COMBINED SAFETY DATA FOR SUTIMLIMAB IN COLD AGGLUTININ DISEASE: A POST HOC ANALYSIS OF THE PHASE 3 CARDINAL AND CADENZA STUDIES

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INTRODUCTION

- Cold agglutinin disease (CAD) is a rare, autoimmune hemolytic anemia, characterized by chronic hemolysis, which is mediated by activation of the classical complement pathway (CP)
- Sutimlimab is a first-in-class, humanized, monoclonal antibody that selectively inhibits C1s of the C1 complex, preventing CP activation and CP-mediated hemolysis[1,2]
- CARDINAL (NCT03347396) was an open-label, single-arm, Phase 3 study of sutimlimab in patients with CAD and recent history of transfusion[1]; CADENZA (NCT03347422) was a randomized, double-blind, placebo-controlled, Phase 3 study of sutimlimab in patients with CAD and no recent history of transfusion[3]
- Both studies had a 26-week treatment period (Part A) followed by a long-term extension period (Part B), reporting data up to 2 years after the last patient finished Part A of CARDINAL and up to 1 year after the last patient finished Part A of CADENZA[1–4]
- With long-term treatment in both individual studies, sutimlimab demonstrated sustained efficacy with improvements in hemolysis and anemia, sustained clinically meaningful improvements in quality of life, and a favorable safety profile[1–4]

AIM

To report combined safety data from Parts A and B of the Phase 3 CARDINAL and CADENZA studies in sutimlimab-treated patients with CAD

METHODS

- Data from all enrolled patients who received at least one dose of sutimlimab in CARDINAL (N=24) and CADENZA (N=42), including a post-treatment follow-up 9 weeks after the last dose, were included in the Safety Analysis Set
  - In CARDINAL Part A, patients received sutimlimab on Days 0 and 7, then biweekly until the end of Part B[1,2]
  - In CADENZA Part A, patients received sutimlimab or placebo on Days 0 and 7, then biweekly; in Part B, patients continued to receive biweekly sutimlimab or switched from placebo to sutimlimab and received treatment on Days 0 and 7, then biweekly until the end of Part B[3,4]
- Endpoints for this analysis included the incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs)
- AESIs were selected based on a list of important identified risks and important potential risks for sutimlimab

RESULTS

Study population

- The Safety Analysis Set included 66 patients
- At baseline, the median age was 69.5 years (range 46–88) and the majority (72.7%) were female, with a median duration since CAD diagnosis of 5.7 years (range 0–33)
- The median patient follow-up was 129.1 weeks (range 5–175)

TEAEs

- 64 (97.0%) patients experienced ≥1 TEAE *(see Table 1)*
- 86 TEAEs, assessed by the investigator as possibly related to sutimlimab, occurred in 30 (45.5%) patients
  - Related TEAEs reported in >1 patient included headache, acrocyanosis, cystitis, fatigue, hypertension, injection-site erythema, nausea, and pyrexia

TESAEs

- 53 TESAEs were reported in 22 (33.3%) patients *(see Table 1)*
- 4 (6.1%) patients each experienced one TESAE assessed as possibly related/related to sutimlimab by the investigator (viterous hemorrhage, viral infection, severe cerebral venous thrombosis, hypertension)

Table 1. Incidence of TEAEs and TESAEs by study and overall – Safety Analysis Set

	CARDINAL (N=24)	CADENZA (N=42)	OVERALL (N=66)
Median treatment duration (weeks)	**144**	**125**	
TEAEs			
Number of TEAEs, n	385	425	810
Patients with ≥1 TEAEs, n (%)[a]	24 (100)	40 (95.2)	64 (97.0)
Related TEAEs[b]			
Number of related TEAEs, n	16	70	86
Patients with ≥1 related TEAEs, n (%)[a]	11 (45.8)	19 (45.2)	30 (45.5)
TESAEs			
Number of TESAEs, n	40	13	53
Patients with ≥1 TESAEs, n (%)[a]	14 (58.3)	8 (19.1)	22 (33.3)
Related TESAEs[b]			
Number of related TESAEs, n	2	2	4
Patients with ≥1 related TESAEs, n (%)[a]	2 (8.3)	2 (4.8)	4 (6.1)

Events are coded using MedDRA version 21.0. [a]Percentages are based on the number of subjects in each study cohort (or total) of the Safety Analysis Set; [b]Assessed as possibly related by the investigator. MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

AESIs

- Treatment-emergent AESIs were selected based on a list of important identified and potential risks for sutimlimab (*Table 2*). The following AESIs were reported:
  - 18 TEAEs of serious infection in ten patients (15.1%; one assessed as possibly related to sutimlimab by the investigator)
  - 36 TEAEs of hypertension in 20 patients (30.3%; ten assessed as probably or possibly related to sutimlimab by the investigator)
  - 39 TEAEs of acrocyanosis and/or Raynaud's phenomenon in 17 patients (25.7%; 16 acrocyanosis events and one Raynaud's event assessed as possibly related to sutimlimab by the investigator)
  - 4 TEAEs of thromboembolic events in four patients (6.1%; none assessed as possibly related to sutimlimab by the investigator)
- No TEAEs of serious hypersensitivity reaction and/or anaphylaxis, meningococcal infection or development of systemic lupus erythematosus were reported

Table 2. Incidence of AESIs by study and overall – Safety Analysis Set

	CARDINAL (N=24)	CADENZA (N=42)	OVERALL (N=66)
Serious infections[a]			
Number of TEAEs, n	16	2	18
Patients with ≥1 TEAEs, n (%)[b]	8 (33.3)	2 (4.8)	10 (15.1)
Hypertension[c]			
Number of TEAEs, n	12	24	36
Patients with ≥1 TEAEs, n (%)[b]	6 (25.0)	14 (33.3)	20 (30.3)
Acrocyanosis and/or Raynaud's phenomenon[d]			
Number of TEAEs, n	14	25	39
Patients with ≥1 TEAEs, n (%)[b]	5 (20.8)	12 (28.6)	17 (25.8)
Thromboembolic events[e]			
Number of TEAEs, n	2	2	4
Patients with ≥1 TEAEs, n (%)[b]	2 (8.3)	2 (4.8)	4 (6.1)

Events are coded using MedDRA version 21.0. [a]Serious infections were identified based on a search for all preferred terms with System Organ Class matching 'Infections and infestations' and marked as serious; [b]Percentages are based on the number of subjects in each study cohort (or total) of the Safety Analysis Set; [c]Identified based on a search for the following AE preferred terms: 'Hypertension', 'Blood pressure increased', 'Essential hypertension', 'Hypertensive crisis', 'White coat hypertension'; [d]Acrocyanosis and/or Raynaud's phenomenon were identified based on a search for the following AE preferred terms: 'Cyanosis', 'Raynaud's phenomenon'; [e]Thromboembolic events were identified based on a search for the following AE preferred terms: 'Ischemic stroke', 'Device related thrombosis', 'Peripheral artery thrombosis', 'Transient ischemic attack', 'Deep vein thrombosis'.

AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Discontinuations and deaths

- 7 patients discontinued sutimlimab treatment and/or the studies due to ≥1 TEAE: four in CARDINAL and three in CADENZA
- 2 discontinuations in CARDINAL were assessed as related to sutimlimab:
  - 1 patient with a history of recurrent uveitis and latent tuberculosis discontinued due to vitreous hemorrhage;
  - 1 patient discontinued due to acrocyanosis and gastrointestinal symptoms, including erosive grastritis
- 1 patient in CADENZA discontinued due to an infusion-related reaction (pain in lumbar spine and both legs during sutimlimab infusion) assessed as possibly related to sutimlimab by the investigator
- 4 patients died during the studies; however, no deaths resulted from TEAEs assessed as possibly related to sutimlimab by the investigator:
  - 1 patient in CADENZA with a TESAE of lung squamous cell carcinoma and sutimlimab was withdrawn due to this TESAE prior to the patient's death
  - 1 patient in CARDINAL after premature discontinuation of sutimlimab due to AEs (fatal infection of *Klebsiella pneumoniae*, acrocyanosis)
  - 1 patient in CARDINAL due to a newly diagnosed hepatic cancer in the first month of the study
  - 1 patient in CARDINAL due to exacerbation of CAD during the 9-week washout period approximately 1.5 months after the last dose of sutimlimab

CONCLUSION

The combined safety analysis of the Phase 3 CARDINAL and CADENZA studies (Parts A and B) demonstrated that sutimlimab was generally well tolerated, with the type and frequency of TEAE consistent with an older and medically complex population.

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ACKNOWLEDGMENTS

Medical writing and editing support were provided by Alexander Teahan and David Campbell from Lucid Group Communications Ltd, First Floor, Jubilee House, Third Avenue, Globe Park, Marlow, Buckinghamshire, SL7 1EY, UK, and was funded by Sanofi in accordance with Good Publication Practice (GPP 2022) guidelines. This work and the CARDINAL and CADENZA studies were funded by Sanofi.