SERUM BIOMARKERS AS PREDICTORS OF RESPONSE TO SUTIMLIMAB IN COLD AGGLUTININ DISEASE (CAD): A POST-HOC ANALYSIS OF PHASE 3 CARDINAL AND CADENZA STUDY DATA

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Introduction

- CAD is a rare, chronic autoimmune haemolytic anaemia characterised by classical complement pathway-mediated haemolysis[1,2]
  - Activation of the classical complement pathway is induced by cold agglutinins; these are usually immunoglobulin (Ig)M antibodies (rarely IgG and IgA)[1]
- Sutimlimab, a first-in-class, humanised, monoclonal antibody selectively inhibits the C1 complex, thereby preventing classical complement pathway activation[3]
- The Phase 3 CARDINAL (NCT03347386) and CADENZA (NCT03347422) studies demonstrated that sutimlimab results in sustained improvements in anaemia, haemolytic markers, and quality of life in patients with CAD[4,5]
- Sutimlimab is currently approved for use in the EU, Japan and USA[6,7]
- Here, we present a post hoc analysis of biomarkers from the CARDINAL and CADENZA studies to investigate potential predictors of response to sutimlimab

Objective

- To assess if baseline serum biomarkers are associated with a clinical response as defined by the primary endpoints of the CARDINAL and CADENZA studies

Methods

- All patients who received sutimlimab and completed Part A (26 weeks) of the CARDINAL and CADENZA Phase 3 trials were included in this combined post hoc analysis
- Serum biomarkers collected at baseline from both Phase 3 studies were evaluated for predicting responder status
- CARDINAL was an open-label, single-arm, Phase 3 study that enrolled symptomatic CAD patients with evidence of active haemolysis and who had a history of recent blood transfusion in the prior 6 months
  - In Part A, sutimlimab was administered on Days 0 and 7, then biweekly through Week 25
  - For a patient to be a responder in the CARDINAL trial, a haemoglobin (Hb) increase ≥2.0 g/dL from baseline at the treatment assessment timepoint (TAT; defined as the mean value from Weeks 23, 25 and 26) or an Hb level ≥12.0 g/dL at TAT was required
- CADENZA was a randomised, placebo-controlled Phase 3 study that enrolled symptomatic CAD patients with evidence of active haemolysis and without a history of recent blood transfusion (≤1 during the previous 12 months; 0 during the last 6 months)
  - In Part A, patients were randomized 1:1 to receive intravenous sutimlimab or placebo on Days 0 and 7, followed by biweekly dosing through Week 25
  - For a patient to be a responder in the CADENZA trial, an Hb increase ≥1.5 g/dL from baseline at TAT was required
- Other mandatory conditions for both trials for responder status were: no blood transfusions from Week 5 through TAT; and no treatment for CAD beyond what was permitted per protocol
- Descriptive statistics, frequency, or percentage were used to compare participant characteristics as well as outcomes. Baseline markers comparing responders to non-responders were evaluated based on difference in means and tested using the two-sample t-test. Differences in medians were estimated by univariate quantile regression with p-values from the Mann-Whitney U test

Results

Study population

- The analysis included 41 patients (n=22 CARDINAL; n=19 CADENZA); the patients were mainly female (73.2%)
  - Of the 41 patients, 29 (70.7%) were classified as responders (n=13 CARDINAL; n=16 CADENZA)
- Mean age (standard deviation; SD) of responders (67.0 [9.9]) years) was significantly lower than non-responders (74.3 [7.3] years; p-value=0.0262)
- No significant differences were noted for sex, geographic location, body mass index (BMI), history of transfusions, number of transfusions and duration of CAD **(Table 1)**

Table 1 | Demographic and baseline characteristics comparing responders and non-responders

	Responders (N=29)	Non-responders (N=12)	p-value[a]
Age (years)			
Mean (SD)	67.0 (9.9)	74.3 (7.3)	0.0262
Median	68.0	75.5	
Q1 : Q3	63.0 : 72.0	69.0 : 80.5	
Min : Max	46 : 88	62 : 85	
Age group, n (%)			
<70	17 (58.6)	3 (25.0)	0.0855
≥70	12 (41.4)	9 (75.0)	
Sex, n (%)			
Male	5 (17.2)	6 (50.0)	0.0522
Female	24 (82.8)	6 (50.0)	
Geographic Location, n (%)			
Europe	18 (62.1)	9 (75.0)	0.3632
North America	6 (20.7)	0	
Asia	4 (13.8)	2 (16.7)	
Other	1 (3.4)	1 (8.3)	
BMI (kg/m²)			
n	13	9	0.8084
Mean (SD)	24.8 (3.9)	24.3 (4.7)	
Median	23.9	23.5	
Q1 : Q3	22.4 : 26.0	22.9 : 25.3	
Min : Max	18 : 33	18 : 32	
History of transfusions (within 1 year of screening) , n (%)			
Yes	8 (27.6)	5 (41.7)	0.4686
No	21 (72.4)	7 (58.3)	
Number of transfusions (within 1 year of screening)			
Mean (SD)	1.7 (3.0)	5.1 (8.2)	0.1515
Median	1.0	1.5	
Q1 : Q3	0.0 : 2.0	0.5 : 5.0	
Min : Max	0 : 14	0 : 23	
0	21 (72.4)	7 (58.3)	
≥1	8 (27.6)	5 (41.7)	
Duration of CAD (years)			
n	29	12	
Mean (SD)	7.9 (6.6)	10.0 (8.4)	1.0000
Median	7.0	7.5	
Q1 : Q3	2.0 : 12.0	5.5 : 12.0	
Min : Max	1 : 21	1 : 34	

[a]p-values are from Fisher exact test and two-sample t-test for categorical and continuous demographic variables respectively

Predictors of response

- Significant differences between reticulocyte count, reticulocyte index, IgM levels and C4 levels at baseline were observed between responders and non-responders
  - The median (range) reticulocyte count in responders (164.9 [28–301] 10^9/L) was significantly higher at baseline than in non-responders (102.0 [4–185] 10^9/L; p-value=0.0055) **(Figure 1A)**
  - Significant differences in the baseline median (range) reticulocyte index (semi-quantitative index of the adequacy of bone marrow response to anaemia) between responders (4.7 [1–9]) and non-responders (2.6 [1–5]; p-value=0.0091) were observed **(Figure 1B)**
    - Reticulocyte index = reticulocyte rate (%) x (patient's haemoglobin [g/dL] / lower limit of normal haemoglobin [g/dL])
    - Reticulocyte rate (%) = (patient's reticulocytes [10^9/L] / patient's erythrocytes [10^{12}/L] x 0.1)
  - Lower levels of baseline median (range) IgM antibodies were noted in responders (2.37 [0.5–22.4 g/L]) compared with non-responders (6.22 [1.2–12.4] g/L; p-value=0.0080); upper limit of normal for IgM was 3.0 g/L **(Figure 1C)**
    - The IgM Spearman correlation coefficient (range) with the reticulocyte index was -0.14 (-0.45:0.20)
  - Responders had higher C4 levels at baseline than non-responders, with a median (range) of 0.04 (0.0–0.2 [g/L]) and 0.01 (0.0–0.1 [g/L]; p-value=0.0305), respectively (Figure 1D)

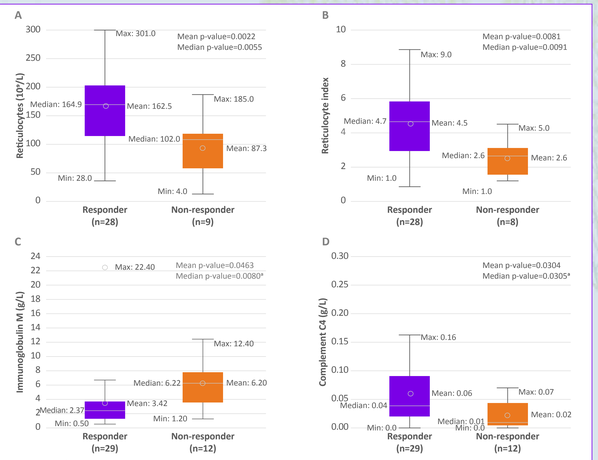

Figure 1 | Boxplots of biomarker baseline levels for responders and non-responders including (A) reticulocyte count, (B) reticulocyte index[a], (C) IgM levels, and (D) C4 levels

The central box represents the interquartile range and includes the mean (circle) and median (line) values. Whiskers extend to display the range of the majority of the data, with any outliers depicted as individual points

[a]p-value based on Mann-Whitney U test since data is not normally distributed

- A greater extent of bilirubin normalisation at TAT in responders (86.2%, n=25) than in non-responders (50.0%, n=6) was observed
- A significant difference in ferritin level mean value (95% confidence interval [CI]) between responders vs non-responders (p=0.0335) was determined
- No significant differences in haemoglobin levels, bilirubin, haptoglobin, lactate dehydrogenase (LDH), cold agglutinin titre, erythropoietin, total iron-binding capacity (TIBC), or Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue **(Table 2)**

Table 2 | Baseline serum biomarkers for responder status in the CARDINAL and CADENZA studies

	Responders (N=29)	Non-responders (N=12)	Mean/median difference (95 %CI)	p-value[a]
Haemoglobin (g/dL), n	**29**	**12**		
Mean (SD)	8.85 (1.25)	9.02 (1.69)	**-0.2 (-1.1 : 0.8)**	0.7181
Median	9.00	9.05	**0.0 (-1.2 : 1.2)**	0.6670[b]
Q1 : Q3	8.40 : 9.35	8.33 : 10.24		
Min : Max	5.0 : 11.1	4.9 : 11.1		
Bilirubin (µmol/L), n	**29**	**12**		
Mean (SD)	43.03 (16.65)	42.05 (19.88)	**1.0 (-11.3 : 13.2)**	0.8724
Median	41.40	33.85	**6.6 (-10.4 : 23.6)**	0.6989[b]
Q1 : Q3	28.30 : 54.70	29.45 : 50.30		
Min : Max	19.2 : 76.0	21.4 : 92.2		
LDH (U/L), n	**29**	**12**		
Mean (SD)	414.8 (242.5)	493.1 (281.0)	**-78.3 (-254.6 : 98.02)**	0.3746
Median	295.0	384.0	**-51.0 (-337.5 : 235.5)**	0.4307[b]
Q1 : Q3	254.0 : 452.0	263.0 : 756.5		
Min : Max	162 : 1040	160 : 960		
Haptoglobin (g/L), n	**29**	**12**		
Mean (SD)	0.20 (0.00)	0.22 (0.07)	**-0.02 (-0.05 : 0.01)**	0.1214
Median	0.20	0.20		0.1334[b]
Q1 : Q3	0.20 : 0.20	0.20 : 0.20		
Min : Max	0.2 : 0.2	0.2 : 0.4		
FACIT-Fatigue, n	**29**	**11**		
Mean (SD)	31.1 (11.9)	36.7 (7.7)	**-5.6 (-13.5 : 2.3)**	0.1566
Median	31.0	38.0	**-7.0 (-17.4 : 3.4)**	0.2029
Q1 : Q3	22.0 : 41.0	28.0 : 43.0		
Min : Max	9 : 51	25 : 47		
Ferritin (pmol/L), n	**29**	**12**		
Mean (SD)	1422.3 (1257.5)	3010.6 (3405.8)	**-1588.3 (-3045.8 : -130.8)**	0.0335
Median	1027.0	1122.5	**499.0 (-3283.6 : 4281.6)**	0.9657[b]
Q1 : Q3	530.0 : 1731.0	182.5 : 6188.5		
Min : Max	31 : 5174	110 : 8689		
Erythropoietin (mIU/mL), n	**29**	**12**		
Mean (SD)	108.80 (90.69)	98.87 (64.22)	**9.9 (-48.4 : 68.3)**	0.7326
Median	69.50	68.10	**3.8 (-73.05 : 80.6)**	0.8974[b]
Q1 : Q3	50.60 : 142.10	47.05 : 175.25		
Min : Max	28.6 : 448.7	35.0 : 193.7		
TIBC (umol/L), n	**21**	**7**		
Mean (SD)	49.5 (8.4)	51.0 (10.0)	**-1.5 (-9.4 : 6.4)**	0.7031
Median	50.0	50.0	**0.0 (-13.3 : 13.3)**	0.6514
Q1 : Q3	45.0 : 54.0	42.0 : 61.0		
Min : Max	35 : 71	35 : 61		
Log10 CAD titer, n	**27**	**12**		
Mean (SD)	3.4 (1.2)	4.3 (1.7)	**-0.9 (-1.8 : 0.1)**	0.0789
Median	3.1	3.9	**-0.6 (-2.3 : 1.1)**	0.1373[b]
Q1 : Q3	2.5 : 4.0	3.1 : 6.3		
Min : Max	2 : 7	2 : 7		

[a]Median differences (95% CI) were estimated using quantile regression whereas the corresponding p-value is from the Mann-Whitney U test
[b]The normality assumption was not met based on the Shapiro-Wilk test

Conclusions

- There was a high proportion (70.7%) of responders to sutimlimab in this pooled analysis
- Post hoc analysis of Phase 3 trial data suggests that predictive serum biomarkers for sutimlimab response in patients with CAD may exist (such as reticulocyte count, reticulocyte index, IgM levels, and C4 levels) and should be explored further
  - Reticulocyte count and reticulocyte index data are suggestive that non-responders may have impaired capability of bone marrow to respond to anaemia
  - High levels of IgM may be suggestive of an underlying non-clinically overt haematological process
- No significant baseline differences were observed between responders and non-responders for markers of anaemia, other markers of haemolysis, and fatigue

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