REAL-WORLD SAFETY OF SUTIMLIMAB IN PATIENTS WITH CAD/CAS: A MULTINATIONAL, MULTI-CENTER, OBSERVATIONAL, PROSPECTIVE COHORT STUDY

Alexander Röth,[1] Marc Michel,[2] Wilma Barcellini,[3] Ulrich Jäger,[4] Yasutaka Ueda,[5] Quentin A. Hill,[6] Joan Cid,[7] Kelley C. Dacus,[8] Mounia Beloueche,[9] Catherine M. Broome[10]

[1]Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [2]Henri-Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, UPEC, Créteil, France; [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Division of Haematology and Haemostasis, Department of Medicine I, Medical University of Vienna, Vienna, Austria; [5]The University of Osaka Graduate School of Medicine, Osaka, Japan; [6]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [7]Department of Hemotherapy and Hemostasis, ICAMS, Clínic Barcelona, IDIBAPS, Barcelona, Spain; [8]Recordati, Bridgewater, NJ, USA; [9]Recordati, Hemel Hempstead, UK; [10]Division of Hematology, MedStar Georgetown University Hospital, Washington, DC, USA.

6242

INTRODUCTION

- Cold agglutinin disease (CAD) and cold agglutinin syndrome (CAS) are cold antibody driven autoimmune hemolytic anemias, characterized by hemolysis via the classical complement pathway; CAS, unlike CAD, is typically linked to an underlying condition[1]
  - CAD substantially burdens patients. It is associated with an increased risk of thromboembolic events and mortality, and negatively impacts patient quality of life (QoL);[2,3] the main drivers are severe fatigue, shortness of breath, joint pain, headaches, and acrocyanosis[2]
  - Approaches to managing patients with CAD can be heterogenous. Therefore, it is important to study real-world patient characteristics and disease burden, as well as clinical and patient-reported outcomes[4]
- Sutimlimab is the first and only approved treatment for CAD; it is a humanized monoclonal antibody that selectively inhibits the classical complement pathway by targeting C1s[5–7]
- CADENCE is the first multinational, prospective, longitudinal registry for patients with CAD or CAS, collecting data on over 400 patients to better characterize long-term clinical and patient-reported outcomes[8,9]
  - CADENCE documents real-world treatment patterns and regimens in patients with CAD/CAS, including a sutimlimab-treated cohort

AIMS

To report the updated real-world safety analysis of the sutimlimab-treated cohort in the CADENCE registry of patients with CAD or CAS

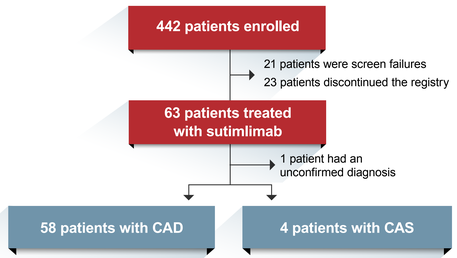
METHODS

- The CADENCE registry recruited adults aged ≥18 years, diagnosed with CAD or CAS (**Figure 1**)
- Adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs)/other events of interest were collected for patients on sutimlimab, regardless of whether they were related to sutimlimab. Medication errors and off-label use were also collected for these patients

Figure 1 | CADENCE enrollment and patient flow as of data cut off (February 4, 2025)

Enrollment Criteria[a]
Main inclusion criteria: Adults ≥18 years of age diagnosed with CAD or CAS
- ***CAD diagnostic criteria:*** Monospecific direct antiglobulin test strongly positive for C3d and negative or weakly positive for immunoglobulin G and a cold agglutinin titer of ≥1:64
- ***CAS diagnostic criteria:*** Meet CAD diagnostic criteria, with causative infection, autoimmune disorder, or overt malignancy (including overt evidence of a B-cell lymphoproliferative disease)

Main exclusion criteria: Diagnosis of warm or mixed autoimmune hemolytic anemia, and active participation in a CAD or CAS interventional trial



CAD, cold agglutinin disease; CAS, cold agglutinin syndrome.

RESULTS

Baseline Demographics of Patients in the Sutimlimab Cohort

- Between December 12, 2019 and February 4, 2025, 442 patients were enrolled in the CADENCE registry (**Figure 1**)
- Patient enrollment in the registry is now complete
- A total of 63 patients were included in the sutimlimab cohort, comprising 58 patients diagnosed with CAD and 4 patients diagnosed with CAS
  - There was 1 patient for whom diagnosis information was not provided during the reporting period
- Patients were recruited from across the US (n=24), Germany (n=20), Japan (n=7), Italy (n=6), Austria (n=2), Spain (n=2), and France (n=2)
- The mean (SD [standard deviation]) age of patients treated with sutimlimab was 72.7 (8.8) years at the time of enrollment and the proportion of female patients was 76.2% (**Table 1**)
- At data cut-off, the median (Q1; Q3) and mean (SD) sutimlimab treatment duration was 22.7 (10.4; 32.6) and 25.1 (18.7) months, respectively

Table 1 | Summary of Demographics of Patients in the Sutimlimab Cohort

Parameters	Sutimlimab cohort N=63	Total N=442[a]
Patients included, n	63	439[b]
Age (years)		
Mean (SD)	72.7 (8.8)	71.3 (11.0)
Median (Q1; Q3)	73 (67; 79)	73 (65; 79)
Min, max	45, 91	21, 96
Sex		
Male, n (%)	15 (23.8)	159 (36.2)
Female, n (%)	48 (76.2)	280 (63.8)

[a]357 patients had CAD, 75 had CAS, 2 had an undetermined CAD/CAS diagnosis, and diagnosis information was not provided during the reporting period for 8 patients. [b]Missing data for age and sex for 3 patients.
SD, standard deviation.

Summary of Adverse Events

- In the sutimlimab cohort, 33 (52.4%) patients experienced a total of 159 AEs, including 31 (53.4%) patients with CAD who had a total of 156 AEs, and 2 (50%) patients with CAS who had a total of 3 AEs (**Table 2**)
  - There were 6 patients (9.5%) with AEs considered to be related or possibly related to sutimlimab by the investigator; 5 (8.6%) patients with CAD (total of 5 AEs) and 1 (25.0%) patient with CAS (1 AE)
    - Ectopic atrial rhythm (CAD), 1 patient
    - Headache (CAD), 1 patient
    - Dyspnea (CAD), 1 patient
    - Chest pain/stable angina (CAS), 1 patient
      - Considered an SAE
    - Acrocyanosis (CAD), 2 patients

Table 2 | Summary of Adverse Events in the Sutimlimab Cohort

	CAD (N=58)		CAS (N=4)		Total (CAD + CAS + unconfirmed) (N=63)[b]	
Type of event	**Patients with an event**	**Number of events**	**Patients with an event**	**Number of events**	**Patients with an event**	**Number of events**
AEs, n (%)	31 (53.4)	156	2 (50.0)	3	33 (52.4)	159
AEs related[a] to sutimlimab, n (%)	5 (8.6)	5	1 (25.0)	1	6 (9.5)	6
SAEs, n (%)	10 (17.2)	36	1 (25.0)	1	11 (17.5)	37
SAEs related[a] to sutimlimab, n (%)	0	0	1 (25.0)	1	1 (1.6)	1
AESIs, n (%)	12 (20.7)	17	0	0	12 (19.0)	17
AESIs related[a] to sutimlimab, n (%)	2 (3.4)	2	0	0	2 (3.2)	2
Other events of interest, n (%)	3 (5.2)	3	0	0	3 (4.8)	3
Deaths, n (%)	1 (1.7)	1	0	0	1 (1.6)	1
SUSARs[a], n (%)	0	0	1 (25.0)	0	1 (1.6)	1

[a]Related or possibly related to sutimlimab. [b]Includes 1 patient for whom diagnosis information was not provided.
AE, adverse event; AESI, adverse event of special interest; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction.

Summary of Serious Adverse Events

- Overall, 11 (17.5%) patients experienced a total of 37 SAEs (**Table 2**); 10 (17.2%) patients with CAD experienced a total of 36 SAEs, and 1 patient (25.0%) with CAS experienced 1 SAE
  - One patient with CAD, who developed sepsis due to recent untreated *Capnocytophaga canimorsu*s bacteremia infection, experienced a total of 18 SAEs (all were resolved)
  - A 90-year-old male patient with CAD had a fatal AE of low right lung pneumonia that was considered not related to sutimlimab by the investigator
  - None of the SAEs reported in patients with CAD were considered related to sutimlimab by the investigator
  - The SAE experienced by the patient with CAS (chest pain/stable angina) was a suspected unexpected serious adverse reaction (SUSAR) and considered related to sutimlimab

Summary of Adverse Events of Special Interest/Other Events of Interest

- AESIs reported in the sutimlimab cohort are listed in **Table 3**
- Among the AESIs:
  - Three patients with CAD experienced 7 serious infections (see **Table 4** for the list of serious infections experienced by these 3 patients)
  - Three patients with CAD had concomitantly used rituximab
  - There were 2 cases of arterial hypertension and 8 cases of acrocyanosis – all these were reported as non-serious
- Two AESIs of acrocyanosis were considered possibly related to sutimlimab; none of the other AESIs/other events of special interest were considered related to sutimlimab
- There were no occurrences of the following AESIs:
  - Meningococcal infection
  - Development of systemic lupus erythematosus (SLE) (or other autoimmune disorder)
  - Hypersensitivity reactions and anaphylaxis
  - Female exposure to sutimlimab during pregnancy (including pregnancy occurring in a female partner of a male patient exposed to sutimlimab) and/or during breastfeeding
  - Symptomatic overdose
  - Thromboembolic events

Table 3 | AESIs/Other Events of Interest in the Sutimlimab Cohort

Type of AESI	Total patients (N=63)[a]	Patients with CAD (N=58)	Patients with CAS (N=4)
Serious infections, n (%)	3 (4.8)	3 (5.2)	0
Arterial hypertension, n (%)	2 (3.2)	2 (3.4)	0
Concomitant use of rituximab or a rituximab combination product, n (%)	3 (4.8)	3 (5.2)	0
Acrocyanosis and Raynaud's phenomenon, n (%)	8 (12.7)	8 (13.8)	0

[a]Includes 1 patient for whom diagnosis information was not provided.
AESI, adverse event of special interest; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome.

Table 4 | Serious Infections in the Sutimlimab Cohort

	Total patients N=63	Number of events
Serious infections[a], n (%)	3 (4.8)	7
Bilateral pneumonia	1 (1.6)	1
Positive GNR blood culture (klebsiella) with gallbladder as likely source	1 (1.6)	1
Sepsis due to recent untreated *Capnocytophaga canimorsus* bacteremia infection	1 (1.6)	1
Severe sepsis due to lower extremity cellulitis	1 (1.6)	1
Skin infection – cellulitis	1 (1.6)	1
Urinary tract infection	1 (1.6)	1
Urinary tract infection positive urine culture, positive for *Klebsiella pneumoniae*	1 (1.6)	1

[a]Three patients experienced a total of 7 serious infections (1 patient had 4 serious infections, and 1 patient had 2 serious infections).
GNR, Gram-negative rods.

CONCLUSIONS

- **After a mean treatment duration of 25 months, no new safety concerns were identified in this updated analysis of CADENCE registry patients with CAD and CAS treated with sutimlimab**
- **Sutimlimab was generally well tolerated. Safety findings were consistent with an elderly population with CAD/CAS, as well as with earlier clinical trial data, and continue to support the long-term safety profile of sutimlimab in patients with CAD[6,10]**
- **Final follow-up results are expected from the CADENCE registry in 2031 and will further inform the understanding of the long-term safety and efficacy of sutimlimab**
- **CADENCE adds to the growing body of evidence supporting the role of sutimlimab in classical complement pathway inhibition in patients with CAD[6,10]**

ACKNOWLEDGMENTS

Thank you to the patients, their families, and investigators for making this research possible. Study management and statistical analysis were provided by ICON plc and funded by Recordati. Medical writing and editing support were provided by Richard Amoroso of Lucid Group Communications Ltd. and funded by Recordati.

REFERENCES

1. Berentsen S, et al. *J Blood Med.* 2019;10:93–103; **2.** Joly F, et al. *JMIR Form Res.* 2022;6(7):e34248; **3.** Bylsma LC, et al. *Blood Adv.* 2019;3(20):2980–5; **4.** Mullins M, et al. *Blood Adv.* 2017;1(13):839–48; **5.** Berentsen S. *Front Immunol.* 2020;11:590; **6.** Röth A, et al. *N Engl J Med.* 2021;384(16):1323–34; **7.** Bioverativ Therapeutics Inc. ENJAYMO® (sutimlimab-jome). Prescribing Information. Last updated February 2024. Accessed October 15, 2025; **8.** ClinicalTrials.gov. NCT05791708. Last updated October 14, 2025. Accessed October 14, 2025; **9.** Röth A, et al. *Blood.* 2023;142 (Suppl. 1):7341; **10.** Röth A, et al. *Blood.* 2022;140(9):980–91.