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EFFICACY OF SUTIMLIMAB STRATIFIED BY BASELINE HEMOGLOBIN IN PATIENTS WITH COLD AGGLUTININ DISEASE: A POST HOC ANALYSIS FROM CARDINAL AND CADENZA

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Introduction

- Cold agglutinin disease (CAD) is a rare subtype of autoimmune hemolytic anemia mediated by the classical complement pathway, leading to chronic hemolysis, fatigue, and a poor quality of life (QoL)[1–3]
- Sutimlimab is a first-in-class, humanized, monoclonal antibody approved for the treatment of hemolysis in adults with CAD. It selectively inhibits C1s, preventing complement pathway activation while leaving lectin and alternative pathways intact[2,4,5]
- CARDINAL (NCT03347396) was a Phase 3 open-label, single-arm study, with an open-label extension period, assessing the efficacy and safety of sutimlimab in patients with CAD and a recent history of transfusion; CADENZA (NCT03347422) was a randomized, double-blind, placebo-controlled Phase 3 study, with an open-label extension period, assessing the efficacy and safety of sutimlimab in patients with CAD and no recent transfusion history[4,6]
  - During these studies, sutimlimab rapidly halted hemolysis, increased hemoglobin levels, improved fatigue, and demonstrated a favorable safety profile in patients with CAD
  - The effects of sutimlimab were sustained over a median of 144 weeks of treatment in CARDINAL7 and over a median treatment duration of 99 weeks in CADENZA[8]

Aims

- To report on a post hoc analysis of data combined from the Phase 3 CARDINAL and CADENZA trials to examine the efficacy of sutimlimab across subgroups defined by baseline anemia severity

Methods

- All patients enrolled in CARDINAL (N=24) and those in the sutimlimab-treated arm of CADENZA (N=22) were stratified into subgroups based on their hemoglobin level at baseline: mild anemia (≥10 g/dL; n=10), moderate anemia (≥8 to <10 g/dL; n=29), or severe anemia (<8 g/dL; n=7)
- The following parameters were compared and statistically analyzed across subgroups:
  - Changes from baseline to treatment-assessment timepoint (TAT; mean value from Weeks 23, 25, 26) in hemoglobin, bilirubin, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score
- Time to an increase of hemoglobin level by ≥1.5 and ≥2.0 g/dL, normalization of bilirubin to ≤1.5x upper limit of normal (ULN), and a clinically meaningful improvement in FACIT-Fatigue by >5 points

Results

Study Population

- At baseline, the mean (standard deviation [SD]) age of patients was 68.5 (8.9) years in the mild, 68.7 (10.5) years in the moderate, and 67.3 (9.9) years in the severe anemia subgroups (**Table 1**)
- Two patients in the mild, 8 in the moderate, and 6 in the severe subgroup received transfusions during the screening process, with a mean (SD) number of transfusions of 0.9 (0.7), 2.2 (4.6), and 6.3 (8.3), respectively
- Mean (SD) baseline hemoglobin levels were 10.6 (0.4), 8.9 (0.5), and 6.5 (1.2) g/dL in the mild, moderate, and severe subgroups, respectively
- Mean (SD) baseline bilirubin levels were 46.6 (17.2), 38.5 (15.2), and 77.2 (41.6) µmol/L in the mild, moderate, and severe subgroups, respectively
- Mean (SD) baseline FACIT-Fatigue scores were 37.9 (11.8), 30.5 (11.4), and 30.9 (11.6) in the mild, moderate, and severe subgroups, respectively
  - All baseline FACIT-Fatigue scores were lower than the general population,[8] highlighting the burden of fatigue even in patients with mild anemia
- Other disease markers assessed at baseline included lactate dehydrogenase, haptoglobin, reticulocyte count, immunoglobulin M, and C4

Table 1 | Baseline characteristics for patients in the post hoc analysis.

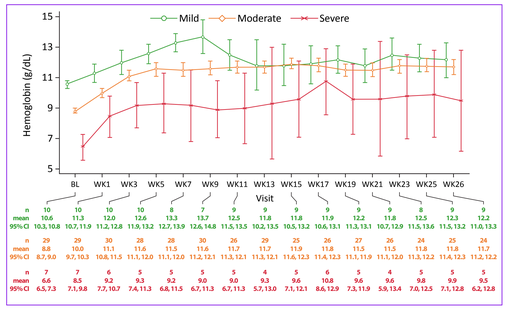
Characteristic	Mild Anemia (Hb ≥10 g/dL) n=10[a]	Moderate Anemia (Hb ≥8 to <10 g/dL) n=29[b]	Severe Anemia (Hb <8 g/dL) n=7[c]
Age, mean (SD)	68.5 (8.9)	68.7 (10.5)	67.3 (9.9)
Sex, n (%)			
Male	2 (20.0)	9 (31.0)	3 (42.9)
Female	8 (80.0)	20 (69.0)	4 (57.1)
History of transfusion (screening period)			
Yes	2 (20.0)	8 (27.6)	6 (85.7)
No	8 (80.0)	21 (72.4)	1 (14.3)
≥1 transfusion	2 (20.0)	8 (27.6)	6 (85.7)
Transfusions, mean (SD)	0.9 (0.7)	2.2 (4.6)	6.3 (8.3)
Received prior CAD therapies in the past 5 years (%)	7 (70.0)	20 (69.0)	4 (57.1)
Hb g/dL, mean (SD)	10.6 (0.4)	8.9 (0.5)	6.5 (1.2)
Bilirubin µmol/L, mean (SD)	46.6 (17.2)	38.5 (15.2)	77.2 (41.6)
FACIT-Fatigue score, mean (SD)[d]	37.9 (11.8)	30.5 (11.4)	30.9 (11.6)
Lactate dehydrogenase U/L, mean (SD)	332.5 (182.2)	433.2 (252.0)	557.0 (250.9)
Haptoglobin g/L, mean (SD)	0.2 (0.0)	0.3 (0.3)	0.2 (0.0)
Reticulocyte count 10^9/L, mean (SD)	179.6 (87.8)	137.7 (59.4)	155.2 (81.7)
IgM g/L, mean (SD)	3.4 (2.0)	4.2 (4.6)	8.5 (11.3)
C4 g/L, mean (SD)	0.0 (0.0)	0.1 (0.1)	0.1 (0.1)

[a]Mild subgroup: CARDINAL n=6 and CADENZA n=4; [b]Moderate subgroup: CARDINAL n=13 and CADENZA n=16; [c]Severe subgroup: CARDINAL n=5, CADENZA n=2; [d]Number of patients included with FACIT-Fatigue score was 9 and 28 in the mild and moderate subgroups, respectively.
CAD, cold agglutinin disease; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; IgM, immunoglobulin M; SD, standard deviation.

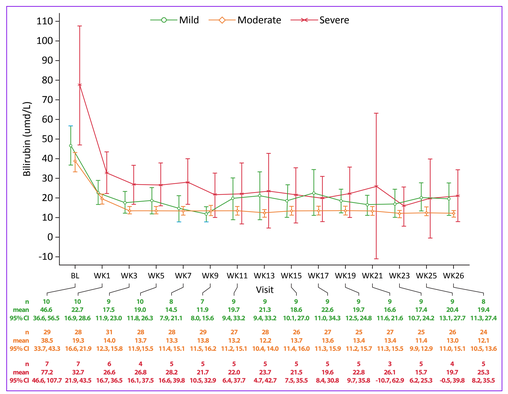
Changes from Baseline to Treatment Assessment Timepoint

- The numerical magnitude of improvement in hemoglobin level generally corresponded with severity of anemia, and the difference between subgroups was not statistically significant
  - Mean (SD) increases in hemoglobin levels from baseline to treatment assessment timepoint (TAT) were 1.7 (1.6), 2.8 (1.5), and 3.5 (2.9) g/dL in the mild, moderate, and severe subgroups, respectively (**Figure 1A**)
  - Mean (95% CI [confidence interval]) difference between the subgroups was –1.1 (–2.3, 0.1; p=0.07) for the mild/moderate, –0.7 (–2.4, 1.1; p=0.63) for the moderate/severe, and –1.8 (–4.3, 0.8; p=0.15), for the mild/severe subgroups
- A reduction in bilirubin levels was seen across all 3 subgroups, and there were no significant differences between subgroups (**Figure 1B**)
  - Mean (SD) decreases in bilirubin levels from baseline to TAT were –26.1 (15.3), –25.5 (15.4), and –37.5 (18.0) in the mild, moderate, and severe subgroups, respectively
  - Mean (95% CI) difference was –0.6 (–12.6, 11.4; p=0.92) for the mild/moderate, 12.0 (–3.6, 27.7; p=0.13) for the moderate/severe, and 11.4 (–8.3, 31.2; p=0.23), for the mild/severe subgroups
- An improvement in FACIT-Fatigue scores was seen across all 3 subgroups, and there were no significant differences between subgroups (**Figure 1C**)
  - Mean (SD) increases in FACIT-Fatigue scores from baseline to TAT were 7.3 (5.9), 10.7 (13.6), and 9.4 (11.7), respectively, all indicating a clinically important change of >5 points
  - Mean (95% CI) difference was –3.4 (–13.5, 6.7; p=0.32) for the mild/moderate, 1.3 (–12.0, 14.6; p=0.84) for the moderate/severe, and –2.1 (–12.8, 8.6; p=0.67), for the mild/severe subgroups
- For the other disease markers, lactate dehydrogenase, haptoglobin, reticulocyte count, IgM, and C4, there were no significant differences between subgroups

(A) Hemoglobin levels with sutimlimab by baseline anemia subgroups



(B) Bilirubin levels with sutimlimab by baseline anemia subgroup



(C) FACIT-Fatigue scores with sutimlimab by baseline anemia subgroups

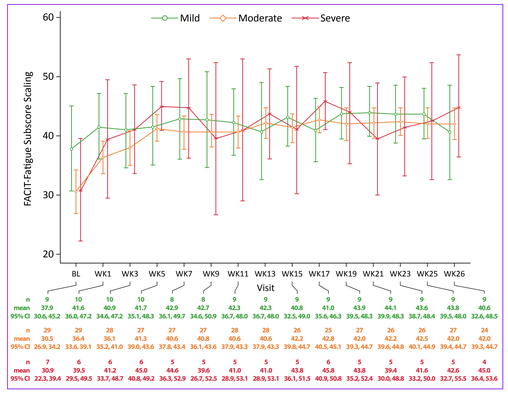


Figure 1 | Mean (A) hemoglobin levels, (B) bilirubin levels, and (C) FACIT-Fatigue scores from baseline to TAT with sutimlimab, by subgroup.
BL, baseline; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; TAT, treatment-assessment timepoint; WK, week.

Time to Efficacy Endpoint Changes

- Sutimlimab rapidly improved hemoglobin levels across all 3 anemia subgroups, with no statistically significant differences between the groups
  - The median (95% CI) time to hemoglobin increase by 1.5 g/dL was 3.0 (1.1, 5.1) weeks in the mild subgroup, 3.1 (2.7, 3.3) weeks in the moderate subgroup, and 1.1 (1.0, not estimatable [NE]) weeks in the severe subgroup (**Figure 2**)
  - The median (95% CI) time to hemoglobin increase by 2.0 g/dL was 4.1 (2.1, NE) weeks in the mild subgroup, 3.1 (3.1, 5.3) weeks in the moderate subgroup, and 5.0 (1.1, NE) weeks in the severe subgroup (**Figure 3**)
- The median (95% CI) time to reaching bilirubin levels ≤1.5x ULN was 1.6 (1.1, 3.1), 1.1 (1.1, 1.3), and 2.3 (1.1, NE) weeks in the mild, moderate, and severe subgroups, respectively (**Figure 4**)
- The median (95% CI) time to FACIT-Fatigue score increase by 5 points was 5.1 (1.1, NE), 3.1 (1.1, 3.1), and 1.1 (1.0, NE) weeks in the mild, moderate, and severe subgroups, respectively (**Figure 5**)

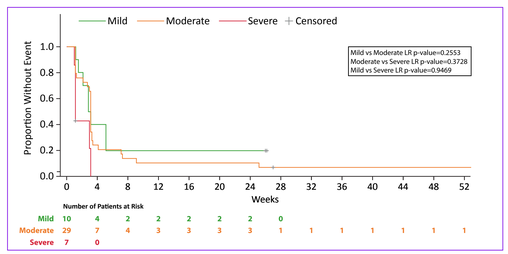


Figure 2 | Time to hemoglobin increase by 1.5 g/dL, by subgroup.
LR, log rank test.

Conclusions

- This post hoc analysis demonstrated no significant differences between the anemia subgroups in the changes from baseline of hemoglobin, bilirubin, and FACIT-Fatigue scores in patients with CAD treated with sutimlimab. However, a trend for greater improvements in hemoglobin levels with increasing severity of anemia was observed
- Despite the disparity in patient numbers between subgroups, clinically meaningful improvements were observed in hemoglobin levels, bilirubin levels, and fatigue in patients with mild anemia
- Clinically meaningful improvement was observed in patients with severe anemia as quickly as in patients with mild and moderate anemia
- This analysis further highlights the benefit of sutimlimab treatment in CAD, regardless of baseline anemia severity

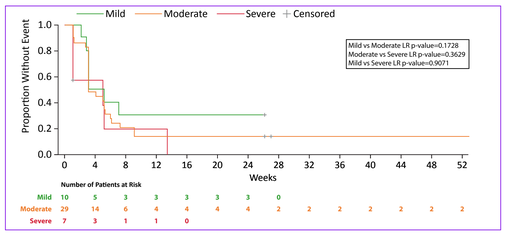


Figure 3 | Time to hemoglobin increase by 2.0 g/dL, by subgroup.
LR, log rank test.

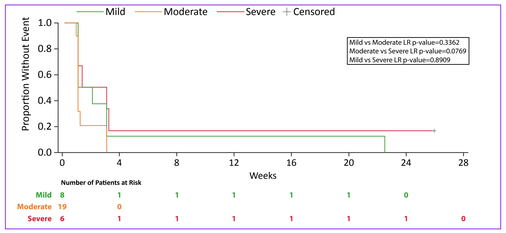


Figure 4 | Time to bilirubin levels ≤1.5x ULN, by subgroup.
LR, log rank test; ULN, upper limit of normal.

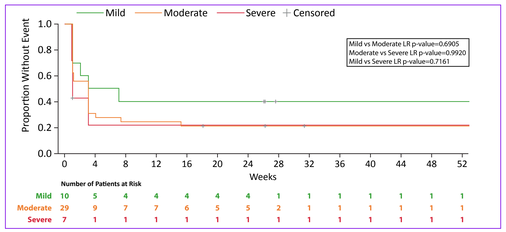


Figure 5 | Time to FACIT-Fatigue increase by 5 points, by subgroup.
FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; LR, log rank test.

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Disclosures

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