Thromboembolic (TE) Events in Cold Agglutinin Disease (CAD): Post hoc Analysis PRE- and ON-sutimlimab Treatment in the Phase 3 CARDINAL and CADENZA Studies

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INTRODUCTION

- Cold agglutinin disease (CAD) is a rare chronic autoimmune hemolytic anemia mediated by classical complement pathway activation[1]
- Patients with CAD often have classical complement pathway-mediated symptoms of chronic anemia, profound fatigue, and acute hemolytic crisis, and may have cold-induced circulatory symptoms such as acrocyanosis[2]
- An association has also been found between CAD and an increased risk of thromboembolic (TE) events compared with the general population[2–4]
- Ongoing hemolysis and anemia contribute to an increased risk for TE events in patients with CAD[3,5]
- Sutimlimab is a first-in-class humanized monoclonal antibody that inhibits complement C1s and is approved for the treatment of CAD in the US, EU, and Japan[6,7]
- Phase 3 clinical studies CARDINAL and CADENZA demonstrated that long-term treatment with sutimlimab resulted in sustained inhibition of hemolysis, and improvements in anemia and quality of life in patients with CAD[6–9]
  - The impact of sutimlimab on TE events in CAD patients is unknown
- Here we present the results of a post hoc analysis of the TE events PRE- and ON-sutimlimab treatment in the CARDINAL and CADENZA studies

OBJECTIVE

To assess the TE events in CAD patients PRE- and ON-sutimlimab treatment from the Phase 3 CARDINAL (NCT03347396) and CADENZA (NCT03347422) studies

METHOD

- Participants from Part A (26-week treatment period) and Part B (open-label extension) of the CARDINAL and CADENZA trials who had initiated sutimlimab, had a CAD diagnosis date, and had a treatment start and end date were included in the post hoc TE event analysis
- Pre-study TE events and TE events recorded during the study were medically adjudicated before inclusion
- ON-sutimlimab events include all events from sutimlimab treatment initiation until 17 days post last dose of sutimlimab
- PRE-sutimlimab and ON-sutimlimab follow-up times were matched for each patient
- Descriptive statistics were used to compare participant characteristics of those experiencing TE events/no TE events while ON-sutimlimab
  - Statistical testing was used to assess whether the number of TE events/incidence rate differed between PRE and ON-sutimlimab periods
  - Details of all TE events while ON-sutimlimab were additionally included

RESULTS

Study population

- 66 participants (24 from CARDINAL and 42 from CADENZA), were included in the analysis **(Table 1)**
- Participants were mainly female (72.7%) and had a median age (range) of 70 (46–88) years
- The majority of participants (69.7%) had been treated with ≥1 targeted prior therapy within the last 5 years
- Most participants ON-sutimlimab who had a TE event had previously been treated for CAD with corticosteroids (4/5, 80.0%) and/or a single agent therapy, i.e., rituximab (3/5, 60.0%), and not with combination regimens (0, 0%), whereas a greater proportion of participants ON-sutimlimab who did not have a TE event had previously been treated with combination regimens (12/61, 19.7%)

Table 1: Summary of Baseline Characteristics of Patients Who Met the Inclusion Criteria for the Post hoc Analysis by Matched[a] Thromboembolic (TE) Events After Treatment in the CARDINAL and CADENZA Studies

	ON-sutimlimab – No TE n=61	ON-sutimlimab – Yes TE n=5	Overall N=66
Summary of demographics for targeted prior therapy			
Age (years)			
Mean (SD)	68 (10)	75 (10)	68 (10)
Median	68	71	70
Min, Max	46, 85	62, 88	46, 88
Sex, n (%)			
Male	18 (29.5)	0	18 (27.3)
Female	43 (70.5)	5 (100)	48 (72.7)
Summary of concomitant medications for targeted prior therapy			
Subjects with ≥1 targeted prior therapy within last 5 years	42 (68.9%)	4 (80.0%)	46 (69.7%)
Corticosteroids	26 (42.6%)	4 (80.0%)	30 (45.5%)
Single-agent therapy	30 (49.2%)	3 (60.0%)	33 (50.0%)
Ibrutinib	1 (1.6%)	0	1 (1.5%)
Rituximab	30 (49.2%)	3 (60.0%)	33 (50.0%)
Combination regimens	12 (19.7%)	0	12 (18.2%)
Bendamustine/rituximab	8 (13.1%)	0	8 (12.1%)
CHOP-R[b]	1 (1.6%)	0	1 (1.5%)
CVP[c]	1 (1.6%)	0	1 (1.5%)
Fludarabine/rituximab	3 (4.9%)	0	3 (4.6%)
Rituximab/corticosteroid	1 (1.6%)	0	1 (1.5%)
Other combination regimen	4 (6.6%)	0	4 (6.1%)
Summary of lab parameters at baseline			
Hemoglobin (g/dL)			
Mean (SD)	9.1 (1.2)	7.6 (1.6)	9.0 (1.3)
Bilirubin (µmol/L)			
Mean (SD)	42.5 (22.7)	51.4 (11.2)	43.1 (22.1)
Lactate dehydrogenase (U/L)			
Mean (SD)	410.1 (240.4)	477.8 (287.4)	415.2 (242.4)
D-dimer (µg/L FEU)			
Mean (SD)	647.5 (1058.2)	701.4 (403.6)	651.6 (1021.1)
Thrombin/antithrombin (µg/L)			
Mean (SD)	16.0 (19.7)	8.0 (6.5)	15.4 (19.1)

[a]Participants were matched on the basis of follow-up time. For each participant, the minimum follow-up time between their respective PRE-sutimlimab and ON-sutimlimab period was selected; [b]Combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; [c]Combination of cyclophosphamide, vincristine, and prednisolone.
n, number; SD, standard deviation; TE, thromboembolic.

TE events

- The median (min, max) follow-up time in each period was 1.8 (0.1, 3.4) years, amounting to 113.7 patient years in each group **(Table 2)**
- Of the 66 participants included in the analysis, 8 participants in the PRE-sutimlimab and 5 participants in the ON-sutimlimab group had ≥1 TE event (p=0.3657)
- In the PRE-sutimlimab period, the TE incidence rate was 7.5 per 100 patient-years compared with 4.4 ON-sutimlimab (p=0.3056), showing a trend towards a decrease in TE incidence with sutimlimab treatment

Table 2: Summary of Matched[a] Adjudicated Thromboembolic (TE) Events for CARDINAL and CADENZA Studies

Prevalence activity	PRE-sutimlimab (N=66)	ON-sutimlimab (N=66)
Number of patients with ≥1 event, n (%)	8 (12.1)	5 (7.6)
p-value[b]		0.3657
Number of events, n	9	5
p-value[c]		0.2885
Follow-up time, years		
Mean (SD)	1.7 (1.0)	1.7 (1.0)
Median	1.8	1.8
Min, max	0.1, 3.4	0.1, 3.4
Total patient-years, years[d]	113.7	113.7
Incidence rate per 100 patient-years (95 % CI)[e]	7.5 (4.0, 14.2)	4.4 (1.9, 10.1)
Rate ratio (95 % CI)[e]		0.6 (0.2, 1.6)
p-value[e]		0.3056

[a]For the matched analysis, minimum follow-up time between PRE-sutimlimab and ON-sutimlimab is considered; [b]p-value calculated based on McNemar's test for comparing proportions with ≥1 event; [c]p-value calculated based on paired t-test for difference in number of events (ON-sutimlimab and PRE-sutimlimab); [d]Total patient-years is the sum of follow-up time (measured in years) for all patients from full analysis set; [e]Derived from Poisson regression model with exchangeable covariance type.
CI, confidence interval; n, number; SD, standard deviation.

Sites of TE events

- TE events in the ON-sutimlimab period included: cerebral venous sinus thrombosis (CVST) (n=1), device-related thrombosis (n=1), peripheral artery thrombosis (n=1), transient ischemic attack (TIA) (n=1), and deep vein thrombosis (n=1) **(Table 3)**
- The CVST and peripheral artery thrombosis were reported as serious events, and all other events were reported as nonserious
- Only the CVST was assessed as related to sutimlimab by the investigator
  - The participant who experienced the CVST was 88 years of age with a medical history of "steroid diabetes"
    - 2 months and 24 days after the first dose of sutimlimab administration, the participant was hospitalized with headache and fever
    - After several tests, the participant was diagnosed with grade 3 cerebral thrombophlebitis and treatment with sutimlimab was temporarily interrupted
    - The event of CVST was reported as resolved within 2 days of treatment with tinzaparin and warfarin, and treatment with sutimlimab was restarted
- Of the participants who experienced a TE event in the ON-sutimlimab period, 4/5 had a history of TE risk factors; this includes the participant who experienced CVST as described above and three additional patients
  - The participant who experienced device-related thrombosis had a history of tachycardia and ventricular extrasystole
  - The participant who experienced the TE event of TIA had a medical history of cerebrovascular accident and two previous TIAs
  - The participant who experienced the deep vein thrombosis also had a TE event in the PRE-sutimlimab period, which was described as a major vascular adverse event
- TE events occurred between 86 days and 656 days of initiation of sutimlimab

Table 3: Sites of Thromboembolic (TE) Events for CARDINAL and CADENZA Studies ON-sutimlimab[a]

TE sites	Number of events, n	Days from sutimlimab initiation to event, n	Age, years	TE risk factors (Y/N)	Medical history (outside the observed period)
CVST (reported as a cerebral thrombophlebitis, grade 3)	1	86	88	Y	Participant with history of "steroid diabetes"
Device-related thrombosis	1	336	81	Y	Participant with history of tachycardia and ventricular extrasystole
Peripheral artery thrombosis	1	656	73	N	Participant with no reported risk factors for TE
TIA	1	175	71	Y	Participant with history of cerebrovascular accident and two TIAs
Deep vein thrombosis	1	288	62	Y	Participant with history of peripheral vascular disorder reported as "both lower extremities blood flow disorders" in the context of CAD

[a]The 9 TE events in 8 patients in the PRE-sutimlimab period included major vascular adverse events, deep vein thrombosis, brain stem ischemia, myocardial infarction, and pulmonary embolism.
CVST, cerebral venous sinus thrombosis; N, no; TIA, transient ischemic attack; Y, yes.

CONCLUSIONS

- **In this limited number of medically complex CAD patients from the CARDINAL and CADENZA studies, analysis of matched adjudicated TE events suggests a trend toward a reduced risk of TE ON-sutimlimab compared with the PRE-sutimlimab period**
- **Across the CARDINAL and CADENZA studies TE events were approximately 40% less likely to occur after initiation of treatment with sutimlimab than before treatment**
- **Further studies into the impact of sutimlimab on TE events in CAD patients are needed**

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UK, KK, MW, FS, and RY are employees of Sanofi and may hold stock options in the company.

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