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# SUSTAINED INHIBITION OF COMPLEMENT C1s WITH SUTIMLIMAB

## Over 2 years in patients with Cold Agglutinin Disease

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## Background[1,2]

Cold Agglutinin Disease (CAD) is a rare, classical complement pathway-mediated, autoimmune hemolytic anemia. ENJAYMO is a humanized monoclonal antibody designed to target C1s, which is responsible for activating the classical complement pathway. ENJAYMO selectively inhibits C1s of the C1 complex while leaving the alternative and lectin pathways intact.

## ENJAYMO, the first and only approved treatment for CAD[2,3]

ENJAYMO® (sutimlimab-jome) is a classical complement inhibitor indicated for the treatment of hemolysis in adults with Cold Agglutinin Disease (CAD).

## Methods[1,3]

CARDINAL, a phase 3, global, multicenter, open-label, single-arm, 6-month trial, demonstrated efficacy and safety of ENJAYMO in patients* (N=24) with CAD who received ≥1 transfusion during the preceding 6 months.

Following the completion of the 6-month treatment period (Part A), patients continued to receive ENJAYMO in a long-term safety and durability of response extension phase (Part B) over 2 years.

Efficacy was based on the proportion of patients who met the trial's composite endpoint.

*Patients with CAS secondary to infection, rheumatologic disease, SLE, or overt hematologic malignancy were excluded, whereas patients with a history of concomitant low-grade lymphoproliferative disease were not excluded.

CAD=Cold Agglutinin Disease; CAS=cold agglutinin syndrome; SLE=systemic lupus erythematosus.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

ENJAYMO is contraindicated in patients with known hypersensitivity to sutimlimab-jome or any of the inactive ingredients.

**WARNINGS AND PRECAUTIONS**

**Serious Infections Including Those Caused by Encapsulated Bacteria**

- ENJAYMO, a proximal classical complement C1s inhibitor, increases susceptibility to serious infections, including infections caused by encapsulated bacteria e.g. *Neisseria meningitidis* (any serogroup, including non-groupable strains), *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B.
- Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

**Please see Important Safety Information throughout and full Prescribing Information.**

CARDINAL PART A RESULTS

## Stop the unpredictability of complement-mediated hemolysis in CAD[2,3]

Efficacy and safety of ENJAYMO was demonstrated in CARDINAL, a phase 3, global, multicenter, open-label, single-arm, 6-month trial.

**A MAJORITY OF PATIENTS ACHIEVED**

**ALL 3 COMPOSITE ENDPOINT MEASURES**

**54%**
(13/24)

- ✓ Substantial hemoglobin increase*
- ✓ Transfusion independence†
- ✓ No additional treatment used†‡§

**63%**
(15/24)

**ACHIEVED A CLINICALLY MEANINGFUL Hb INCREASE to ≥12 g/dL OR of ≥2 g/dL**
from baseline (mean Hb 8.6 g/dL [SD: 1.16])*

**71%**
(17/24)

**ACHIEVED TRANSFUSION INDEPENDENCE**
from baseline (median 2 [range 1-19]) through Weeks 5 to 26

**92%**
(22/24)

**RECEIVED NO ADDITIONAL TREATMENT**
from Weeks 5 to 26‡§

Treatment assessment time point (TAT) was defined as the mean value from Weeks 23, 25, and 26.

*Hb level ≥12 g/dL achieved in 38% of patients (9/24); increase in Hb level of ≥2 g/dL achieved in 63% of patients (15/24).
†From Weeks 5 to 26.
‡Prohibited therapies included rituximab alone or in combination with cytotoxic agents.
§Two patients discontinued prior to Week 23, and their status was considered unknown for the purposes of this analysis.
CAD=Cold Agglutinin Disease; Hb=hemoglobin; LS=least squares; TAT=treatment assessment time point.

### WARNINGS AND PRECAUTIONS (continued)

#### Serious Infections Including Those Caused by Encapsulated Bacteria (continued)

- Serious infections (bacterial and viral) were reported in 15% (10/66) of patients receiving ENJAYMO in the two phase 3 trials. These infections included urinary tract infection with sepsis, respiratory tract infection, pneumonia, otomastoiditis, and skin infections. One patient (1.5%) died due to Klebsiella pneumoniae.
- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to administration of the first dose of ENJAYMO, according to the most current ACIP recommendations for patients receiving a complement inhibitor.
- If urgent ENJAYMO therapy is indicated in a patient who is not up to date on their vaccine(s), administer as soon as possible.
- Vaccination does not eliminate the risk of serious encapsulated bacterial infections. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected.
- If ENJAYMO treatment is administered to patients with active systemic infections, monitor closely for signs and symptoms of worsening infection. Some infections may become rapidly life-threatening or fatal if not recognized and treated promptly. Inform patients of these signs and symptoms and steps to be taken to seek immediate medical care.
    - Consider interruption of ENJAYMO treatment in patients who are undergoing treatment for serious infection.
    - Consider patients' immune status when initiating treatment with ENJAYMO.

#### Infusion-Related Reactions

- Administration of ENJAYMO may result in infusion-related reactions. In the two phase 3 trials, 29% (19/66) of patients treated with ENJAYMO experienced infusion-related reactions. One patient permanently discontinued ENJAYMO due to an infusion-related reaction.
- Monitor patients for infusion-related reactions and interrupt if a reaction occurs.
- Discontinue ENJAYMO infusion and institute appropriate supportive measures if signs of hypersensitivity reactions, such as cardiovascular instability or respiratory compromise, occur.

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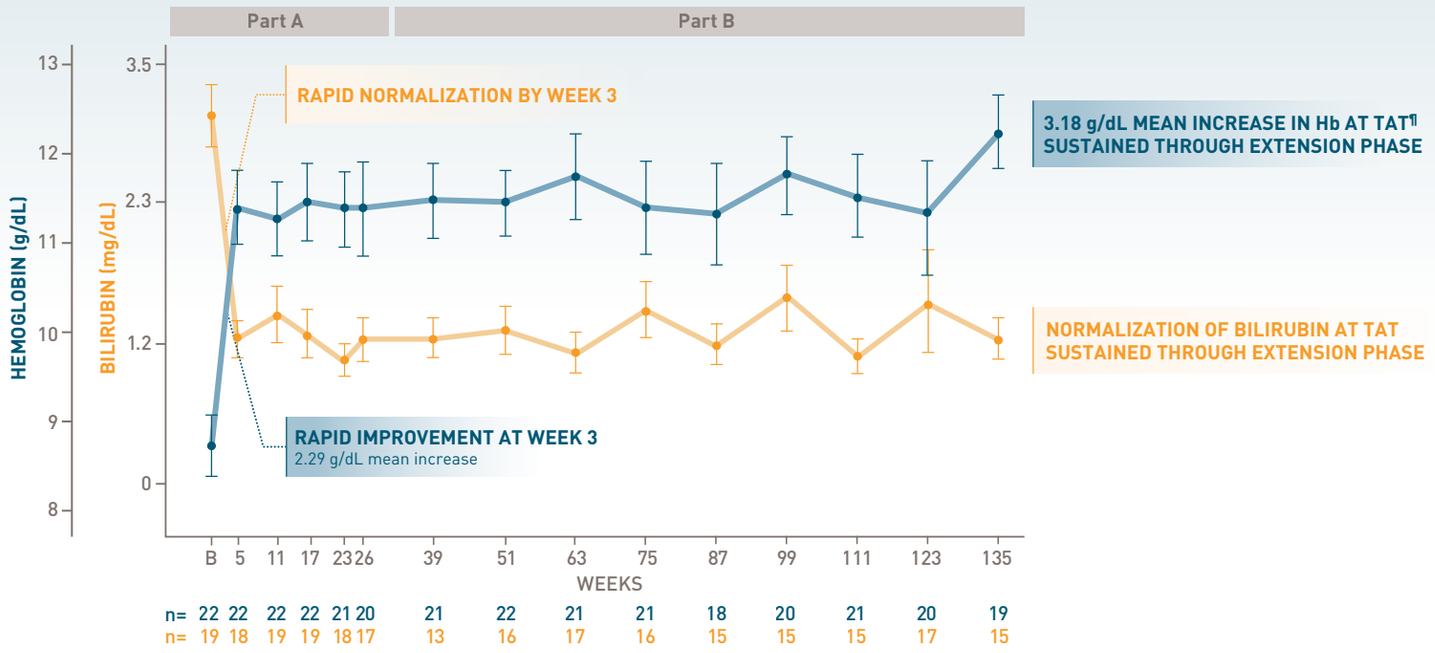
# Rapid and sustained improvement in anemia and hemolysis over 2.5 years with continuous biweekly infusions[1,3‖]

## Mean Hb and bilirubin levels through CARDINAL Part B trial end (N=24)[¶#]




**Hb and bilirubin data at each time point between baseline and trial end are the observed mean. Interpret these data with discretion given small sample and descriptive statistics.**

‖The recommended dosing regimen for adults with CAD consists of an initial dose and a dose 1 week later, followed by 1 dose every 2 weeks.

¶Trial end refers to last available on-treatment value. Treatment Assessment Timepoint (TAT) was defined as the mean value from Weeks 23, 25, and 26.

#Mean baseline values: Hb was 8.6 g/dL (SD: 1.16); bilirubin was 3.1 mg/dL (SD: 1.41). Improvement at TAT: LS mean change in Hb was 2.60 g/dL; LS mean change in bilirubin was −2.23 mg/dL (95% CI: −2.49 to −1.98). Mean Hb level of 12.23 g/dL and mean bilirubin level of 0.96 mg/dL were observed at the last on-treatment visit.

# A well-tolerated safety profile studied over 2.5 years[1,3]

ENJAYMO safety was evaluated in CADENZA, a 6-month placebo-controlled study (Part A [n=42]), followed by a 1-year, open-label, single-arm study (Part B [n=39]) and CARDINAL (an open-label, single-arm study [n=24]) over 143 weeks.

## Adverse reactions (≥15%) in patients receiving ENJAYMO in the CARDINAL study

| Adverse reactions | n (%) (n=24) |
|---|---|
| Urinary tract infection | 9 (38%) |
| Respiratory tract infection | 6 (25%) |
| Bacterial infection | 6 (25%) |
| Nasopharyngitis | 5 (21%) |
| Viral infection | 5 (21%) |
| Dizziness | 7 (29%) |
| Headache | 5 (21%) |
| Fatigue | 8 (33%) |
| Peripheral edema | 6 (25%) |
| Pyrexia | 5 (21%) |
| Arthralgia | 6 (25%) |
| Hypertension | 6 (25%) |
| Acrocyanosis | 5 (21%) |
| Nausea | 6 (25%) |
| Abdominal pain | 5 (21%) |
| Cough | 6 (25%) |
| Infusion-related reaction | 4 (17%) |

**Serious adverse reactions occurred in 10/24 (42%) patients who received ENJAYMO**

- The most common adverse reaction (>5%) was acrocyanosis (n=2). A fatal adverse reaction of *pneumonia klebsiella* occurred in 1 patient who received ENJAYMO

**Permanent discontinuation of ENJAYMO due to an adverse reaction occurred in 2/24 (8%) patients**

- Adverse reactions which resulted in permanent discontinuation of ENJAYMO included *pneumonia klebsiella* (n=1) and acrocyanosis (n=2)

**No meningococcal infections were reported with ENJAYMO**

- ENJAYMO may increase susceptibility to serious infections, including infections caused by encapsulated bacteria such as *Neisseria meningitidis* (any serogroup), *Streptococcus pneumoniae*, and *Haemophilus influenzae*

**Dosage interruptions of ENJAYMO due to an adverse reaction occurred in 7/24 (29%) patients**

- Adverse reactions which required dosage interruption included pneumonia, COVID-19 pneumonia, abdominal pain upper, urinary tract infection bacterial, urosepsis, acrocyanosis, viral infection, blood creatinine increased and infusion-related reaction

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## Conclusions[1-3]

The rapid effects of ENJAYMO treatment on hemolysis and anemia were sustained long term in patients with Cold Agglutinin Disease who continue on therapy.


### EFFECTS ON Hb AND BILIRUBIN WERE MAINTAINED THROUGHOUT A TREATMENT PERIOD OF MORE THAN 2 YEARS*

- **Most patients achieved an improvement in Hb, transfusion independence, and required no additional CAD treatments (13/24)†**
- **Rapid and sustained improvement in anemia over 2.5 years**
  Mean Hb increased 2.29 g/dL by Week 3, with levels sustained through trial end (last on-treatment levels were 12.23 g/dL)
- **Rapid and sustained improvement in bilirubin over 2.5 years**
  Mean total bilirubin was normalized below 1.2 mg/dL from Week 3 to trial end with occasional excursions (last on-treatment levels were 0.96 mg/dL)

## CARDINAL data demonstrated that targeting the classical complement pathway at C1s represents an effective therapeutic approach for the management of hemolysis in CAD[1-3]

Treatment responses as early as Week 3 and a favorable tolerability profile show a continued long-term risk/benefit of ENJAYMO for management of patients with CAD over 2 years.

*Efficacy was based on the proportion of patients who met the following criteria: an increase from baseline in Hgb level ≥2 g/dL or a Hgb level ≥12 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.
†Prohibited therapies included rituximab alone or in combination with cytotoxic agents.

### IMPORTANT SAFETY INFORMATION (continued)

### WARNINGS AND PRECAUTIONS (continued)

#### Risk of Autoimmune Disease

- Based on its mechanism of action, ENJAYMO may potentially increase the risk for developing autoimmune diseases such as systemic lupus erythematosus (SLE). Development of SLE has been associated with inherited classical complement deficiency.
- In clinical trials, 4.5% (3/66) of patients developed a relapse or worsening of previously diagnosed autoimmune disease.
- Monitor ENJAYMO patients for signs and symptoms and manage medically.

#### Recurrent Hemolysis After ENJAYMO Discontinuation

- If treatment with ENJAYMO is interrupted, closely monitor patients for signs and symptoms of recurrent hemolysis, eg, elevated levels of total bilirubin or lactate dehydrogenase (LDH) accompanied by a decrease in hemoglobin, or reappearance of symptoms such as fatigue, dyspnea, palpitations, or hemoglobinuria. Consider restarting ENJAYMO if signs and symptoms of hemolysis occur after discontinuation.

### ADVERSE REACTIONS

- The most common adverse reactions in the CADENZA trial (Part A) (incidence ≥18%) are rhinitis, headache, hypertension, acrocyanosis, and Raynaud's phenomenon. The most common adverse reactions in the CARDINAL trial (incidence ≥25%) are urinary tract infection, respiratory tract infection, bacterial infection, dizziness, fatigue, peripheral edema, arthralgia, cough, hypertension, and nausea.

**Please see Important Safety Information throughout and full Prescribing Information.**

**References: 1.** Röth A, Barcellini W, D'Sa S, et al. Sustained inhibition of complement C1s with sutimlimab over 2 years in patients with cold agglutinin disease. *Am J Hematol*. 2023;98(8):1246-1253. doi:10.1002/ajh.26965 **2.** Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med*. 2021;384(14):1323-1334. doi:10.1056/NEJMoa2027760 **3.** ENJAYMO. Prescribing information.

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