Caplacizumab for the treatment of acquired Thrombotic Thrombocytopenic Purpura (aTTP)

ICD-10 Coordination and Maintenance Meeting

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SANOFI GENZYME

Coding Issue

- Current ICD-10-PCS codes do not uniquely identify the caplacizumab administration

- A unique ICD-10-PCS code:
  - Would facilitate New Technology Add-on Payment (NTAP) recognition and allow for appropriate claims tracking to generate data
    - Sanofi applied for NTAP for fiscal year 2020
  - Allow for tracking and research of caplacizumab use and resolution of aTTP cases
- Caplacizumab was approved for the treatment of aTTP by the FDA in February 2019

An acute episode of aTTP is a medical emergency– a rapid diagnosis is essential

- aTTP is a rare, rapidly progressing, life-threatening thrombotic microangiopathy characterized by severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ ischemia[1]

- **90% acute mortality rate of TTP if untreated[2,3]**

- 9 days to median time **from diagnosis to death** in acute phase of TTP in patients treated with plasma exchange (retrospective claims analysis, n=8203)[3]

- **About 20% acute mortality rate** in TTP despite plasma exchange and immunosuppression[4]

aTTP is sometimes referred to as *immune thrombocytopenia (ITP).*

1. Joly BS, Coppo P, Veyradier A. *Blood.* 2012;129(21):2836-2846. 2. Scully M, Hunt BJ, Benjamin S, et al. *Br J Haematol*. 2012;158(3):323-335. 3. Goel R et al. *Transfusion.* 2016;56(6):1451-1458. 4. Kremer Hovinga JA et aal. *Blood.*. 2010;115:1500-1511

What is acquired Thrombotic Thrombocytopenic Purpura (aTTP)?

- aTTP is a rare, life-threatening blood clotting disorder, with a reported annual incidence of 4 to 5 cases per million people in the U.S.
- aTTP is characterized by the formation of microthrombi in the body's smallest blood vessels, particularly in those of the heart, brain and kidneys
- aTTP patients develop autoantibodies that inhibit the activity of the enzyme ADAMTS13, which cleaves ultra-large vWF multimers
- Rather than being cut, ultra-large vWF multimers are released into the circulation and spontaneously bind to platelets, resulting in the formation of circulating microthrombi

aTTP, acquired thrombotic thrombocytopenic purpura; vWF, von Willebrand factor; UL-vWF, ultra-large von Willebrand factor; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

Kremer Hovinga JA, et al. Nat Rev Dis Primers 2017;3(17020)1-17 | Scully M, et al. Br J Haematol. 2012;158(3):323–35 | Terrell DR, et al. J Thromb Haemost. 2005;3(7):1432–6 | Rajan S. BMJ. 2016:1–32

Current Treatment Options

- Current therapy is based on 2 pillars:
  - Daily Plasma Exchange
    - Removes ultra-long van Wilibrand Factor
    - Removes autoantibodies
    - Replenishes ADAMTS13
  - Immunosuppressants
    - Inhibits autoantibody function

- Despite PE and immunosuppression aTTP patients remain at risk of:
  - Thrombotic complications like myocardial infarction, ischaemic stroke, kidney failure and other organ damage2
  - Up to 20% acute mortality, with a median time from diagnosis to death of 9 days3
  - Up to 42% unpredictable refractoriness to therapy, associated with poor outcomes4
  - Up to 50% unpredictable exacerbations5

Notes: aTTP, acquried thrombotic thrombocytopenic purpura; ULvWF, ultra-large von Willebrand factor, PE, plasma exchange

1. Sayani FA, et al. Blood. 2015;125(25):3860–7 | 2. Kremer Hovinga JA, et al. Blood. 2010; 115(8):1500–11 | 3. Goel R, et al. Transfusion. 2016;56(6):1451–8 | 4. Thejeel B, et al. Am J Hematol. 2016;91(6):623–30 | 5. Coppo P, et al. Presse Med. 2012;41:e163–76 |

How does caplacizumab work?

- Caplacizumab prevents further platelet adhesion in aTTP patients by inhibiting the binding of platelets to the A1 domain of vWF

Following injection

1. Caplacizumab binds specifically to the A1 domain on vWF multimers in the circulation

2. Caplacizumab bound to the A1 domain on vWF blocks the spontaneous binding of circulating platelets to the vWF strings

aTTP, acquired thrombotic thrombocytopenic purpura; vWF, von Willebrand factor.

CABLIVI (caplacizumab-yhdp) [prescribing information]. Cambridge, MA: Genzyme Corporation; 2019.

How is caplacizumab administered?

CABLIVI should be administered upon the initiation of plasma exchange therapy. The recommended dose of CABLIVI is as follows:

- First day of treatment: 11 mg bolus intravenous injection at least 15 minutes prior to plasma exchange followed by an 11 mg subcutaneous injection after completion of plasma exchange on day 1.
- Subsequent treatment during daily plasma exchange: 11 mg subcutaneous injection once daily following plasma exchange.
- Treatment after the plasma exchange period: 11 mg subcutaneous injection once daily for 30 days beyond the last plasma exchange.
- If after initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.
- Discontinue CABLIVI if the patient experiences more than 2 recurrences of aTTP, while on CABLIVI.

We expect patients to be started in the hospital inpatient setting along with plasma exchange and immunosuppressants.

PE, plasma exchange

CABLIVI (caplacizumab-yhdp) [prescribing information]. Cambridge, MA: Genzyme Corporation; 2019.

Caplacizumab Clinical Development in Patients with aTTP

Hercules Study:

- The efficacy and safety of caplacizumab in adults experiencing an episode of aTTP was evaluated in a randomized, controlled study: Phase III study ALX0681-C301 “HERCULES” in a total of 145 patients.
- aTTP patients who had received one PE treatment were randomized 1:1 to placebo or 11 mg caplacizumab, in addition to receiving daily PE and corticosteroids
- A single IV dose of study drug was given before the first on-study PE and a SC dose was given daily during the PE period and 30 days thereafter
- If at the end of the 30-day period there was evidence of ongoing disease, such as suppressed ADAMTS13 activity, investigators were encouraged to extend the blinded treatment for a maximum of 4 weeks together with optimization of immunosuppression
- All patients entered a 28-day treatment-free follow up period after the last dose of study drug

PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura [published online ahead of print January 9, 2019]. N Engl J Med. doi:10.1056/NEJMoa1806311

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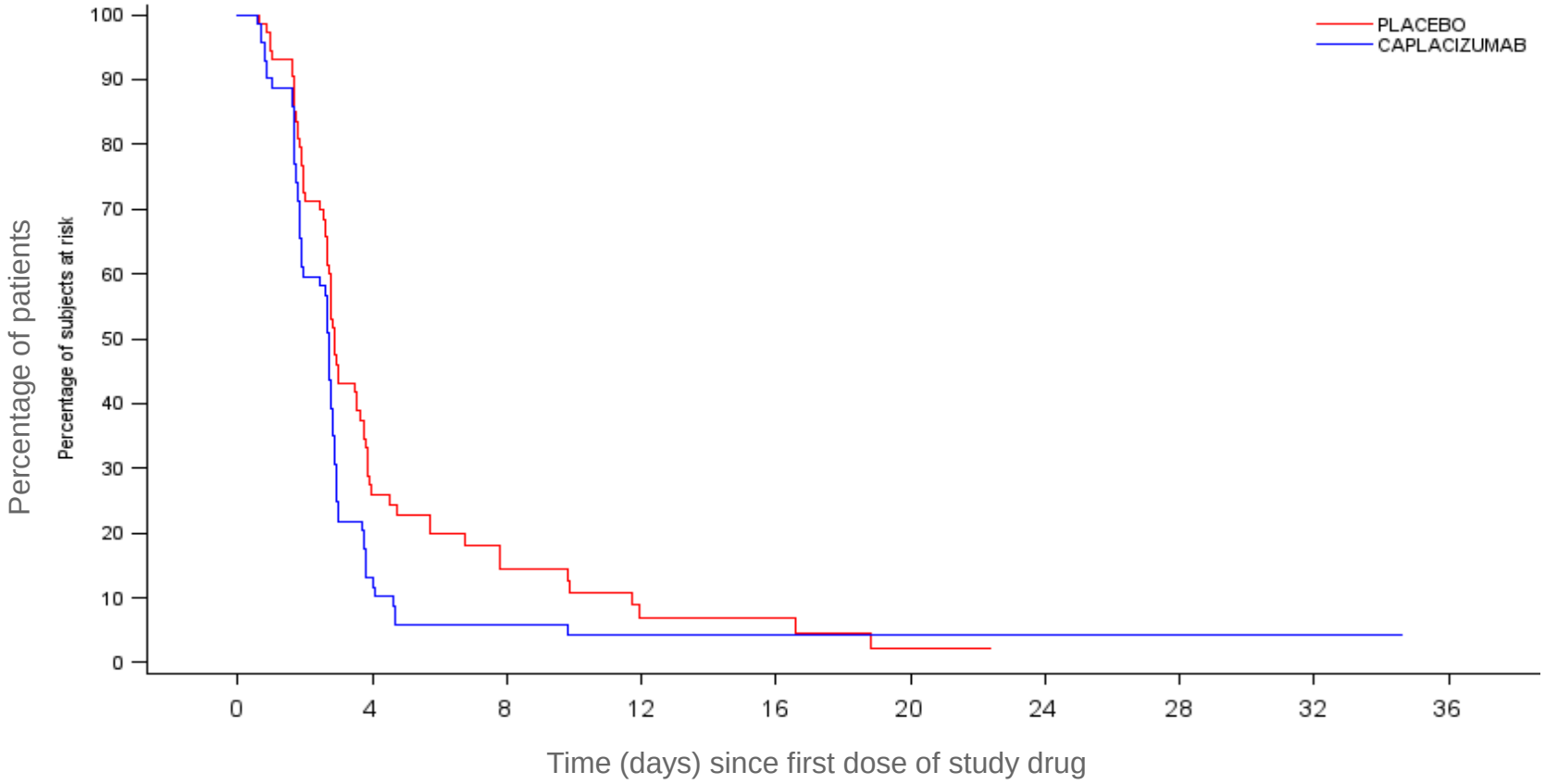
Primary endpoint: time to platelet count response*



Hazard ratio: 1.55, CI=1.095; 2.195 p=0.01

- Platelet count response was defined as reaching a platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

CI, confidence interval; 1.095

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First secondary endpoint

Subjects with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period (composite endpoint)

Number of subjects (%)	Caplacizumab N=72*	Placebo N=73
Total number of subjects with at least one of the events[1]	**9 (12.7)**	**36 (49.3)**
aTTP-related death[2]	0[4]	3 (4.1)
recurrence of aTTP[3] (exacerbation)	3 (4.2)	28 (38.4)
at least one treatment emergent major thromboembolic event[2]:	6 (8.5)	6 (8.2)
- cerebrovascular accident	2 (2.8)	3 (4.1)
- myocardial infarction	1 (1.4)	1 (1.4)
- pulmonary embolism	1 (1.4)	0
- deep venous thrombosis (spontaneous)	0	1 (1.4)
- deep venous thrombosis (catheter-associated)	3 (4.2)	2 (2.7)

p-value <0.0001

* percentages are based on 71 subjects entering the study drug treatment period;
[1] patients could have more than 1 event;
[2] adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee;
[3] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PE
[4] One patient in the Cablivi group died during the treatment free follow-up period; the death was aTTP related and not treatment related.

aTTP, acquired thrombotic thrombocytopenic purpura; PE, plasma exchange.

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Second secondary endpoint

Subjects with aTTP recurrence during the overall study period

Number of subjects (%)	Caplacizumab N=72*	Placebo N=73
aTTP recurrence[1]	**9 (12.7)**	**28 (38.4)**
During the study drug treatment period (exacerbations)	3 (4.2)	28 (38.4)
During the follow-up period (relapses)	6 (9.1)[2]	0

p-value <0.001

* percentages are based on 71 subjects entering the study drug treatment period and 66 subjects in the follow-up period
[1] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PE
[2] ADAMTS13 activity levels were < 10% at the end of the study drug treatment period in all of these patients

Definitions	
Exacerbation	Recurrent thrombocytopenia after initial recovery of platelet count (platelet count ≥150,000/μL with subsequent stop of daily plasma exchange within 5 days) that required reinitiation of daily plasma exchange, ocurring during the 30-day post daily plasma exchange period
Relapse	Recurrent thrombocytopenia after initial recovery of platelet count (platelet count ≥150,000/μL) that required reinitiation of daily plasma exchange, occurring after the 30-day post daily plasma exchange period

aTTP, acquired thrombotic thrombocytopenic purpura; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PE, plasma exchange.

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Other secondary endpoints – HERCULES study

Plasma exchange parameters, plasma volume, duration of ICU stay, and overall hospitalization days

In the phase 3 trial, data for patient time spent on PEX, in hospital, in ICU, and volume of PEX were collected prospectively. Descriptive statistics were run, but these data were not tested for significance. The clinical significance of these data is unknown

Overall study drug treatment period (mean±SE)	Caplacizumab N=71	Placebo N=73	% relative reduction
Number of days of PEX	5.8±0.5	9.4±0.8	↓38%
Volume of plasma (L)	21.3±1.6	35.9±4.2	↓41%
Number of days in ICU	3.4±0.4 (n=28)	9.7±2.1 (n=27)	↓65%
Number of days in hospital	9.9±0.7	14.4±1.2	↓31%

PEX, plasma exchange; ICU, intensive care unit; L, liter.

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Summary Caplacizumab for the treatment of aTTP

- The addition of caplacizumab, when used in conjunction with PEX and immunosuppressants, significantly improved some clinical outcomes for patients with an episode of aTTP when compared to the use of currently available treatments (PE and immunosuppressants) alone, as shown in the HERCULES study by:
  - A significant **reduction in time to platelet count response**, which is consistent with the halting of platelet adhesion
  - Cablivi showed a significant reduction on a composite endpoint of aTTP-related death, recurrence of aTTP (exacerbation), or a major thromboembolic event during study drug treatment versus plasma exchange and immunosuppression alone (12.7% vs. 49.3%; p <0.0001)
  - A reduction in proportion of patients with recurrence of aTTP in the overall study period
  - A **reduction in the number of days of PE**, in the mean length of **intensive care unit stay** and in the mean **length of hospitalization**[3]

- The principal risk of treatment with caplacizumab is bleeding
  - The most frequently reported adverse reactions were epistaxis, headache, and gingival bleeding

aTTP, acquired Thrombotic Thrombocytopenic Purpura; PE, plasma exchange; TEAEs, Treatment-Emergent Adverse Events

Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura.. ¦ Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. ¦ Ablynx. Integrated Summaries of Efficacy and Safety. April 2018.

Indications and Important Safety Information

INDICATIONS: CABLIVI (caplacizumab-yhdp) is indicated for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

CONTRAINDICATIONS: CABLIVI is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or to any of its excipients. Hypersensitivity reactions have included urticaria.

WARNINGS AND PRECAUTIONS: Bleeding Risk: CABLIVI increases the risk of bleeding. If clinically significant bleeding occurs, interrupt use of CABLIVI. Von Willebrand factor concentrate may be administered to rapidly correct hemostasis. If CABLIVI is restarted, monitor closely for signs of bleeding.

The risk of bleeding is increased, in patients with underlying coagulopathies and concomitant use of CABLIVI with drugs affecting hemostasis. Withhold CABLIVI for 7 days prior to elective surgery, dental procedures or other invasive interventions. If emergency surgery is needed, the use of von Willebrand factor concentrate may be considered to correct hemostasis. After the risk of surgical bleeding has resolved, and CABLIVI is resumed, monitor closely for signs of bleeding.

ADVERSE REACTIONS: The most common adverse reactions (>15% of patients) were epistaxis, headache and gingival bleeding.

You are encouraged to report suspected adverse reactions to Sanofi Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying Full Prescribing Information.