab,ti. (4) 13. Chronic TTP.ab,ti. (0) 14. Thrombotic Microangiopathies.ab,ti. (16) 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (2,124) 16. Caplacizumab.ab, ti. (67) 17. Caplacizumab-yhdp. ab,ti. (0) 18. ALX-0081.ab,ti. (6) 19. "ALX 0081".ab,ti. (6) 20. Cablivi.ab,ti. (0) 21. exp Single-Domain Antibodies/ (8) 22. exp ADAMTS13 Protein/ (0) 23. Factor VIII concentrate.ab,ti. (54) 24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (128) 25. exp Plasma Exchange/ (213) 26. "Plasma Exchange\*".ab,ti. (904) 27. (Plasma adj3 exchange\*).ab,ti. (987) 28. PEX.ab,ti. (169) 29. (therap\* adj3 plasma adj3 Exchange\*).ab,ti. (264) 30. TPE.ab,ti. (214) 31. exp Rituximab/ (0) 32. Rituximab.ab,ti. (5,520) 33. Current treatment.ab,ti. (2,512) 34. Conventional treatment.ab,ti. (5,176) 35. "Glucocorticoid\*".ab,ti. (5,596) 36. "Steroid\*".ab,ti. (26,778) 37. exp Glucocorticoids/ (189,962) 38. "Corticosteroid\*".ab,ti. (22,881) 39. "Immunosuppress\*".ab,ti. (11,402) 40. (Immunosuppress\* adj3 therap\*).ab,ti. (2,288) 41. exp "Standard of Care"/ (348) 42. "Care Standard\*".ab,ti. (1,247) 43. "Standard\* of Care".ab,ti. (33,112) 44. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (111,587) 45. 15 and 24 (66) 46. 44 and 45 (54) |
| **References identified** | 54 |
| **Electronic search report No. 4** | |
| **Type of search** | New |
| **Database** | WHO International Clinical Trials Registry Platform |
| **Platform** | ICTRP portal |
| **Date of search** | 01/03/2022 |
| **Range of search dates** | Without restriction |
| **Language restrictions** | Without restriction |
| **Other limits** | None |
| **Search strategy (results)** | Caplacizumab AND acquired thrombotic thrombocytopenic purpura |
| **References identified** | 8 |

# Supplementary Table 3. Matrix inputs for the classification of technology

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Caplacizumab plus standard regimen vs standard regimen** | | | | |
| **Statistical estimator \***  **(95% CI)** | **Certainty of the evidence** | **Therapeutic threshold** | **Estimator with respect to threshold** | **Acceptability** |
| **Response to treatment (critical)** | | | | |
| **Relative\*** | Low | 8 patients more than the comparator for every 100 patients | **Greater** | YES |
| 1.55  (1.09 to 2.19) |
| **Absolute** |
| 48 more per 100 (from 8 more to 100 more) |
| **Composite outcome (aTTP-related death, aTTP recurrence, or at least one major thromboembolic event) – (critical)** | | | | |
| **Relative** | Low | 25 patients fewer than the comparator for every 100 patients | **Greater** | YES |
| 0.25 (0.13 to 0.49) |
| **Absolute** |
| 37 fewer per 100 (from 25 fewer to 43 fewer) |
| **Recurrences (exacerbation and relapse) –(critical)** | | | | |
| **Relative** | Low | 25 patients fewer than the comparator for every 100 patients | **Same** | YES |
| 0.33 (0.17 to 0.64) |
| **Absolute** |
| 26 fewer per 100 (from 14 fewer to 32 fewer) |
| **Composite outcome (death and refractoriness at 30 days after diagnosis) – (critical)** | | | | |
| **Relative** | Very low | 7 patients fewer than the comparator for every 100 patients | **Same** | YES |
| 0.18  (0.04 to 0.75) |
| **Absolute** |
| 10 fewer per 100 (from 3 fewer to 12 fewer) |
| **Refractoriness (critical)** | | | | |
| **Relative** | Very low | 6 patients fewer than the comparator for every 100 patients | **Same** | YES |
| 0.12  (0.02 to 0.93) |
| **Absolute** |
| 8 fewer per 100 (from 1 fewer to 9 fewer) |
| **Exacerbations (critical)** | | | | |
| **Relative** | Very low | 24 patients fewer than the comparator for every 100 patients | **Greater** | YES |
| 0.09  (0.03 to 0.26) |
| **Absolute** |
| 36 fewer per 100 (from 29 fewer to 38 fewer) |
| **Response time to treatment (critical)** | | | | |
| **Median (IQR)** | Very low | Minimum reduction of 3 days in median response time to treatment. | **Less** | YES |
| 4∙0(3 ‐ 8) |
| **Absolute** |
| Reduction of 2 days in median response time to treatment. |
| **Number of days of plasma exchange (critical)** | | | | |
| **Median (Q1-Q3)** | Very low | Minimum reduction of 5 days in median hospital stay. | **Same** | YES |
| 5 (4-7) |
| **Absolute** |
| Reduction of 5 days in the median number of days of plasma exchange. |
| **Number of days of hospitalization (critical)** | | | | |
| **Median (Q1-Q3)** | Very low | Minimum reduction of 8 days in median hospital stay | **Greater** | YES |
| 13 (9-19) |
| **Absolute** |
| Reduction of 9 days in median hospital stay. |
| **Serious adverse events (critical)** | | | | |
| **Relative** | Low | 15 patients more than the comparator for every 100 patients | **Same** | YES |
| 1.98  (1.06 to 3.7) |
| **Absolute** |
| 16 more per 100 (from 1 more to 44 more) |
| **Bleeding adverse events (critical)** | | | | |
| **Relative** | Low | 20 patients more than the comparator for every 100 patients | **Same** | YES |
| 1.35  (1.01 to 1.81) |
| **Absolute** |
| 17 more per 100 (from 0 fewer to 39 more) |
| **Serious bleeding adverse events (critical)** | | | | |
| **Relative** | Low | 1 patient more than the comparator for every 100 patients | **Same** | YES |
| 8.23  (1.06 to 64) |
| **Absolute** |
| 10 more per 100 (from 0 fewer to 86 more) |
| **Gingival bleeding (critical)** | | | | |
| **Relative** | Low \* | 20 patients more than the comparator for every 100 patients | **Same** | YES |
| 13.4  (1.8 to 99.5) |
| **Absolute** |
| 17 more per 100 (from 1 more to 100 more) |
| **Epistaxis (critical)** | | | | |
| **Relative** | Low\* | 18 patients more than the comparator for every 100 patients | **Same** | YES |
| 11.9  (2.9 to 48) |
| **Absolute** |
| 30 more per 100 (from 5 more to 100 more) |
| \* Relative risk of the comparison of Caplacizumab plus plasma exchange versus the standard regimen  CI= Confidence interval | | | | |

# Supplementary Table 4. Classification categories - IETS

|  |  |
| --- | --- |
| **Health technology classification categories, according to the IETS** | |
| Superior | The technology offers a better benefit-risk balance than its comparator or comparators, that is, the benefits and risks exceed the therapeutic thresholds, they are acceptable to the users of the technology (health professionals and patients) and there is certainty in the evidence used. |
| No difference  (regarding equivalence in Resolution 586 of 2021 as no difference) | The technology offers a benefit-risk balance similar to that of its comparator or comparators, that is, the benefits and risks do not exceed the therapeutic thresholds, but are as acceptable by the users of the technology (health professionals and patients) as the comparator and there is certainty in the evidence used. |
| Inferior | The technology offers a lower benefit-risk balance than its comparator or comparators, that is, the benefits are less and the risks are greater or equal, so that they are not acceptable to the users of the technology (health professionals and patients) and there is certainty in the evidence used |
| Grounds for non-pronunciation and rejection | When the certainty of the evidence is very low or there is not enough information to carry out the classification. |
| Taken from: IETS. Manual for the request and issuance of concepts on the evaluations of health technologies carried out by third parties. Instituto de Evaluación Tecnológica en Salud -IETS. 2021. | |

# Supplementary Table 5. Characteristics of the randomized clinical trials

|  |  |  |
| --- | --- | --- |
| **Randomized clinical trials** | | |
| **Name of study** | **HERCULES** | **TITAN** |
| **NCT** | NCT02553317 | NCT01151423 |
| **(Author, year)** | Scully et al. 2019 | Peyvandi et al. 2016 |
| **Status of publication** | Published | Published |
| **Design** | Randomized, phase III, double-blind, placebo-controlled, multicenter clinical trial | Phase II randomized, single-blind, placebo-controlled, multicenter clinical trial |
| **Eligible population** | Adult patients (≥18 years of age) with a clinical diagnosis of aTTP whose clinical presentation included thrombocytopenia and hemolytic anemia and who had received prior treatment with plasma exchange were included. | Adult patients (≥18 years) who had shown an acute episode of aTTP, with a platelet count less than 100,000 per cubic millimeter, without active bleeding, and who required plasma exchange. |
| **Location** | 92 sites in 16 countries: Australia (6), Austria (1), Belgium (4), Canada (4), Czech Republic (4), France (9), Germany (9), Hungary (2), Israel (7), Italy (5), the Netherlands (4), Spain (6), Switzerland (2), Turkey (6), the United Kingdom (4) and the United States (19). | 56 sites in 13 countries: Australia (4), Austria (2), Belgium (4), Bulgaria (1), France (1), Germany (9), Israel (3), Italy (5), Romania (2), Spain (4), Switzerland (3), United Kingdom (4) and United States (14). |
| **Intervention** | **Caplacizumab** | **Caplacizumab** |
| * Caplacizumab 10 mg (intravenous) before the first plasma exchange after randomization. * Subsequent caplacizumab doses of 10 mg (subcutaneous) once daily, up to 30 days after the last daily plasma exchange. * ● Administration of caplacizumab or placebo could be extended for a maximum of 28 days beyond 30 days, depending on risk factors for aTTP recurrence. | * Caplacizumab 10 mg (intravenous) at any time from 6 hours before to 15 minutes before the start of the first plasma exchange after randomization. * Subsequent caplacizumab doses of 10 mg (subcutaneous) daily within 30 minutes after the end of each plasma exchange. This subcutaneous administration was continued for 30 days after the last plasma exchange. * The maximum duration of the administration of the drug in the study was 90 days. |
| **Glucocorticoids** | **Glucocorticoids** |
| * Prednisone or prednisolone at a dose of ≥1 mg per kilogram of body weight per day during the period of daily plasma exchange and continuing for the first week after the end of the period of daily plasma exchange. * Other immunosuppressive therapy was allowed in accordance with clinical practice at each site. * Subsequently, glucocorticoid treatment could be reduced at the discretion of the investigator, with the goal of completely discontinuing glucocorticoid treatment within 30 days of the last plasma exchange. | Depending on local practice and the judgment of the Investigator, it could include one or more of the following:   * Immunosuppressive treatment (including glucocorticoids and rituximab) |
| **Plasma exchange** | **Plasma exchange** |
| * 1 to 1.5 times the estimated plasma volume, until at least 2 days after normalization of the platelet count. | Based on local practice and judgment of the investigator. Discontinuation was dependent on normalization of platelet count, neurological status, and other clinical and laboratory parameters. Gradual reduction of plasma exchange was left to the discretion of the investigator. |
| **Comparators** | **Placebo** | **Placebo** |
| * As caplacizumab but without the active ingredient | * As caplacizumab but without the active ingredient |
| **Glucocorticoids** | **Glucocorticoids** |
| * As the comparator | * As the comparator |
| **Plasma exchange** | **Plasma exchange** |
| * As the comparator | * As the comparator |
| **Outcomes** | **Clinical effectiveness**   * Response time to treatment (normalization of platelet count). * Composite outcome of aTTP-related death, aTTP recurrence, or an important thromboembolic event. * aTTP recurrences. * Exacerbations. * Relapses. * Refractory aTTP. * Major thromboembolic events. * Time until normalization of the three markers of organ damage (lactate dehydrogenase, cardiac troponin I and serum creatinine) * Number of days of plasma exchange * Total volume of plasma used * Number of days in an intensive care unit * Number of days of hospitalization * Mortality rate.   Safety   * Adverse events * Serious adverse events * Adverse events related to bleeding | **Clinical effectiveness**   * Time to normalization of platelet count * Exacerbations * Relapses * Complete remission * Number of days of plasma exchange * Mortality rate * Total volume of plasma used * Time until normalization of the three markers of organ damage (lactate dehydrogenase, cardiac troponin I and serum creatinine) * Major thromboembolic events.   Safety   * Adverse events * Serious adverse events * Adverse events related to bleeding |
| **Hypothesis testing. Statistical analysis** | The hypothesis tested was the superiority of caplacizumab versus placebo with respect to time to normalization of platelet count (baseline platelet count ≥150 x 109/L with discontinuation the administration of plasma exchange within 5 days).  The main outcome was compared between study groups using a two-sided stratified log-rank test based on a Kaplan-Meier analysis; the stratification factor was the severity of neurologic involvement at the baseline (i.e, Glasgow Coma Scale score of ≤12 vs >13). In addition, data for this outcome was also analyzed using a Cox regression model, with time to normalization of platelet count as the dependent variable and treatment group and Glasgow Coma Scale category as independent variables, in order to calculate the hazard ratio.  For their part, the first three secondary results were analyzed using a Cochran-Mantel-Haenszel test; the model included adjustments for baseline severity of neurologic involvement. The fourth outcome was analyzed using a stratified log-rank test that was based on a Kaplan-Meier analysis, adjusting for severity of baseline neurologic involvement and baseline lactate dehydrogenase level. | The hypothesis tested was the superiority of caplacizumab versus placebo with respect to time to confirmed normalization of platelet count (platelet recovery ≥150 × 109/L confirmed at 48 hours by a de novo measurement of platelet counts ≥150 x 109/L and LDH ≤2 x ULN).  Time to response was compared between groups using a one-sided stratified log-rank test based on a Kaplan-Meier analysis; the stratification factor was the absence/presence of a plasma exchange session prior to randomization.  The hazard ratio for response time was estimated using a Cox proportional-hazards regression model, with a covariate of a plasma exchange session before randomization (yes/no). |
| **Sample size** | 145  Caplacizumab group 72; Placebo group 73 | 75  Caplacizumab group 36; Placebo group 39 |
| **Period of study** | October 2010 to January 2014 | November 2015 to April 2017 |
| **Losses (discontinuation)** | 1 patient in the placebo group | 1 patient in the Caplacizumab group |
| **Sources of funding** | Ablynx. | Ablynx. |
| **Conclusions** | Among TTP patients, caplacizumab treatment was associated with more rapid normalization of platelet count; a lower incidence of a combination of TTP-related death, TTP recurrence, or a thromboembolic event during the treatment period; and a lower rate of TTP recurrence during the trial than the placebo. | Caplacizumab induced faster resolution of the acute TTP episode than the placebo. The platelet protective effect of caplacizumab was maintained during the treatment period. In addition, caplacizumab was associated with an increased risk of bleeding, compared with the placebo. |

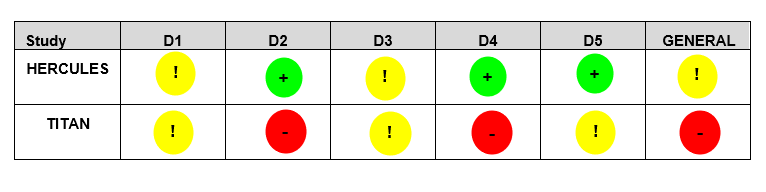
# Supplementary Table 6. Characteristics of the real-world studies

|  |  |  |  |
| --- | --- | --- | --- |
| **Study (Author, year)** | **Völker et al. 2020** | **Coppo et al. 2021** | **Dutt et al 2021** |
| **Status of publication** | Published | Published | Published |
| **Design** | Retrospective observational study | Prospective observational study | Retrospective observational study |
| **Eligible population** | Patients with a diagnosis of aTTP who received caplacizumab at 29 German centers. | Patients with a confirmed diagnosis of aTTP, who were treated with a triple regimen of caplacizumab, plasma exchange, glucocorticoids and rituximab as the first line at 32 French centers | Patients of any age, who had received ≥1 doses of caplacizumab via the access regimen, following a confirmed diagnosis of acute TTP, at 22 UK centers. |
| **Location** | Germany | France | United Kingdom (England, Scotland and Wales) |
| **Intervention** | * Caplacizumab * Daily plasma exchange * Glucocorticoids * Czuon or without other immunosuppressant | * Daily plasma exchange * Corticosteroids (prednisone 1.0 mg/kg per day [maximum dose, 100 mg/day]) * Caplacizumab (10 mg intravenous loading dose followed by 10 mg subcutaneous doses daily) * Rituximab (375 mg/m2) was administered intravenously on a schedule of days 1-4-8-15. | * Caplacizumab * Daily plasma exchange * Glucocorticoids * Rituximab |
| **Comparators** | NA  Only the cohort of patients who received caplacizumab was analyzed | * Plasma exchange and glucocorticoids in association with rescue rituximab in patients experiencing refractoriness or a disease exacerbation | * Daily plasma exchange * Glucocorticoids * Rituximab |
| **Outcomes** | * Time to normalization of platelet count * Number of days of hospitalization * Number of days in intensive care unit * Exacerbations * Relapses * Death * Refractory aTTP * Clinical remission * Adverse events. | * Composite outcome of death and refractoriness within 30 days of diagnosis * Refractoriness * Death * Exacerbations * Time to lasting recovery of platelet count * Number of days of plasma exchange * Total plasma volume used * Number of days of hospitalization * Adverse events related to caplacizumab | * Time to normalization of platelet count * Recurrences * Exacerbations * Relapses * Refractoriness * Number of days of plasma exchange * Mortality * Number of days of hospitalization * Adverse events |
| **Sample size** | n=60 | n=270  Caplacizumab cohort 90; historic cohort with standard regimen 180 | 124  Caplacizumab cohort 85 (4 pediatric patients); historic cohort with standard regimen 39 |
| **Period of study** | June 2018 to December 2019  The median follow-up was 108.5 days (range 3-330), for a total of 7484 patient-days. | Caplacizumab cohort  September 2018 to December 2019 | Caplacizumab cohort  May 2018 to January 2020  The median follow-up period (from caplacizumab start date to last documented clinical follow-up) was 80 days (IQR, 59-166). |
| Historic cohort  June 2015 to September 2018 | Historic cohort  2014 to 2018 |
| **Losses %** | NA | Does not report any loss to prospective follow-up. | NA |
| **Techniques to control confounding** | NA  No comparison was made with another cohort. | The authors carried out a formal statistical comparison of the baseline clinical and demographic characteristics of the study patients, showing that the clinical presentation and demographic characteristics of the patients in the triple regimen cohort were comparable to the patients of the historical cohort, except for the LDH level (P = 0.01), providing evidence that the cohort of patients with caplacizumab that was studied is representative of the aTTP population.  In addition, because the follow-up time varied between the patients, the authors used Poisson regression for the evaluation of the results.  Despite all of the above, they do not specify or identify any other technique for controlling confounding. | The authors performed a formal statistical comparison of the baseline clinical and demographic characteristics of the study patients, showing that the clinical presentation and demographic characteristics of the patients in the caplacizumab cohort were comparable to those of the historical cohort for all main characteristics.  The authors do not report any type of adjustment for the estimates made. In addition, they do not specify or identify any technique for controlling confounding. |
| **Sources of funding** | Not reported | French Ministry of Health (Projet Hospitalier de Recherche Clinique, P120118, AOM12259).  National Plan for Rare Diseases from the French Ministry of Health (Direction Générale de l'Offre de Soin). | Not reported |
| **Conclusions** | Caplacizumab is effective in the treatment of aTTP regardless of timing and method of auxiliary treatment.  The study data confirm the results reported in the TITAN and HERCULES trials in the German population in a real care setting despite considerably heterogeneous treatment regimens. This real evidence allows for a generalization of the effectiveness of caplacizumab to treat acute episodes of aTTP beyond the internal validity of randomized controlled trials.  In addition, based on these data and the available literature, the authors propose administering caplacizumab to all patients with an acute episode of aTTP and administering plasma exchange until thrombocytes exceed the limits of 100 x 10 9 /L to 150 × 10 9 /L. | This study provides evidence that patients treated with the triple regimen have a favorable outcome regardless of the severity of the disease at diagnosis, suggesting that caplacizumab eliminates the negative impact of brain involvement and the very high level of LDH.  Additionally, the data from this study confirm the results of trials of caplacizumab in unselected aTTP patients.  Finally, a triple strategy that systematically combines plasma exchange, immunosuppression with corticosteroids and rituximab and caplacizumab prevents unfavorable disease outcomes and substantially alleviates the burden of care in these patients. | This real evidence study confirms the therapeutic benefits of caplacizumab and the bleeding risk inherent with this drug.  In addition, this study describes the severe disease phenotype of patients displaying acute aTTP, along with a reduced time to normalization of platelet count and duration of plasma exchange in patients receiving caplacizumab, which are comparable to clinical trial data.  The authors report that caplacizumab is in wide use in the UK and present in current clinical practice. |

# Supplementary Table 7. Quality of evidence from clinical trials RoB2

|  |  |  |
| --- | --- | --- |
| **Domain** | **Scully et al. 2019^** | **Peyvandi et al. 2016£** |
| (1) Bias derived from the randomization process. | Some concerns | Some concerns |
| (2) Bias due to deviations from planned interventions | Low risk of bias | High risk of bias. |
| (3) Bias due to lack of outcome data. | Some concerns | Low risk of bias |
| (4) Bias in outcome measurement. | Low risk of bias | High risk of bias |
| (5) Bias in the selection of the reported outcome. | Low risk of bias | Some concerns |
| Overall risk of bias | Some concerns ¶ | High risk of bias **‡** |
| ¶ The trial is judged to raise **some concerns** in at least one domain for this outcome, but does not have a high risk of bias for any domain  ‡ The trial is judged to have a **high risk of bias** in at least one domain for this outcome.  **£** Observed in this study: early study termination, 12 protocol amendments (some major), problems with central and local laboratories, missing data (to an extent often unclear to the assessor), blinding performed only to patients, several important post-hoc analyzes were performed, 64% of patients had a deviation from the protocol and an imbalance was identified between patients in relation to gender, the proportion of patients with an ADAMTS13 activity level of 10% or higher, the proportion of patients treated with plasma exchange before randomization, and the use of rituximab.  **^** Censoring methods were used in the data analysis to account for missing event data in the analysis of KM. In addition, missing data were only imputed for the criterion of evaluating patients with refractory TTP. In addition, compared with the placebo group, patients in the caplacizumab group had fewer prior aTTP episodes, were characterized as having more severe conditions, had fewer patients with ADAMTS13 levels less than 10%, and had higher levels of cardiac troponin I and higher levels of LDH at the start of the study. | | |

**Supplementary Figure 1. Risk of bias summary.**



# Supplementary Table 8. Quality of evidence from real-world studies

|  |  |  |  |
| --- | --- | --- | --- |
| **Items to assess biases** | **Dutt et al. 2021** | **Völker et al. 2020** | **Coppo et al. 2021** |
| Were the two groups similar and were they recruited from the same population? | Yes | Not applicable | Yes |
| Were exposures measured in a similar way to assign people to exposed and unexposed groups? | Not applicable | Not applicable | Not applicable |
| Was the exposure measured in a valid and reliable way? | Yes | Yes | Yes |
| Were confounding factors identified? | Yes | Not applicable | Yes |
| Were strategies to deal with confounding factors indicated? | No | Not applicable | No |
| Were the groups/participants outcome-free at the start of the study (or at the time of exposure)? | Yes | Yes | Yes |
| Were the outcomes measured in a valid and reliable way? | Yes | Yes | Yes |
| Was the follow-up time reported and was it long enough for the results to be produced? | Yes | Yes | Yes |
| Was the follow-up completed and, if not, were reasons for loss of follow-up described and explored? | Not applicable | Not applicable | Not applicable |
| Were strategies used to address incomplete follow-up? | Not applicable | Not applicable | Not applicable |
| Was an adequate statistical analysis used? | Yes | Yes | Yes |
| **Overall quality level assessed by evaluators:** | **Low ¶** | **Moderate** | **Low¶** |
| **¶** There are differences in some characteristics between the reference groups, which were not adjusted in the estimates made. | | | |

# Supplementary Table 9. Safety results clinical trial Hercules- Treatment-emergent adverse events reported in at least 5% of subjects in either treatment group.

|  |  |  |
| --- | --- | --- |
| **System Organ Class Preferred Term; n (%)** | **Caplacizumab** ¥  **(N = 71)** | **Placebo**†  **(N = 73)** |
| **At least one TEAE** | **68 (95.8)** | **66 (90.3)** |
| **General Disorders and Administration Site Conditions** | **37 (52.1)** | **36 (49.3)** |
| Catheter site hemorrhage | 5 (7.0) | 5 (6.8) |
| Fatigue | 10 (14.1) | 6 (8.2) |
| Pyrexia | 10 (14.1) | 6 (8.2) |
| Edema peripheral | 4 (5.6) | 7 (9.6) |
| Asthenia | 3 (4.2) | 4 (5.5) |
| Chest pain | 1 (1.4) | 5 (6.8) |
| Catheter site pain | 1 (1.4) | 5 (6.8) |
| Injection site pain | 1 (1.4) | 4 (5.5) |
| Pain | 4 (5.6) | 1 (1.4) |
| **Gastrointestinal Disorders** | **36 (50.7)** | **27 (37.0)** |
| Nausea | 10 (14.1) | 7 (9.6) |
| Gingival bleeding | 13 (18.3) | 1 (1.4) |
| Constipation | 7 (9.9) | 5 (6.8) |
| Diarrhea | 7 (9.9) | 5 (6.8) |
| Abdominal pain | 5 (7.0) | 4 (5.5) |
| Vomiting | 3 (4.2) | 4 (5.5) |
| **Nervous System Disorders** | **32 (45.1)** | **27 (37.0)** |
| Headache | 16 (22.5) | 6 (8.2) |
| Dizziness | 7 (9.9) | 8 (11.0) |
| Paresthesia | 8 (11.3) | 6 (8.2) |
| **Skin and Subcutaneous Tissue Disorders** | **23 (32.4)** | **28 (38.4)** |
| Urticaria | 12 (16.9) | 5 (6.8) |
| Rash | 5 (7.0) | 9 (12.3) |
| Pruritus | 5 (7.0) | 6 (8.2) |
| Petechiae | 4 (5.6) | 5 (6.8) |
| Ecchymosis | 2 (2.8) | 4 (5.5) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **32 (45.1)** | **14 (19.2)** |
| Epistaxis | 23 (32.4) | 2 (2.7) |
| Dyspnea | 7 (9.9) | 2 (2.7) |
| **Blood and Lymphatic System Disorders** | **6 (8.5)** | **8 (11.0)** |
| Anemia | 4 (5.6) | 6 (8.2) |
| **Infections and infestations** | **25 (35.2)** | **16 (21.9)** |
| Urinary tract infection | 4 (5.6) | 4 (5.5) |
| Viral upper respiratory tract infection | 4 (5.6) | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | **20 (28.2)** | **20 (27.4)** |
| Pain in extremity | 4 (5.6) | 6 (8.2) |
| Arthralgia | 4 (5.6) | 3 (4.1) |
| Back pain | 5 (7.0) | 3 (4.1) |
| Muscular weakness | 4 (5.6) | 2 (2.7) |
| **Metabolism and Nutrition Disorders** | **15 (21.1)** | **26 (35.6)** |
| Hypokalemia | 6 (8.5) | 14 (19.2) |
| Hyperglycemia | 4 (5.6) | 4 (5.5) |
| Hypocalcemia | 1 (1.4) | 5 (6.8) |
| **Psychiatric Disorders** | **16 (22.5)** | **22 (30.1)** |
| Insomnia | 6 (8.5) | 8 (11.0) |
| Anxiety | 4 (5.6) | 6 (8.2) |
| Agitation | 5 (7.0) | 4 (5.5) |
| **Injury, Poisoning and Procedural Complications** | **11 (15.5)** | **18 (24.7)** |
| Contusion | 5 (7.0) | 10 (13.7) |
| **Vascular Disorders** | **15 (21.1)** | **14 (19.2)** |
| Hypertension | 4 (5.6) | 8 (11.0) |
| Hypotension | 4 (5.6) | 2 (2.7) |
| **Cardiac Disorders** | **16 (22.5)** | **14 (19.2)** |
| Sinus tachycardia | 4 (5.6) | 3 (4.1) |
| Tachycardia | 2 (2.8) | 4 (5.5) |
| **Investigations** | **10 (14.1)** | **12 (16.4)** |
| **Renal and Urinary Disorders** | **8 (11.3)** | **11 (15.1)** |
| Hematuria | 5 (7.0) | 2 (2.7) |
| **Reproductive System and Breast Disorders** | **12 (16.9)** | **4 (5.5)** |
| Vaginal Hemorrhage | 4 (5.6) | 2 (2.7) |
| **Eye Disorders** | 8(11) | 7 (9.6) |
| Vision blurred | 5 (6.8) | 5 (7.0) |
| Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; TEAE = treatment-emergent adverse event Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator.  ¥ Caplacizumab + plasma exchange + glucocorticoids, with or without another immunosuppressant  † Plasma exchange + glucocorticoids, with or without another immunosuppressant  Source: Scully, Marie, et al. "Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 380.4 (2019): 335-346. | | |

# Supplementary Table 10. Safety results clinical trial Hercules-Treatment-emergent SAEs (excluding SAEs of TTP) per treatment group.

|  |  |  |
| --- | --- | --- |
| **System Organ Class Preferred Term; n (%)** | **Caplacizumab**¥  **(N = 71)** | **Placebo**†  **(N = 73)** |
| **At least one SAE** | **23 (32.4)** | **12 (16.4)** |
| **Blood and Lymphatic System Disorders**  Thrombotic microangiopathy | **0**  0 | **1 (1.4)**  1 (1.4) |
| **Gastrointestinal Disorders** | **5 (7.0)** | **1 (1.4)** |
| Gingival bleeding | 1 (1.4) | 0 |
| Upper gastrointestinal hemorrhage | 1 (1.4) | 0 |
| Colitis | 1 (1.4) | 0 |
| Gastric ulcer hemorrhage | 1 (1.4) | 0 |
| Gastrointestinal necrosis | 0 | 1 (1.4) |
| Hematemesis | 1 (1.4) | 0 |
| Intestinal ischemia | 0 | 1 (1.4) |
| Intestinal perforation | 0 | 1 (1.4) |
| Small intestinal obstruction | 0 | 1 (1.4) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **5 (7.0)** | **2 (2.7)** |
| Epistaxis | 4 (5.6) | 0 |
| Hypoxia | 0 | 1 (1.4) |
| Respiratory failure | 0 | 1 (1.4) |
| Pulmonary embolism | 1 (1.4) | 0 |
| **Cardiac Disorders** | **4 (5.6)** | **1 (1.4)** |
| Myocardial infarction | 1 (1.4) | 1 (1.4) |
| Arteriospasm coronary | 1 (1.4) | 0 |
| Cardiac tamponade | 1 (1.4) | 0 |
| Cardiogenic shock | 1 (1.4) | 0 |
| Ventricular fibrillation | 1 (1.4) | 0 |
| **Nervous System Disorders** | **4 (5.6)** | **2 (2.7)** |
| Headache | 2 (2.8) | 0 |
| Cerebral ischemia | 1 (1.4) | 0 |
| Encephalopathy | 1 (1.4) | 0 |
| Hemorrhagic transformation stroke | 0 | 1 (1.4) |
| Hemiparesis | 0 | 1 (1.4) |
| **Infections and infestations** | **3 (4.2)** | **2 (2.7)** |
| Septic shock | 0 | 2 (2.7) |
| Bacteremia | 1 (1.4) | 0 |
| Device related sepsis | 1 (1.4) | 0 |
| Diverticulitis | 1 (1.4) | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | **2 (2.8)** | **0** |
| Pain in extremity | 1 (1.4) | 0 |
| Arthropathy | 1 (1.4) | 0 |
| **Reproductive System and Breast Disorders** | **2 (2.8)** | **0** |
| Menorrhagia | 1 (1.4) | 0 |
| Hemorrhagic ovarian cyst | 1 (1.4) | 0 |
| **Injury, Poisoning and Procedural Complications** | **1 (1.4)** | **3 (4.1)** |
| Anaphylactic transfusion reaction | 0 | 3 (4.1) |
| Subarachnoid hemorrhage | 1 (1.4) | 0 |
| **Investigations** | **1 (1.4)** | **1 (1.4)** |
| Gamma-glutamyltransferase increase | 0 | 1 (1.4) |
| Platelet count decreased | 1 (1.4) | 0 |
| **General Disorders and Administration Site Conditions** | **1 (1.4)** | **1 (1.4)** |
| Asthenia | 1 (1.4) | 0 |
| Systemic inflammatory response syndrome | 0 | 1 (1.4) |
| **Hepatobiliary Disorders** | **1 (1.4)** | **1 (1.4)** |
| Bile duct stone | 1 (1.4) | 0 |
| Cholecystitis | 0 | 1 (1.4) |
| Gallbladder necrosis | 0 | 1 (1.4) |
| **Immune System Disorders** | **1 (1.4)** | **0** |
| Serum sickness | 1 (1.4) | 0 |
| **Vascular Disorders** | **0** | **2 (2.8)** |
| Deep vein thrombosis | 0 | 1 (1.4) |
| Jugular vein thrombosis | 0 | 1 (1.4) |
| Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; SAE = serious adverse event. Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator.  ¥ Caplacizumab + plasma exchange + glucocorticoids, with or without another immunosuppressant  † Plasma exchange + glucocorticoids, with or without another immunosuppressant  Source: Scully, Marie, et al. "Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 380.4 (2019): 335-346. | | |

# Supplementary Table 11. Safety results clinical trial Hercules- Bleeding TEAEs

|  |  |  |
| --- | --- | --- |
| **System Organ Class Preferred Term; n (%)** | **Caplacizumab (N = 71)** | **Placebo (N = 73)** |
| **Any bleeding TEAE (SMQ)** | **46 (64.8)** | **35 (47.9)** |
| **General disorders and administration site conditions** | **12 (16.9)** | **14 (19.2)** |
| Catheter site hemorrhage | 5 (7.0) | 5 (6.8) |
| Injection site bruising | 3 (4.2) | 3 (4.1) |
| Injection site hematoma | 1 (1.4) | 3 (4.1) |
| Injection site hemorrhage | 3 (4.2) | 0 |
| Vessel puncture site bruise | 0 | 2 (2.7) |
| Vessel puncture site hemorrhage | 1 (1.4) | 1 (1.4) |
| **Gastrointestinal disorders** | **20 (28.2)** | **2 (2.7)** |
| Gingival bleeding | 13 (18.3) | 1 (1.4) |
| Hematochezia | 2 (2.8) | 0 |
| Rectal hemorrhage | 3 (4.2) | 0 |
| Mouth hemorrhage | 0 | 1 (1.4) |
| Upper gastrointestinal hemorrhage | 1 (1.4) | 0 |
| Abdominal wall hematoma | 1 (1.4) | 0 |
| Gastric ulcer hemorrhage | 1 (1.4) | 0 |
| Hematemesis | 1 (1.4) | 0 |
| Melena | 1 (1.4) | 0 |
| **Nervous system disorders** | **1 (1.4)** | **1 (1.4)** |
| Hemorrhagic cerebral infarction | 1 (1.4) | 0 |
| Hemorrhagic transformation stroke | 0 | 1 (1.4) |
| **Skin and subcutaneous tissue disorders** | **6 (8.5)** | **8 (11.0)** |
| Petechiae | 4 (5.6) | 5 (6.8) |
| Ecchymosis | 2 (2.8) | 4 (5.5) |
| **Respiratory, thoracic and mediastinal disorders** | **25 (35.2)** | **2 (2.7)** |
| Epistaxis | 23 (32.4) | 2 (2.7) |
| Hemoptysis | 2 (2.8) | 0 |
| **Injury, poisoning and procedural complications** | **6 (8.5)** | **11 (15.1)** |
| Contusion | 5 (7.0) | 10 (13.7) |
| Post procedural hematoma | 0 | 1 (1.4) |
| Subarachnoid hemorrhage | 1 (1.4) | 0 |
| **Vascular disorders** | **3 (4.2)** | **2 (2.7)** |
| Hematoma | 3 (4.2) | 2 (2.7) |
| **Renal and urinary disorders** | **5 (7.0)** | **2 (2.7)** |
| Hematuria | 5 (7.0) | 2 (2.7) |
| **Reproductive system and breast disorders** | **7 (9.9)** | **3 (4.1)** |
| Vaginal hemorrhage | 4 (5.6) | 2 (2.7) |
| Menorrhagia | 3 (4.2) | 1 (1.4) |
| Hemorrhagic ovarian cyst | 1 (1.4) | 0 |
| **Eye disorders** | **1 (1.4)** | **0** |
| Eye hemorrhage | 1 (1.4) | 0 |
| **Surgical and medical procedures** | **1 (1.4)** | **0** |
| Astringent therapy | 1 (1.4) | 0 |
| Abbreviations: N = total number of subjects in treatment group; n = number of subjects with events; TEAE = treatment-emergent adverse event. Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator  Note: Percentage was calculated using the number of subjects in the Safety Population as the denominator.  ¥ Caplacizumab + plasma exchange + glucocorticoids, with or without another immunosuppressant  † Plasma exchange + glucocorticoids, with or without another immunosuppressant  Source: Scully, Marie, et al. "Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura." *New England Journal of Medicine* 380.4 (2019): 335-346. | | |

# Supplementary Table 12. Safety results - Coppo et al.

|  |  |  |
| --- | --- | --- |
| **Adverse event** | **Number of adverse events** | **Description** |
| Major bleeding | 2 | One with hemorrhagic shock with lower digestive bleeding |
| One with abundant menorrhagia with a decrease in hemoglobin level of 2.5 g/dL |
| Clinically relevant nonmajor bleeding | 11 | Three with macroscopic gastrointestinal hemorrhage |
| Seven with epistaxis |
| One with subcutaneous hematoma larger than 25 cm2 |
| Non–clinically relevant nonmajor bleeding | 17 | Nine with ecchymosis or small hematoma |
| Six with gingival bleedings |
| Two with catheter site hemorrhage |
| Inflammatory reaction | 6 | Inflammatory swelling at the injection site, especially at the end of the treatment course |
| Thrombocytosis | 19 | Platelet count (×103/mm3) |
| >450-600: 11 cases |
| >600-900: 7 cases |
| >900: 1 case |
| Source: Coppo, Paul, et al. "A regimen with caplacizumab, immunosuppression, and plasma exchange prevents unfavorable outcomes in immune-mediated TTP." *Blood, The Journal of the American Society of Hematology* 137.6 (2021): 733-742. | | |

# Supplementary Table 13. Safety results - Dutt et al.

| **Summary of adverse events for patients receiving caplacizumab** | | | |
| --- | --- | --- | --- |
| **Episodes** | **No. episodes**[**\***](about:blank) | **Episodes with caplacizumab interruption** | **Major bleeding** |
| **Bleeding** |  |  |  |
| Gum bleeding | 6 | 1 | 1 |
| Epistaxis | 1 | 0 | 0 |
| Bruising | 1 | 0 | 0 |
| Hemarthrosis | 1 | 1 | 1 |
| Lower gastrointestinal bleeding | 3 | 0 | 0 |
| Upper gastrointestinal bleeding | 2 | 1 | 1 |
| Intracranial bleeding | 2 | 2 | 2 |
| Traumatic | 1 | 1 | 0 |
| Total | 17 | 6 | 5 |
| **Nonbleeding** | | | |
| Venous thromboembolism | 5 | 4 | n/a |
| Injection site reaction/allergy | 4 | 1 | n/a |
| Skin rash | 3 | 3 | n/a |
| LFT derangements | 1 | 1 | n/a |
| Neutropenic fever[‡‡](about:blank) | 1 | 1 | n/a |
| Total | 14 | 10 |  |
| LFT, liver function test; n/a, not applicable.  Source: Dutt, Tina, et al. "Real-world experience with caplacizumab in the management of acute TTP." Blood, The Journal of the American Society of Hematology 137.13 (2021): 1731-1740. | | | |

# Supplementary guide questions

* **Effectiveness/Efficacy**

**Dichotomous outcomes, desired outcome (beneficial):**

* How many more patients must experience the event/outcome for caplacizumab to be considered superior?
* Are X number of patients (more with the event/outcome) important from the clinical point of view?
* How relevant is the effect size?
  + - Large effect
    - Moderate effect
    - Small effect (important)
    - Small effect (not important)
    - No effect
* What additional clinical considerations should be taken into account, routes of administration, dose, etc.?
* However, what happens if X patients with response to treatment are not enough, from the clinical point of view, to guarantee superiority of caplacizumab over the standard treatment? What would be the minimum number of patients to ensure the superiority of caplacizumab?

**Dichotomous outcomes, unwanted outcome:**

* How many fewer patients (cases) must be achieved for caplacizumab to be considered superior, based on what was achieved by the comparator?
* Are X number of patients (fewer with the event/outcome) important from the clinical point of view?
* How relevant is the effect size?
  + - Large effect
    - Moderate effect
    - Small effect (important)
    - Small effect (not important)
    - No effect
* What additional clinical considerations should be taken into account, routes of administration, dose, etc.?
* However, what happens if X patients with response to treatment are not enough, from a clinical point of view, to guarantee superiority of caplacizumab over the standard treatment? What would be the minimum number of patients to ensure the superiority of caplacizumab?

**Continuous outcomes:**

* How much should the reduction in the median be to consider that caplacizumab is superior?
* Are X days/liters (less) important from the clinical point of view?
* How relevant is the effect size?
  + - Large effect
    - Moderate effect
    - Small effect (important)
    - Small effect (not important)
    - No effect
* What additional clinical considerations should be taken into account, routes of administration, dose, etc.?

What would be the minimum reduction in the median to ensure the superiority of caplacizumab?

* **Safety**
* How many more patients with an adverse event are expected, in order to conclude that caplacizumab is less safe?
* Are X patients (more with a serious adverse event) important from the clinical point of view?

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Panel member** | **Response to treatment** | | **Composite outcome 1** | | **Recurrences** | | **Composite outcome 2** | | **Refractoriness** | | **Exacerbations** | | **Number of days of hospitalization** | | **Number of days of PE** | | **Response time to treatment** | |
| ES | **V** | ES | **V** | ES | **V** | ES | **V** | ES | **V** | ES | **V** | ES | **V** | ES | **V** | ES | **V** |
| Hematologist-1 | Moderate effect | 8 | Moderate effect | 9 | Large effect | 9 | Moderate effect | 9 | Moderate effect | 9 | Moderate effect | 9 | Moderate effect | 9 | Moderate effect | 9 | Large effect | 9 |
| Hematologist-2 | Moderate effect | 9 | Large effect | 9 | Large effect | 9 | Moderate effect | 7 | Moderate effect | 7 | Moderate effect | 9 | Moderate effect | 8 | Moderate effect | 9 | Large effect | 9 |
| Hematologist /Epidemiologist -1 | Moderate effect | 8 | Moderate effect | 8 | Large effect | 8 | Moderate effect | 8 | Large effect | 8 | Moderate effect | 9 | Moderate effect | 8 | Moderate effect | 8 | Large effect | 9 |
| Hematologist /Epidemiologist -2 | Small effect (important) | 7 | Large effect | 9 | Large effect | 9 | Moderate effect | 8 | Moderate effect | 8 | Moderate effect | 8 | Moderate effect | 8 | Large effect | 8 | Large effect | 9 |
| Pharmaceutical chemist | Moderate effect | 8 | Moderate effect | 9 | Large effect | 9 | Moderate effect | 9 | Large effect | 8 | Moderate effect | 8 | Large effect | 8 | Moderate effect | 9 | Moderate effect | 9 |
| Patient | Moderate effect | 9 | Moderate effect | 9 | Large effect | 9 | Moderate effect | 7 | Moderate effect | 9 | Large effect | 9 | Moderate effect | 8 | Moderate effect | 9 | Large effect | 9 |
| Median or percentage of vote | 8 (7 to 9) threshold passed | | 9 (8-9) threshold passed | | 9 (8-9) threshold passed | | 8 (7 to 9) threshold passed | | 8 (7-9) threshold passed | | 9 (8-9) threshold passed | | 8 (8-9) threshold passed | | 9 (8-9) threshold passed | | Scores between 7 and 9 of more than 80% of the participants | |
| ES= effect size; V: vote | | | | | | | | | | | | | | | | | | |

# Supplementary Table 14. Consensus results and analysis: effectiveness outcomes

# Supplementary Table 15. Consensus results and analysis: Safety outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Panel member** | **Serious adverse events** | **Bleeding adverse events** | **Serious bleeding adverse events** | **Gingival bleeding** | **Epistaxis** |
| **Vote** | **Vote** | **Vote** | **Vote** | **Vote** |
| Hematologist-1 | 9 | 9 | 9 | 9 | 9 |
| Hematologist-2 | 5 | 9 | 9 | 8 | 7 |
| Hematologist/epidemiologist -1 | 8 | 8 | 7 | 9 | 8 |
| Hematologist/epidemiologist -2 | 8 | 8 | 8 | 8 | 9 |
| Pharmaceutical chemist | 9 | 7 | 9 | 9 | 8 |
| Patient | 9 | 9 | 9 | 9 | 9 |
| Median or percentage of vote | Scores between 7 and 9 of more than 80% of the participants | 8.5 (7 to 9) threshold passed | 9 (7 to 9) threshold passed | 9 (8 to 9) threshold passed | 8.5 (7 to 9) threshold passed |

# Supplementary Table 16. Acceptability of results: effectiveness outcomes

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Panel member** | **Response to treatment** | **Composite outcome 1** | **Recurrences** | **Composite outcome 2** | **Refractoriness** | **Exacerbations** | **Number of days of hospitalization** | **Number of days of PE** | **Response time to treatment** |
| **Vote** | **Vote** | **Vote** | **Vote** | **Vote** | **Vote** | **Vote** | **Vote** | **Vote** |
| Hematologist-1 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist-2 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist/epidemiologist -1 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist/epidemiologist -2 | Would be willing | Would be willing | Would not be willing | Would not be willing | Would be willing | Would not be willing | Would be willing | Would be willing | Would be willing |
| Pharmaceutical chemist | Would be willing | Would be willing | Would be willing | Would be willing | Would not be willing | Would be willing | Would be willing | Would not be willing | Would not be willing |
| Patient | Would be willing | Would be willing to | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Acceptability of the effect of technology | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

# Supplementary Table 17. Acceptability of results: Safety outcomes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Panel member** | **Serious adverse events** | **Bleeding adverse events** | **Serious bleeding adverse events** | **Gingival bleeding** | **Epistaxis** |
| **Vote** | **Vote** | **Vote** | **Vote** | **Vote** |
| Hematologist-1 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist-2 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist/epidemiologist -1 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Hematologist/epidemiologist -2 | Would be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Pharmaceutical chemist | Would not be willing | Would be willing | Would be willing | Would be willing | Would be willing |
| Patient | Would be willing | Would not be willing | Would not be willing | Would not be willing | Would not be willing |
| Acceptability of the effect of the technology | Yes | Yes | Yes | Yes | Yes |

# Supplementary Table 18. Results: classification of the technology

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Panel member** | **Treatment response** | **Composite outcome (aTTP-related death, aTTP recurrence, or at least one major thromboembolic event)** | | **Recurrences** | **Serious adverse events** | **Bleeding events** | **Serious bleeding events** | **Gingival bleeding** | **Epistaxis** |
| **Vote** | **Vote** | **Vote** | | **Vote** | **Vote** | **Vote** | **Vote** | **Vote n** |
| Hematologist-1 | 9 | 9 | 9 | | 9 | 9 | 9 | 9 | 9 |
| Hematologist-2 | 7 | 9 | 6 | | 9 | 8 | 8 | 9 | 9 |
| Hematologist/epidemiologist -1 | 7 | 9 | 9 | | 9 | 8 | 7 | 7 | 8 |
| Hematologist/epidemiologist -2 | 8 | 8 | 8 | | 8 | 8 | 8 | 8 | 8 |
| Pharmaceutical chemist | 7 | 8 | 9 | | 8 | 8 | 8 | 9 | 8 |
| Patient | 9 | 9 | 8 | | 9 | 9 | 9 | 6 | 9 |
| Median or decision criterion | Scores between 7 and 9 from more than 80% of the participants. | 9 (8-9) | Scores between 7 and 9 from more than 80% of the participants. | | 9 (8-9) | 8 (8-9) | Scores between 7 and 9 from more than 80% of the participants. | Scores between 7 and 9 from more than 80% of the participants. | 8.5 (8-9) |
| Classification of technology | Superior | Superior | No difference | | No difference | No difference | No difference | No difference | No difference |

## Supplementary Table 19. Overall ranking of the technology by the panel

From the analysis of the evidence on effectiveness and safety, the panel members determined that treatment using caplacizumab together with the standard regimen is superior to the standard regimen for the treatment of patients with aTTP, with a low certainty of the evidence.

**Voting results and consensus:**

|  |  |
| --- | --- |
| **Member** | **Vote** |
| Hematologist-1 | 9 |
| Hematologist-2 | 9 |
| Hematologist/epidemiologist -1 | 8 |
| Hematologist/epidemiologist -2 | 7 |
| Pharmaceutical chemist | 2 |
| Patient | 9 |
| Median (95% CI) | 8.5 (2-9) |
| Proportion of responses | Scores between 7 and 9 from more than 80% of the participants. |
| ***The classification of the technology was accepted*** | |