Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING NOVEMBER 2018

Sutimlimab for primary cold agglutinin disease

NIHRIO ID	21726	**NICE ID**	9968
Developer/Company	Sanofi and Bioverativ	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Sutimlimab is a first-in-class monoclonal antibody in development for the treatment of cold agglutinin disease, a rare form of autoimmune haemolytic anaemia, caused by cold-reacting autoantibodies. These antibodies bind to red blood cell membranes and destroy them, leading to anaemia. Symptoms include chronic debilitating fatigue, acrocyanosis, shortness of breath and other anaemia-related symptoms, leading to a poor quality of life and increased health resource utilization. In chronic cold agglutinin disease, the patient is more symptomatic during winter months. Therapeutic options may range from using warm clothing and avoiding exposure to cold weather to blood transfusions and chemotherapy.

Sutimlimab takes a novel approach by binding to the cold-reacting autoantibodies and preventing them from attacking the red blood cells. Sutimlimab acts by selectively inhibiting one of the three complement pathways in the immune system leaving the other two pathways intact. This potentially preserves some of complement's immune functions although it is unclear whether this would provide a clinical benefit and data from the clinical trials will be needed to better understand this. If approved, sutimlimab has the potential to become the first treatment option for cold agglutinin disease.

PROPOSED INDICATION

Primary Cold Agglutinin Disease.[1,2]

TECHNOLOGY

DESCRIPTION

Sutimlimab (BIVV009, TNT009) is a first-in-class humanized IgG4 monoclonal antibody that directly targets and inhibits C1s in the classical complement pathway. This inhibition of C1s halts the activity of the downstream components of complement as reflected by the decreased deposition of C4 and C3 cleavage products. Deposition of C3 cleavage products is a key step in the destruction of red blood cells and development of haemolysis in Cold Agglutinin Disease (CAD). In addition, sutimlimab was designed to selectively inhibit the classical complement pathway and therefore preserve the function of the other two complement pathways, lectin and alternative.[3-5]

Sutimlimab was previously known as TNT009, and is a variant of TNT003, a mouse IgG monoclonal antibody. TNT003 has been shown to inhibit cold agglutinin-induced complement deposition on red blood cells.[6]

Sutimlimab is in clinical development in patients with CAD with and without a recent history of blood transfusion. In the currently ongoing phase III clinical trials; Cardinal study (NCT03347396) and Cadenza study (NCT03347422), sutimlimab is administered as intravenous infusion at a concentration of 50mg/ml.[1,2,7]

INNOVATION AND/OR ADVANTAGES

Most symptoms and complications of CAD are secondary to haemolysis, which is dependent on activation of the classical complement pathway at the level of the C1 complex. Sutimlimab directly inhibits C1s, a critical component of the C1 complex. Through this mechanism, sutimlimab has the potential of stopping haemolysis, thereby resolving or improving the anaemia and other symptoms that these patients experience.[4,5]

Complement plays an important immune surveillance role for protecting against certain infections. It is composed of 3 pathways: classical, lectin and alternative. If complement is blocked downstream, all 3 pathways are inhibited. Sutimlimab, a selective inhibitor of C1s, only affects the classical pathway, leaving the other two pathways intact, and potentially preserving some of complement's immune functions.[8] Whether this would provide a clinical benefit is currently unknown and data from the clinical trials will be needed to better understand this.[a]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sutimlimab does not currently have Marketing Authorisation in the EU/UK for any indication.[9]

- Sutimlimab has received orphan designation from the EMA in 2016 for the treatment of autoimmune haemolytic anaemia, including CAD.[4]

[a] Information provided by Bioverativ

- In the US, sutimlimab has been granted Breakthrough Therapy Designation for the treatment of haemolysis in patients with primary CAD.[3]

PATIENT GROUP

DISEASE BACKGROUND

Cold agglutinin disease (CAD) is a rare type of autoimmune haemolytic anaemia caused by cold-reacting autoantibodies in which the body's immune system mistakenly attacks and destroys its own red blood cells.[10] When affected people's blood is exposed to cold temperatures (0° to 10° C), IgM antibodies attach themselves to red blood cells and bind them together into clumps (agglutination). This eventually causes red blood cells to be prematurely destroyed (haemolysis) leading to anaemia and other associated signs and symptoms. Cold agglutinin disease can be primary (unknown cause) or secondary, due to an underlying condition such as an infection (Epstein-Barr virus, mycoplasma), another autoimmune disease, or certain cancers such as lymphoma.[b]

Symptoms may be triggered or exacerbated by cold temperatures or a viral infection, however CAD is known to occur in all geographies and climates. The disease course is chronic and typically life-long. Symptoms may arise suddenly or gradually. Most people with CAD have symptoms of haemolytic anaemia (destruction of red blood cells, causing low levels of red blood cells) which can life-threatening in some cases. However, the number of symptoms and severity of symptoms may depend on how severe the anaemia is.[11]

Typical manifestations of CAD include debilitating fatigue, dyspnea, hemoglobinuria, weakness and acrocyanosis or Raynaud's disease. These symptoms result from poor circulation and can range from mild to disabling. Other signs and symptoms of CAD may include enlargement of the spleen (splenomegaly) and mottled discoloration of the skin (livedo reticularis).[11]

CLINICAL NEED AND BURDEN OF DISEASE

Current therapies for CAD have a limited efficacy and these patients continue to have a significant unmet need. A recent analysis of CAD patients from the Stanford Health Care System found that the average number of therapies per patient was 3.5, two-thirds of patients had a severe anaemia event in the first 6 months after their initial therapy and half of the patients experienced a severe anaemia event after their last reported treatment. In addition, this study demonstrated that these patients have a significant transfusion burden and high health resource utilization.[12]

Patients with CAD are also at risk of developing acute haemolytic events which are characterized by sudden unpredictable severe anaemia that can be life-threatening. Moreover, these patients suffer from ongoing chronic haemolysis. It is well-understood that having haemolysis is a risk factor for developing thrombolytic events (TEs). A recent study demonstrated that CAD patients indeed had an increased risk of TE, and that occurrence of these TEs was associated with elevated markers of haemolysis. A population study from the Danish National Registries indicated a shorter survival probability for people with CAD compared with the general population.[5]

The incidence of autoimmune haemolytic anaemia in Europe is 2.02 per 100,000.[13] CAD accounts for approximately 15% of autoimmune haemolytic anaemia cases, with an estimated prevalence of 16 per million people and incidence of 1 case per million person years. The risk of CAD onset increases

[b] Information provided by Bioverativ

after age 55 years.[14] CAD affects men and women in roughly equal proportions. The slight preponderance in women in some studies is likely due to women living to an older age, where the onset of the disease is more common.[12]

Data regarding the incidence of CAD in the UK are lacking. In the United States, the development of CAD is relatively uncommon, at least in the primary form. Various reports state that 7-25% of cases of autoimmune haemolytic anaemia are cold agglutinin mediated.[15]

Thus, while the incidence of cold and warm autoimmune haemolytic anaemia (combined) is approximately 1 in 80,000, the incidence of cold agglutinin disease is approximately 1 in 300,000. Among autoimmune haemolytic anaemias, cold agglutinin disease is the second most common cause, after warm autoantibody–induced immune haemolysis. Frequency figures listed for the United States probably also apply to Canada and the United Kingdom.[15] Other sources cite an annual incidence estimated to be between 1 in 35,000 and 1 in 80,000 in North America and Western Europe.[14]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Currently, there are no approved therapies for CAD. CAD should not be regarded as an indication for therapy in every case, and the decision to treat should be based on an individualised assessment. Reasonable criteria for initiating drug therapy are symptom-producing anaemia, transfusion dependence, or disabling circulatory symptoms.[10]

Immunomodulatory and chemotherapy options have limited efficacy in controlling haemolysis with limited magnitude of haemoglobin response and noted delayed treatment effect onset as well as limited durability of treatment effect in the setting of significant side effects and safety concerns. While red blood cell (RBC) transfusion support can be used in CAD, it has limited efficacy due to the ubiquitous presence of the I antigen on all RBCs, including the donor RBC. Thus, donor RBCs are rapidly hemolyzed after a transfusion contributing to even higher haemolytic activity and have limited ability to alleviate anaemia.[c]

CURRENT TREATMENT OPTIONS

Treatment of CAD has traditionally been dependent upon disease severity. Avoiding exposure to cold temperatures is only variably effective in very mild cases. Plasmapheresis may be used in an acute haemolytic crisis, but the response is temporary.[12]
Pharmacological management of CAD may include:[12,16]

- Rituximab monotherapy
- Rituximab plus chemotherapy (fludarabine or bendamustine)
- Immunosuppressants
- Corticosteroids are contraindicated

PLACE OF TECHNOLOGY

[c] Information provided by Bioverativ

If licensed, sutimlimab would potentially be the first medicinal product targeting this specific complement pathway for the treatment of primary CAD.

CLINICAL TRIAL INFORMATION

Trial	**CARDINAL, NCT03347396, EudraCT 2017-003538-10; sutimlimab; adults aged over 18 years; sutimlimab monotherapy; phase III**
Sponsor	Bioverativ Therapeutics Inc.
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (incl UK), USA, Canada and other countries.
Design	Non-randomised, uncontrolled
Participants	n=20 (planned); aged over 18 years; confirmed diagnosis of primary cold agglutinin disease; history of at least one documented blood transfusion within 6 months of enrolment
Schedule	Assigned to receive an intravenous (IV) infusion of sutimlimab. Participants who complete Part A per protocol through the end of treatment visit (Day 182) will participate in Part B, and continue to receive sutimlimab up to 1 year after last patient out (LPO) in Part A.
Follow-up	Active treatment for 26 weeks
Primary Outcomes	• Part A: Percentage of participants with Response (R); • Part B: Number of Participants with Treatment-emergent Adverse Events (AEs) and Serious AEs (SAEs)
Secondary Outcomes	1. Part A: Mean Change From Baseline in Haemoglobin (Hgb) Level up to Week 26 [Time Frame: Baseline Up to Week 26] 2. Part A: Mean Change From Baseline in Bilirubin up to Week 26 [Time Frame: Baseline up to Week 26] 3. Part A: Mean Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score (Quality of Life) [Time Frame: Baseline up to Week 26] 4. Part A: Mean Change From Baseline in Lactate Dehydrogenase (LDH) up to Week 26 [Time Frame: Baseline up to Week 26] 5. Part A: Percentage of Participants With Solicited Symptomatic Anaemia at End of Treatment (EOT) [Time Frame: At EOT (Day 182)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Dec 2020

Trial	**CADENZA, NCT03347422, EudraCT 2017-003539-12; sutimlimab; adults aged over 18 years; sutimlimab monotherapy; phase III**
Sponsor	Bioverativ Therapeutics Inc.
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled
Participants	n=40 (planned); aged over 18 years; confirmed diagnosis of primary cold agglutinin disease.
Schedule	Assigned to receive an intravenous (IV) infusion of sutimlimab. Participants who complete Part A per protocol through the end of treatment visit (Day 182) will participate in Part B, and continue to receive sutimlimab up to 1 year after last patient out (LPO) in Part A.
Follow-up	Active treatment for 26 weeks
Primary Outcomes	• Part A: Percentage of participants with Response (R); • Part B: Number of Participants with Treatment-emergent Adverse Events (AEs) and Serious AEs (SAEs)
Secondary Outcomes	1. Part A: Mean Change From Baseline in Bilirubin up to Week 26 [Time Frame: Baseline up to Week 26] 2. Part A: Mean Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score (Quality of Life) [Time Frame: Baseline up to Week 26] 3. Part A: Mean Change From Baseline in Lactate Dehydrogenase (LDH) up to Week 26 [Time Frame: Baseline up to Week 26] 4. Part A: Number of Blood Transfusions After the First 5 Weeks of Study Drug Administration [Time Frame: 5 Weeks] 5. Part A: Number of Blood Units Transfused After the First 5 Weeks of Study Drug Administration [Time Frame: 5 Weeks] 6. Part A: Mean Change From Baseline in Haemoglobin (Hgb) Level up to Week 26 [Time Frame: Baseline up to Week 26]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Dec 2020

ESTIMATED COST

The cost of sutimlimab is not yet known.

ADDITIONAL INFORMATION

Sanofi/Bioverativ did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

No NICE guidance has been identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No NHS commissioning policy has been identified.

OTHER GUIDANCE

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