31 August 2018
EMA/541816/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Cablivi (nanobody directed towards the human A1 domain of von Willebrand factor)
Treatment of thrombotic thrombocytopenic purpura
EU/3/09/629 (EMEA/OD/109/08)
Sponsor: Ablynx NV

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Nanobody directed towards the human A1 domain of von Willebrand factor
International Non-Proprietary Name	Caplacizumab
Orphan indication	Treatment of thrombotic thrombocytopenic purpura
Pharmaceutical form	Powder and solvent for solution for injection
Route of administration	Intravenous and subcutaneous use
Pharmaco-therapeutic group (ATC Code)	B01AX07
Sponsor's details:	Ablynx NV Technologiepark 21 B-9052 Zwijnaarde Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ablynx NV
COMP opinion date	4 March 2009
EC decision date	30 April 2009
EC registration number	EU/3/09/629
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	F. Josephson, J. Emmerich
Applicant	Ablynx NV
Application submission date	3 February 2017
Procedure start date	23 February 2017
Procedure number	EMA/H/C/004426
Invented name	Cablivi
Therapeutic indication	Cablivi is indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. Further information on Cablivi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/ European public assessment reports
CHMP opinion date	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	D. Matusevicius, K. Penttilä
Sponsor's report submission date	23 November 2017
COMP discussion and adoption of list of questions	17-19 April 2018
COMP opinion date	19 July 2018

2. Grounds for the COMP opinion

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- thrombotic thrombocytopenic purpura (hereinafter referred to as "the condition") was estimated to be affecting between 2.2 and 2.9 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening, in particular due to the risk of severe neurological impairment, cardiac and renal manifestations;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been provided that containing nanobody directed towards the human A1 domain of von Willebrand factor may be of significant benefit to those affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Thrombotic thrombocytopenic purpura (TTP) is an autoimmune blood clotting disorder manifested by microvascular occlusions and consequent thrombocytopenia, haemolytic anaemia, and organ ischemia.

Acquired TTP is caused by inhibitory autoantibodies to ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13, resulting in a severe deficiency in this von Willebrand Factor-cleaving protease. Decreased ADAMTS13 activity leads to an accumulation of ultra-large (or unusually large) von Willebrand factor multimers which bind to platelets and induce aggregation.

The approved therapeutic indication "Cablivi is indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression" falls within the scope of the designated orphan indication "treatment of thrombotic thrombocytopenic purpura".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified (reference is made to the European public assessment report of Cablivi).

Chronically debilitating and/or life-threatening nature

At the time of initial designation, the COMP agreed that the condition was chronically debilitating and life-threatening. At the time of this review TTP is presented to remain seriously debilitating and life threatening disease with a mortality of 10-20% following acute episodes and significant long-term morbidity and mortality. Patients have decreased cognitive function and increased prevalence of hypertension, systemic lupus erythematosus, major depression, and albuminuria. No new therapies

have been approved in this condition, and the mortality rate has remained unchanged since the initial orphan designation of Cablivi.

The COMP concluded that the condition remains life threatening and chronically debilitating due to the risk of severe neurological impairment, cardiac and renal manifestations.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be between 2.2 and 2.9 per 10,000. For the orphan maintenance, the prevalence was estimated to be 2.2 per 10,000 and remaining less than 5 per 10,000.

No systematic literature search was conducted, but epidemiological data on TTP were identified from TTP registries (UK), dedicated epidemiological studies on TTP (questionnaires or review of medical records in Spain, The Netherlands), and apheresis registries (Hungary, Norway, Sweden, Italy, France) (summarised in table 1). The incidence rate in Europe of TTP was estimated to 0.72 per 10,000, based on the highest identified incidence figure from the UK.

Table 1. Incidence figures for EU Member States

Country	**Number of patients reported with TTP**	**Annual Incidence per 100,000**	**Year**
UK South East England	178	0.72	2002 - 2006
Sweden	35	0.48	2001
Norway	13	0.348	2000
The Netherlands	67	0.083	1991
Hungary	36	0.427	2004
Spain	23	0.36	1983 – 2005

To calculate prevalence from incidence, the sponsor uses the formula P=I*D, where incidence is multiplied with disease duration. In this context, a distinction is made between patients with relapse and without relapse. The scientific literature reports on relapse rates for patients with aTTP ranging between 11% and 50%. The final prevalence calculation therefore incorporates a 50% relapse rate using a modified formula: prevalence= [incidence x EU population x fraction of patients who are not expected to relapse] + [incidence x duration (remaining life span) x EU population x fraction persons expect to relapse]. Incidence was used for patients without relapse. Relapsing patients were estimated to have a disease duration of 60 years. This is considered to be a conservative estimate considering the mean age of diagnosis at 43 years of age.

Based on these calculations, the prevalence of TTP was estimated to be 2.2 (0.036 + 2.16) per 10,000. The COMP accepted this prevalence figure for the maintenance of orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no medicinal products authorised in the EU for the treatment of TTP.

There is a UK guideline on diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies (Scully et al., Br J Haematol. 2012 Aug;158(3):323-35). Outlined treatment options of acute TTP include plasma exchange and off-label use of immunosuppressants such as steroids and – in severe and relapsed cases – rituximab.

Plasma exchange (PE) removes ultra-large (or unusually large) von Willebrand factor and the circulating autoantibodies against ADAMTS13 and replenishes blood levels of von Willebrand Factor - cleaving protease. PE has reduced mortality rates from over 90% to 10–20% and a delay in initiation of PE leads to preventable early mortality. Hence, the COMP re-confirmed its opinion that PE exchange remains a satisfactory method and a demonstration of significant benefit needs to be provided.

Significant benefit

Two clinical studies have been presented to support significant benefit over PE.

Study ALX-0681-2.1/10 was a phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of Cablivi (caplacizumab) administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura. Treatment was given on top of standard of care consisting of PE and adjunctive immunosuppressive treatment (e.g., corticosteroids, rituximab), antiplatelet agents (e.g., aspirin), supportive therapy with red cell transfusion or folate supplementation and treatment with vincristine or cyclosporin in case of refractory TTP. The first study drug administration was as an i.v. bolus within 6 hours to 15 minutes prior to initiation of the first on-study PE or the second PE session (if the subject was randomised after a single PE session). The first on-study PE was followed by s.c. administration of study drug within 30 minutes after the end of the PE procedure. Subsequently, daily s.c. administrations of 10 mg Cablivi or placebo in adult subjects followed each PE session for the duration of PE (including tapering and PE given for exacerbations) and once daily for 30 days following the last PE, including tapering.

The primary endpoint was time to recovery of platelets (≥ 150,000/µL), confirmed at 48 hours after the initial reporting of platelet recovery by a de novo measure of platelets ≥ 150,000/µL and LDH ≤ 2 x ULN. Seventy-five patients were randomised: 36 to the Cablivi group and 39 to the placebo group. The number and proportion of subjects in each treatment group with PE tapering were similar in the Cablivi treatment group compared with the placebo treatment group (11 [30.6%] subjects versus 11 [28.2%] subjects). The primary endpoint was met with a reduction in median days 2.97 versus 4.79 (p-value=0.005, figure 1 and table 2).

Figure 1. Study ALX-0681-2.1/10: time to confirmed platelet response curves (ITT population)

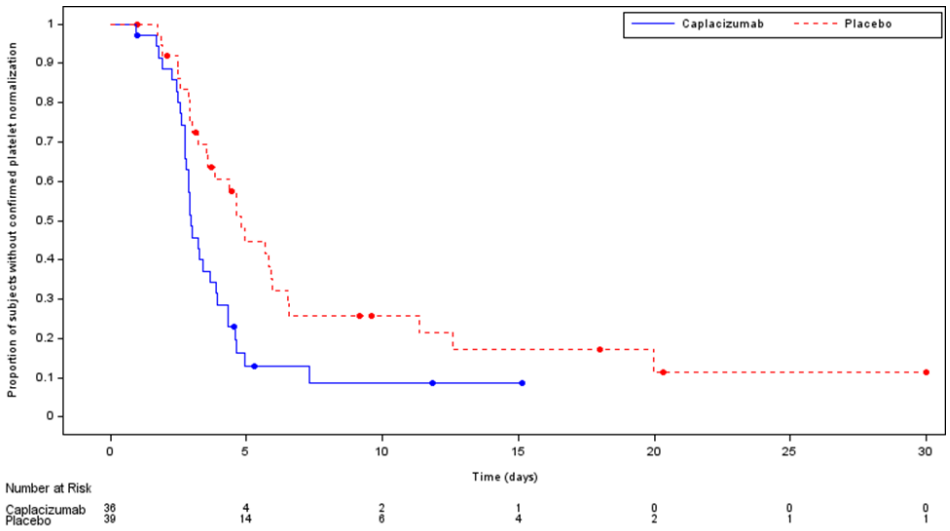


Table 2. Study ALX-0681-2.1/10: analysis of time to confirmed platelet response (ITT population)

		Caplacizumab **N=36**	**Placebo** **N=39**
Overall	Median time to response (95% CI) - days	2.97 (2.74, 3.65)	4.79 (3.51, 5.94)
	Subjects with Confirmed Platelet Response, n (%)	31 (86.1)	28 (71.8)
Time to confirmed platelet response	p-value (Stratified Log-Rank Test)	0.005	
Hazard Ratio	Caplacizumab vs. placebo (95% CI)	2.197 (1.278, 3.778)	

ALX0681-C301 (Hercules) study was a phase III double-blind, randomised, parallel group, multicentre placebo-controlled trial to study the efficacy and safety of Cablivi in adults with a clinical diagnosis of acquired TTP who required initiation of daily PE treatment. All patients received 30 days treatment with study drug. The primary endpoint was time to platelet count response defined as initial platelet count $\geq 150 \times 10^9$/L with subsequent stop of daily PE within 5 days. The effect of treatment with Cablivi on a composite endpoint of TTP-related mortality, recurrence of TTP and major thromboembolic events during study drug treatment and on endpoints assessing recurrence of TTP during the Overall Study Period, refractory TTP and time to normalisation of organ damage marker levels, were evaluated.

A total of 145 subjects (72 subjects to Cablivi and 73 subjects to placebo) were enrolled (i.e., randomised) in the study. 71 subjects in the Cablivi group and 73 in the placebo group received at least one dose of study drug and were included in the Safety Population and in the mITT population. Based on 66 events in each arm time to confirmed platelet response was statistically significantly shorter in the Cablivi arm, p=0.0099, with a HR of 1.55 (1.095; 2.195) (table 3 and figure 2). Opposed to the phase II study, patients were required to have received one PE treatment before randomisation, which likely contributed to the shorter times to platelet response observed in the phase III study. Regarding key secondary endpoints, treatment with Cablivi resulted in a 74% reduction in the

composite endpoint of the percentage of patients with aTTP-related death (0/72; placebo 3/73), exacerbation of aTTP (3/72; placebo 28/73), or at least one major thromboembolic event during study drug treatment (6/72; placebo 6/73) ($p<0.0001$), and in a 67% reduction of the proportion of subjects with a recurrence of aTTP (9/72; placebo 28/73) in the overall study period ($p<0.001$). Of further interest for significant benefit over plasma exchange, Cablivi treatment reduced the mean number of days of PE, the volume of plasma used, the mean length of Intensive Care Unit stay and the mean length of hospitalization during the study drug treatment period.

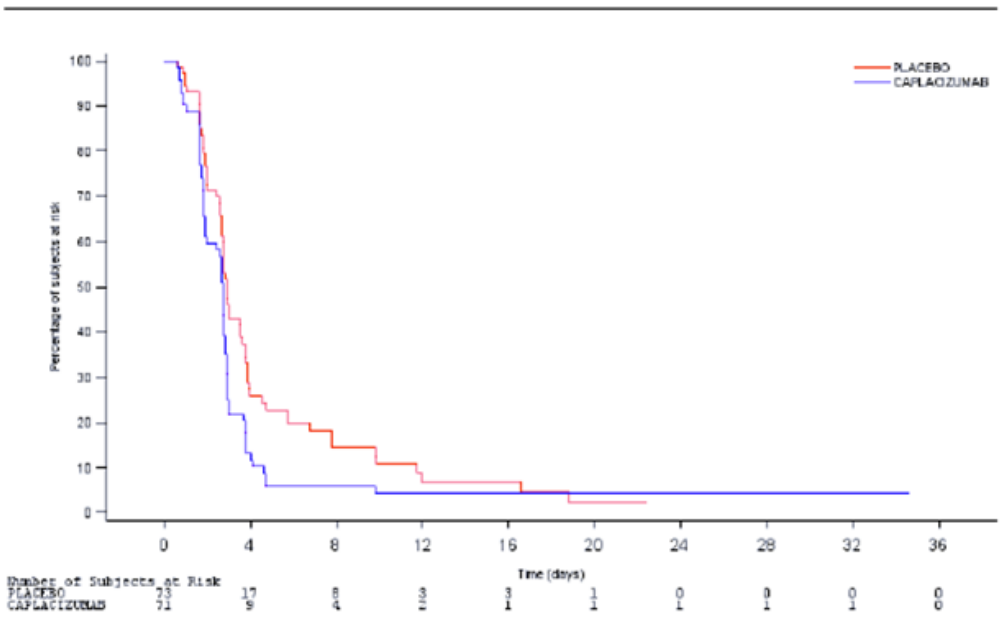
Table 3. Study ALX0681-C301 (Hercules): time to confirmed platelet response curves (ITT population)

POPULATION: INTENT-TO-TREAT
PART 1: OVERALL

SUMMARY STATISTIC	PLACEBO (N=73)	CAPLACIZUMAB (N=72)
TIME TO PLATELET COUNT RESPONSE		
Median (95% CI)	2.88 (2.68; 3.56)	2.69 (1.89; 2.83)
25% Percentile (95% CI)	1.94 (1.70; 2.64)	1.75 (1.65; 1.87)
75% Percentile (95% CI)	4.50 (3.78; 7.79)	2.95 (2.85; 3.81)
Number assessed	73	71
Number censored	7	5
Number events	66	66
Stratified Logrank test (p-value)		0.0099
Hazard Ratio (95% CI) [1]		1.55 (1.095; 2.195)

[1] COX PROPORTIONAL HAZARDS MODEL WITH TREATMENT GROUP AND GCS CATEGORY AS INDEPENDENT VARIABLES, A HAZARD RATIO > 1 INDICATES AN ADVANTAGE OF CAPLACIZUMAB.
TIME TO EVENT IS CALCULATED FROM FIRST STUDY DRUG ADMINISTRATION
STRATIFICATION FACTOR IS GLASGOW COMA SCALE (GCS)
IF A TIME-TO-EVENT PERCENTILE OR CORRESPONDING C.I. DOES NOT EXIST (DUE TO TOO SMALL NUMBER OF EVENTS), IT IS REPLACED BY A DOT.

Figure 2. Study ALX0681-C301 (Hercules): Time to confirmed platelet response curves (ITT population)



Source: Figure 14.2.1.1.1

In conclusion, the design of both clinical studies allow for the establishment of the efficacy of Cablivi on top of best standard of care including PE. The results of the clinical trials confirm a significant benefit of Cablivi over PE on the grounds of a clinically relevant advantage.

4. COMP position adopted on 19 July 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of thrombotic thrombocytopenic purpura (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 2.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to the risk of severe neurological impairment, cardiac and renal manifestations;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Cablivi is of significant benefit to adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. It was demonstrated that treatment with Cablivi on top of plasma exchange led to a statistically significantly shorter time to confirmed platelet response when compared to plasma exchange with placebo. There was also a reduction in the composite endpoint of the percentage of patients with aTTP-related death, exacerbation of aTTP or at least one major thromboembolic event during study drug treatment. The Committee concluded that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Cablivi, nanobody directed towards the human A1 domain of von Willebrand factor, caplacizumab, EU/3/09/629 for treatment of thrombotic thrombocytopenic purpura is not removed from the Community Register of Orphan Medicinal Products.