Sutimlimab in Patients with Cold Agglutinin Disease with Prior Rituximab Use versus Rituximab-naïve Patients: Post-Hoc Analyses From Phase 3 Studies

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INTRODUCTION

- Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia characterized by chronic hemolysis and mediated by activation of the classical complement pathway[1].
- Patients with CAD experience a variety of physical and mental manifestations, including fatigue, acrocyanosis, dyspnoea, haemoglobinuria, weakness, and weight loss[2].
- Sutimlimab is a humanized monoclonal antibody that inhibits the classical complement pathway and is approved for the treatment of CAD[1,2].
- Prior to sutimlimab's approval, rituximab was the most commonly used off-label treatment for patients with CAD[1].

AIM

- This post-hoc analysis aimed to describe the characteristics of patients with CAD who received prior off-label rituximab treatment versus (vs) rituximab-naïve patients and assess the efficacy of sutimlimab in these subgroups, using pooled data from the Phase 3 CARDINAL (NCT03347396) and CADENZA (NCT03347422) trials.

METHODS

Study design

- CARDINAL was a two part (Part A [26-Week], Part B [safety extension]), open-label, single-arm, multi-centre trial in CAD patients with a recent blood transfusion.
- CADENZA was a two part (Part A [26-Week], Part B [safety extension]), randomized, double-blind, placebo-controlled, multi-centre trial in CAD patients without a recent blood transfusion. In Part B, the placebo group was initiated on sutimlimab.
- Data of sutimlimab treated patients from CARDINAL and CADENZA (Part A) and from the first 6 months of CADENZA Part B (patients treated by placebo in Part A) were included in this analysis.

Eligibility criteria

- Patients aged ≥18 years, with a confirmed diagnosis of CAD, and a haemoglobin (Hb) level of ≤10g/dL were enrolled in both trials.
- Patients were excluded if they received rituximab monotherapy (rituximab ± oral corticosteroids) within 3 months, or combination therapy (e.g., with bendamustine, fludarabine, or others) within 6 months, prior to enrollment for Part A, and the start of sutimlimab treatment for ex-placebo patients for Part B.

Study endpoints

- Endpoints were analyzed descriptively as per prior rituximab use, including previous monotherapy, combination therapy, or both.
- Baseline was the last non-missing value prior to receiving sutimlimab (pre-dose value for CARDINAL Part A and CADENZA Part A trials was Day 1; pre-dose value for patients starting sutimlimab in CADENZA Part B was Week 26).

Primary endpoint

- For this analysis, the composite efficacy endpoint was response, defined as follows:
  - No blood transfusions or protocol prohibited medications from Week 5 to 26 for Part A or Week 27 to 53 for Part B), and who had achieved an improvement in Hb of ≥2.0 g/dL from baseline, or Hb ≥12 g/dL at treatment assessment timepoint (TAT).
  - For CARDINAL and CADENZA Part A trials, TAT was defined as the average of values from Week 23, 25, and 26 visits, and for CADENZA Part B (patients initiated on sutimlimab), TAT was the average of values from Week 49, 51, and 53 visits.

Secondary endpoints

- The secondary endpoints included mean change from baseline to TAT in Hb, bilirubin, and lactate dehydrogenase (LDH) (CARDINAL or CADENZA Part A [W0–W26], CADENZA Part B [W26–W53]), and in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score (CARDINAL or CADENZA Part A [W13], CADENZA Part B [W39]).

RESULTS

Study participants

- Overall, 66 patients receiving sutimlimab were included in this analysis (CARDINAL, n=24; CADENZA sutimlimab arm, n=22; and CADENZA ex-placebo arm, n=20).
- At baseline 38 (58%) patients had prior rituximab use (prior rituximab use for Part A was any rituximab therapy prior to screening, for Part B ex-placebo patients, it was any rituximab therapy prior to the start of Part B).
- Mean (SD) age was 67.1 (9.7) years for patients with prior rituximab use and 70.5 (9.9) years for rituximab-naïve patients (**Table 1**).

Baseline clinical and laboratory characteristics

- At baseline, levels of Hb, bilirubin, and LDH, and the FACIT-Fatigue score were similar between subgroups.
  - In CADENZA Part A, mean (SD) immunoglobulin M level and cold agglutinin titer were higher in the rituximab-naïve subgroup vs prior rituximab subgroup (6.2 [6.8] g/L and 472.6 [1189.6] vs 2.9 [2.6] g/L and 214.4 [905.0], respectively) (**Table 1**).

Medical history and prior corticosteroid use

- Patients with prior rituximab use had longer mean (SD) CAD disease duration (8.5 [7.6] years), greater intravenous corticosteroid usage (52.6%) and slightly higher CAD-related hospitalizations (34.2%) compared with rituximab-naïve patients (5.3 [5.1] years, 25.0%, and 28.6%, respectively).

Table 1. Baseline demographics and clinical characteristics for patients with CAD receiving sutimlimab according to prior off-label rituximab use

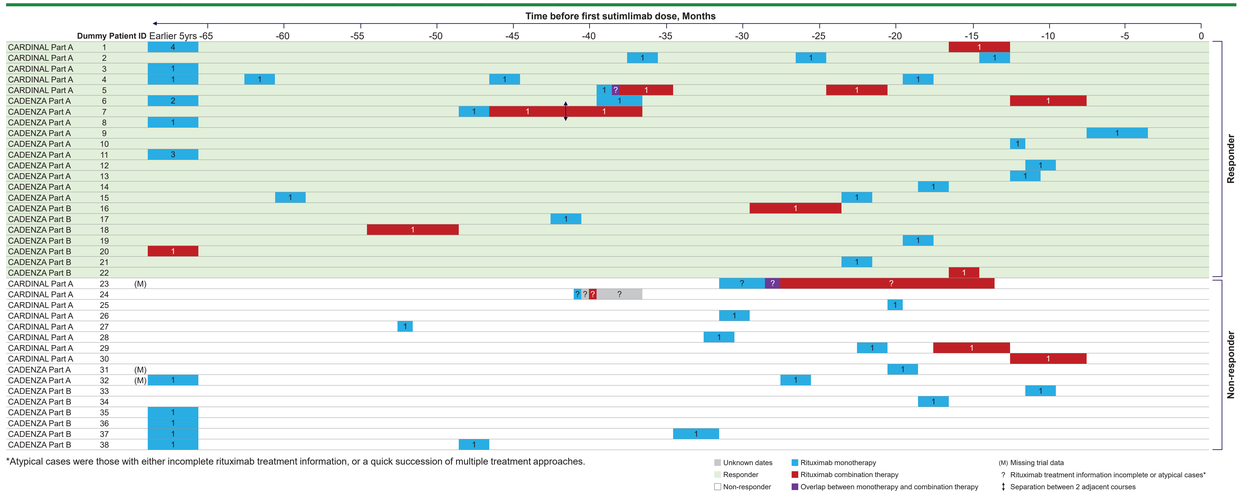
Characteristics	CARDINAL (N=24)		CADENZA sutimlimab arm (Part A) (N=22)		CADENZA ex-placebo arm (Part B) (N=20)		Pooled data (N=66)	
	Prior rituximab (n=13)	No prior rituximab (n=11)	Prior rituximab (n=12)	No prior rituximab (n=10)	Prior rituximab (n=13)	No prior rituximab (n=7)	Prior rituximab (n=38)	No prior rituximab (n=28)
Demographics								
Mean age (SD), yrs	70.8 (9.1)	71.8 (7.4)	64.5 (9.6)	66.3 (12.7)	65.8 (9.9)	74.3 (8.0)	67.1 (9.7)	70.5 (9.9)
Female, n (%)	7 (53.8)	8 (72.7)	10 (83.3)	7 (70.0)	12 (92.3)	4 (57.1)	29 (76.3)	19 (67.9)
Geographic location, n (%)								
Europe	11 (84.6)	6 (54.5)	10 (83.3)	5 (50.0)	9 (69.2)	4 (57.1)	30 (78.9)	15 (53.6)
North America	2 (15.4)	1 (9.1)	2 (16.7)	1 (10.0)	3 (23.1)	0 (0.0)	7 (18.4)	2 (7.1)
Asia (Japan)	0 (0.0)	3 (27.3)	0 (0.0)	3 (30.0)	0 (0.0)	2 (28.6)	0 (0.0)	8 (28.6)
Other (Australia & Israel)	0 (0.0)	1 (9.1)	0 (0.0)	1 (10.0)	1 (7.7)	1 (14.3)	1 (2.6)	3 (10.7)
Medical history								
CAD disease duration								
Mean (SD), yrs	11.1 (8.4)	5.3 (4.4)	7.6 (8.0)	4.4 (5.8)	6.8 (6.3)	6.6 (5.7)	8.5 (7.6)	5.3 (5.1)
Median [range], yrs	10 [0–33]	5.0 [0–14]	4 [1–23]	2.0 [0–16]	3.5 [2–22]	5.5 [1–18]	6.3 [0–33]	4.3 [0–18]
Any hospitalizations related to CAD[a], n (%)	11 (84.6)	5 (45.5)	1 (8.3)	1 (10.0)	1 (7.7)	2 (28.6)	13 (34.2)	8 (28.6)
Any corticosteroid use (intravenous), n (%)	6 (46.2)	2 (18.2)	7 (58.3)	3 (30.0)	7 (53.8)	2 (28.6)	20 (52.6)	7 (25.0)
Number of blood transfusions per patient within one year prior to enrollment[b], mean (SD)	6.0 (7.5)	3.4 (4.1)	1 (0.0)	N/A	N/A	N/A	N/A	N/A
Number of patients with at least one blood transfusion within one year prior to enrollment[c], n (%)	13 (100.0)	11 (100.0)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (42.1)	11 (39.3)
Laboratory measures, mean (SD)								
Hemoglobin (g/dL)	8.5 (1.5)	8.7 (1.8)	9.6 (1.0)	8.6 (0.9)	9.3 (1.7)	9.9 (1.8)	9.1 (1.5)	9.0 (1.6)
Bilirubin (µmol/L)	55.8 (28.5)	45.2 (14.8)	38.6 (14.6)	43.8 (36.1)	40.2 (16.2)	30.2 (7.4)	45.0 (21.8)	40.9 (23.8)
LDH (U/L)	516.2 (328.8)	345.8 (198.1)	384.3 (187.6)	466.1 (203.4)	431.1 (469.1)	355.0 (164.1)	445.5 (346.3)	391.1 (193.8)
Immunoglobulin M (g/L)	3.5 (3.7)	3.8 (2.1)	2.3 (1.6)	9.9 (10.1)	2.9 (2.0)	4.5 (3.5)	2.9 (2.6)	6.2 (6.8)
Cold agglutinin titer − in 1,000s	548.2 (1,525.5)	540.2 (1,571.9)	16.3 (49.0)	649.1 (1,088.2)	62.3 (126.1)	54.7 (61.6)	214.4 (905.0)	472.6 (1,189.6)
PRO measures, mean (SD)								
FACIT-Fatigue score[d]	32.2 (11.3)	32.8 (10.5)	32.7 (12.5)	30.4 (13.7)	36.3 (10.8)	30.1 (15.2)	33.9 (11.4)	31.3 (12.5)

Baseline was defined as the last non-missing value before the first administration of sutimlimab (predose value for CARDINAL and CADENZA Part A trials was Day 1; predose value for CADENZA Part B was Week 26). Prior rituximab use includes rituximab monotherapy (rituximab ± oral corticosteroids), combination therapy (e.g. with bendamustine, fludarabine, or others), or both. [a]Within the last two years, not including blood transfusions unless overnight stay. [b]In CARDINAL, included patients received ≥1 blood transfusion within one year prior to enrollment. [c]In CADENZA, included patients had not received a blood transfusion in the one year prior to enrollment and ≤1 blood transfusion in the previous six months. [d]FACIT-Fatigue scores ranged from 0–52, higher scores indicate less fatigue.
CAD, cold agglutinin disease; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; N/A, not applicable; PRO, patient reported outcome; SD, standard deviation; yrs, years.

Rituximab treatment patterns

- Twelve (31.5%) patients had received at least one course of rituximab combination therapy and 26 (68.4%) received monotherapy only (**Figure 1**).
- The number of rituximab courses received prior to trial enrollment ranged from 1 to 5 with a mean number of 1.66, considering all rituximab use (monotherapy and combination therapy).
- Fifteen patients (39.4%) received their last rituximab treatment in the 3 to 15 months prior to sutimlimab start date; while 10 patients (26.3%) received their last treatment in the 16 to 27 months prior; and finally, 13 patients (34.2%) received their last treatment 27 months or more prior to sutimlimab (**Figure 1**).
  - Per the inclusion criteria, rituximab treatment was ceased at least 3 months (rituximab monotherapy) or 6 months (combination therapy) prior to enrollment.

Figure 1. By-patient history of treatment with rituximab monotherapy and/or combination therapy for patients receiving sutimlimab pooled CARDINAL (Part A) and CADENZA (Part A [sutimlimab arm] and Part B [ex-placebo]) trials by responder status at TAT



*Atypical cases were those with either incomplete rituximab treatment information, or a quick succession of multiple treatment approaches.

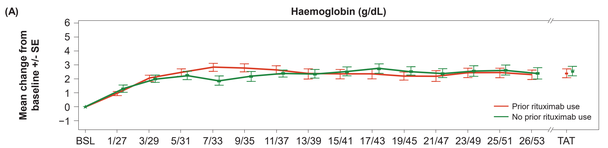
Primary endpoint

- Response rates were similar between subgroups: 60.5% with prior rituximab use and 60.7% in rituximab naïve patients.

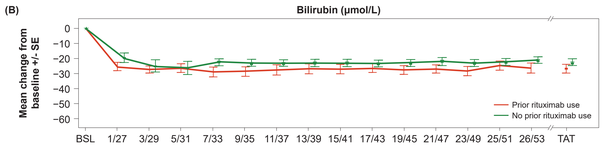
Secondary endpoints

- Mean (SE) change in Hb level from baseline to TAT was 2.4 (0.3) g/dL vs 2.6 (0.4) g/dL, bilirubin level was −26.5 (3.0) µmol/L vs −22.4 (2.3) µmol/L, and for LDH level was −128.9 (45.4) U/L vs −36.4 (35.6) U/L, for patients with vs without prior rituximab use, respectively (**Figure 2A, 2B, 2C**).
- Mean (SE) improvement in FACIT-Fatigue score from baseline was similar in both subgroups (8.7 [2.6] vs 9.7 [2.2], respectively) (**Figure 2D**).

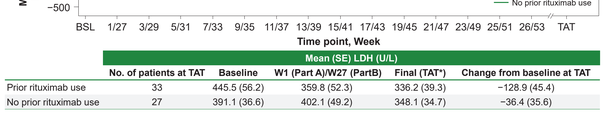
Figure 2. Change from baseline to TAT* in (A) haemoglobin (g/dL), (B) bilirubin (µmol/L) and (C) LDH (U/L) and (D) FACIT-Fatigue score in patients receiving sutimlimab according to prior rituximab use, using pooled CARDINAL Part A/ CADENZA Part A (W0–W26) + Part B (W26–W53)



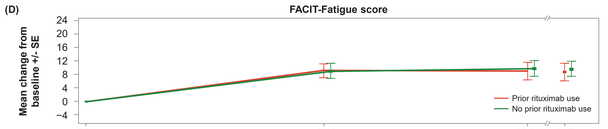
	Mean (SE) Haemoglobin (g/dL)				
	No. of patients at TAT	Baseline	W1 (Part A)/W27 (PartB)	Final (TAT*)	Change from baseline at TAT
Prior rituximab use	33	9.1 (0.2)	10.1 (0.3)	11.5 (0.4)	2.4 (0.3)
No prior rituximab use	27	9.0 (0.3)	10.3 (0.2)	11.6 (0.3)	2.6 (0.4)



	Mean (SE) Bilirubin (µmol/L)				
	No. of patients at TAT	Baseline	W1 (Part A)/W27 (PartB)	Final (TAT*)	Change from baseline at TAT
Prior rituximab use	33	45.0 (3.5)	20.1 (1.6)	17.1 (2.0)	−26.5 (3.0)
No prior rituximab use	27	40.9 (5.0)	21.5 (2.0)	14.7 (1.5)	−22.4 (2.3)



	Mean (SE) LDH (U/L)				
	No. of patients at TAT	Baseline	W1 (Part A)/W27 (PartB)	Final (TAT*)	Change from baseline at TAT
Prior rituximab use	33	445.5 (56.2)	359.8 (52.3)	336.2 (39.3)	−128.9 (45.4)
No prior rituximab use	27	391.1 (36.6)	402.1 (49.2)	348.1 (34.7)	−36.4 (35.6)



	Mean (SE) FACIT-Fatigue				
	No. of patients at TAT	Baseline	W13 (Part A)/W39 (PartB)	Final (TAT*)	Change from baseline at TAT
Prior rituximab use	33	33.9 (1.9)	43.0 (1.7)	42.0 (1.7)	8.7 (2.6)
No prior rituximab use	27	31.3 (2.4)	41.1 (1.6)	41.7 (1.4)	9.7 (2.2)

In this analysis, included patients had data available at baseline and TAT; *TAT was an average of weeks 23, 25, and 26 for Part A; TAT was an average of weeks 49, 51, and 53 for Part B.

BSL, baseline; CAD, cold agglutinin disease; FACIT, The Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; SE, standard error; TAT, treatment assessment timepoint; W, week.

CONCLUSIONS

- **The burden of disease for patients with CAD previously treated with sutimlimab in CARDINAL and CADENZA was greater for those with prior rituximab use compared with rituximab-naïve patients.**
- **This post-hoc analysis shows similar response rates, changes in Hb, bilirubin, and FACIT-Fatigue scores between subgroups of sutimlimab-treated patients with vs without prior rituximab use.**
- **The inclusion of the CADENZA Part B (ex-placebo) patient group to the CARDINAL and CADENZA Part A trials further supports the efficacy of sutimlimab in CAD patients, irrespective of their prior off-label rituximab treatment.**

REFERENCES

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2. Swiecicki PL et al. *Blood*. 2013; 122:7: 1114–1121.

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CONFLICTS OF INTEREST

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