S286
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Long-Term Efficacy and Safety Results From an Ongoing Open-Label Phase 2 Study of Parsaclisib for the Treatment of Autoimmune Hemolytic Anemia

Wilma Barcellini, MD,[1] Irina Murakhovskaya, MD,[2] Louis Terriou, MD,[3] Fabrizio Pane, MD, PhD,[4] Andrea Patriarca, MD,[5] Kathleen Butler, MD,[6] Susan Moran, MSN,[6] Shaoceng Wei, PhD,[6] Ulrich Jäger, MD[7]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA; [3]Univ. Lille, Inserm, CHU Lille, Centre de Référence des Maladies Autoimmunes Systémiques Rares du Nord et Nord-Ouest de France (CeRAINO), INFINITE – Institute for Translational Research in Inflammation, Lille, France; [4]University of Naples "Federico II," Naples, Italy; [5]Department of Translational Medicine, University of Eastern Piedmont and AOU "Maggiore della Carità," Novara, Italy; [6]Incyte Corporation, Wilmington, DE, USA; [7]Medical University of Vienna, Vienna, Austria

Background

- AIHA is a rare acquired condition caused by autoantibody- and complement-mediated hemolysis of red blood cells and typically presents as wAIHA (IgG mediated), CAD (IgM mediated), or mixed-type AIHA[1]
- Primary management typically consists of supportive care, glucocorticoids, rituximab, and splenectomy (for wAIHA) or complement inhibitors (for CAD). Few regimens are available in the relapsed/refractory setting[2]
- Aberrant PI3Kδ signaling has been implicated in the pathogenesis of several B-cell–mediated autoimmune diseases[3]
- Preliminary efficacy and tolerability were observed over 12 weeks of treatment with parsaclisib in a phase 2 study of patients with primary AIHA[4]

Objective: To report updated results from an ongoing multicenter, phase 2, open-label study of the PI3Kδ inhibitor parsaclisib in patients with primary AIHA (NCT03538041)

AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; Ig, immunoglobulin; PI3K, phosphoinositide 3-kinase; wAIHA, warm AIHA.

1. Berensten S and Barcellini W. *N Engl J Med*. 2021;385(15):1407-1419. **2.** Jäger U, et al. *Blood Rev*. 2020;41:100648. **3.** Puri KD and Gold MR. *Front Immunol*. 2012;3:256. **4.** Barcellini W, et al. *HemaSphere*. 2021;5(S2):312.

Study Design

Screening (up to 28 days)

- Age ≥18 years
- Primary AIHA based on the presence of hemolytic anemia and serologic evidence of anti-erythrocyte antibodies
- Failure of ≥1 prior treatment for AIHA
- No evidence of a lymphoproliferative malignancy
- Hgb: 7–10 g/dL
- N≈25

Treatment (12 weeks)

Cohort 1*

1 mg qd† (n=10)

2.5 mg qd‡

1 mg qd

Cohort 2§

2.5 mg qd‡ (n≈15)

Week 0 1 2 4 6 8 10 12

Assess efficacy (Cohort 1)

Extension period:
Until the drug is approved or the sponsor discontinues the study

Extension for patients who continue to derive clinical benefit (1 or 2.5 mg) → **Follow-up¶ (3 months)**

For patients who do not enter the extension period → Follow-up¶ (3 months)

- Concomitant corticosteroids (≤20 mg/d prednisone) were allowed at any time

Hgb, hemoglobin; qd, once daily.

* Cohort 1: n=10, with ≤3 patients with CAD or mixed-type AIHA. † At Week 6, patients who received 1 mg qd parsaclisib and who fulfilled dose increase criteria (continue to require transfusions by Week 6 visit, or do not attain a meaningful clinical response [at least a stabilization ≥2-g/dL increase in Hgb from baseline to Week 6]) could have parsaclisib dose increased to 2.5 mg qd until Week 12. ‡ Parsaclisib dose reduction to 1 mg qd was permitted at any time for tolerability. § Cohort 2: n≈15, with ≈5 patients with CAD and ≤8 with wAIHA; the remainder could be wAIHA, CAD, or mixed-type AIHA. ¶ If relapse of AIHA occurred within this period, pharmacodynamic and clinical laboratory markers of hemolysis were assessed, and the patient was treated based on investigator's decision.

Methods

Primary endpoints

- Percentage of patients with CR (Hgb ≥12 g/dL) or PR (Hgb 10–12 g/dL or ≥2-g/dL increase from baseline, inclusive of CR) at any visit from Weeks 6–12
- Safety and tolerability (TEAEs)

Secondary endpoints

- Percentage of patients with CR or PR at postbaseline visits
- Hgb levels and proportion of patients attaining a ≥2-g/dL increase in Hgb from baseline
- Percentage of patients who achieve normalization of hemolytic markers
- FACIT-F assessment

Assessments

- Efficacy endpoints were assessed at baseline, at Weeks 1, 2, 4, 6, 8, 10, and 12 study visits during the treatment period, at least every 8–12 weeks during the extension period, and monthly during follow-up (3 months after EOT); FACIT-F was assessed at baseline and Weeks 6 and 12
- TEAEs were graded for severity using CTCAE v5.0 and monitored through the safety follow-up period (3 months after EOT)

Statistical Analyses

- The full analysis set included all patients enrolled in the study who received ≥1 dose of parsaclisib and was used for all efficacy and safety analyses; nonresponder imputation was applied to primary efficacy endpoints
- Data were summarized using descriptive statistics

CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; PR, partial response; TEAE, treatment-emergent adverse event.

Patient Demographics and Baseline Clinical Characteristics

Characteristic	All Patients (N=25)	wAIHA (n=16)
Age, mean (SD), y	61.6 (17.0)	56.8 (19.0)
Female, n (%)	14 (56.0)	5 (31.3)
White, n (%)	23 (92.0)	15 (93.8)
Type of AIHA, n (%)		
wAIHA	16 (64.0)	16 (100.0)
CAD	6 (24.0)	—
Mixed	3 (12.0)	—
Disease duration, n (%)		
<2 years	12 (48.0)	8 (50.0)
2–5 years	3 (12.0)	3 (18.8)
>5 years	10 (40.0)	5 (31.3)

Characteristic, cont'd	All Patients (N=25)	wAIHA (n=16)
Hgb, mean (SD), g/dL	8.9 (0.8)	8.7 (0.9)
Transfusion(s) in past year, n (%)	9 (36.0)	6 (37.5)
Splenectomy received, n (%)	3 (12.0)	2 (12.5)
Previous therapies, n (%)*		
Prednisone	18 (72.0)	13 (81.3)
Rituximab	19 (76.0)	12 (75.0)
Other	9 (36.0)	6 (37.5)

* Patients may have received >1 prior therapy.

Patient Disposition

Initial 12-Week Treatment Period

Characteristic	All Patients (N=25)	wAIHA (n=16)
Treated, n (%)	25 (100.0)	16 (100.0)
Treatment duration, median (range), d	85.0 (7–99)	85.0 (7–94)
Discontinued treatment, n (%)	4 (16.0)	2 (12.5)
Adverse event	2 (8.0)	1 (6.3)
Lack of efficacy	1 (4.0)	1 (6.3)
Withdrawal by patient	1 (4.0)	0
Completed 12-week treatment period, n (%)	21 (84.0)	14 (87.5)

Extension Period

Characteristic	All Patients (N=17)	wAIHA (n=11)
Treated, n (%)	17 (100.0)	11 (100.0)
Treatment duration, median (range), d	402.0 (21–938)	408.0 (75–938)
Discontinued treatment, n (%)	9 (52.9)	6 (54.5)
Adverse event	4 (23.5)	3 (27.3)
Lack of efficacy	4 (23.5)	2 (18.2)
Physician decision	1 (5.9)	1 (9.1)
Treatment ongoing, n (%)	8 (47.1)	5 (45.5)

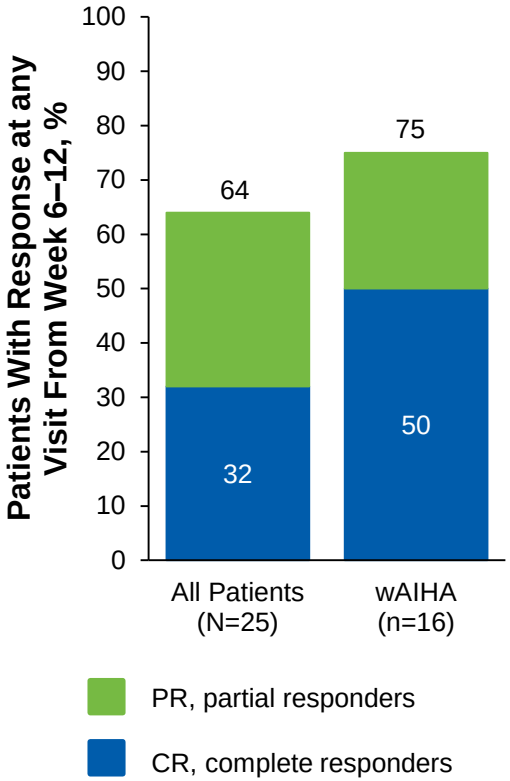
Data cutoff: February 24, 2022

- Overall, 8 patients (32.0%; wAIHA, n=5 [31.3%]) remained on treatment at the data cutoff

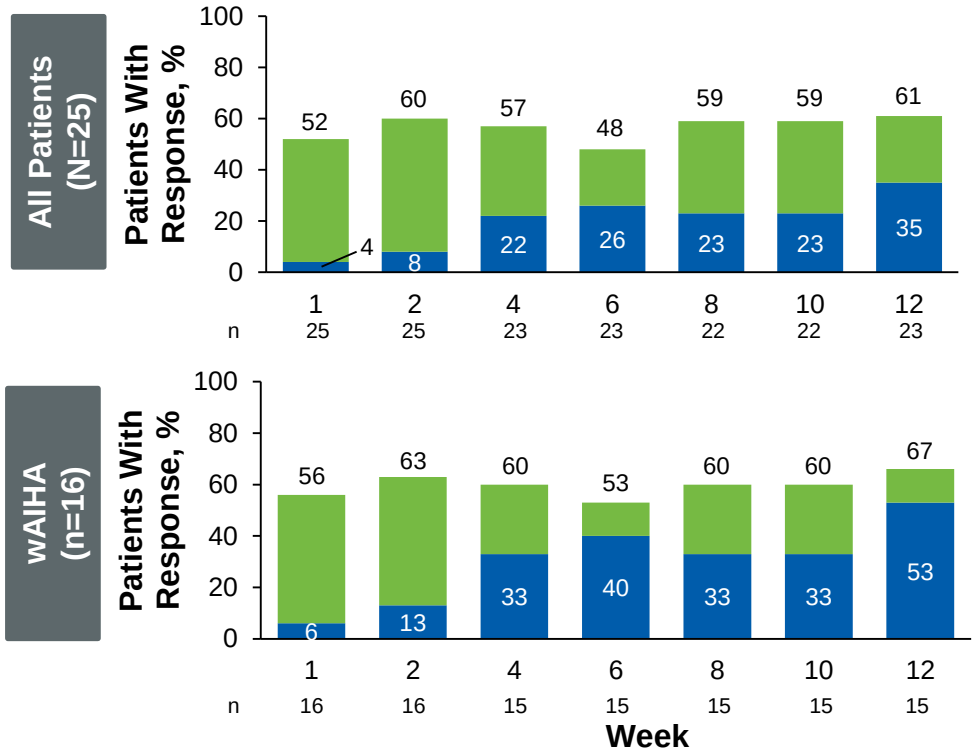
Response

12-Week Initial Treatment Period

Primary Endpoint

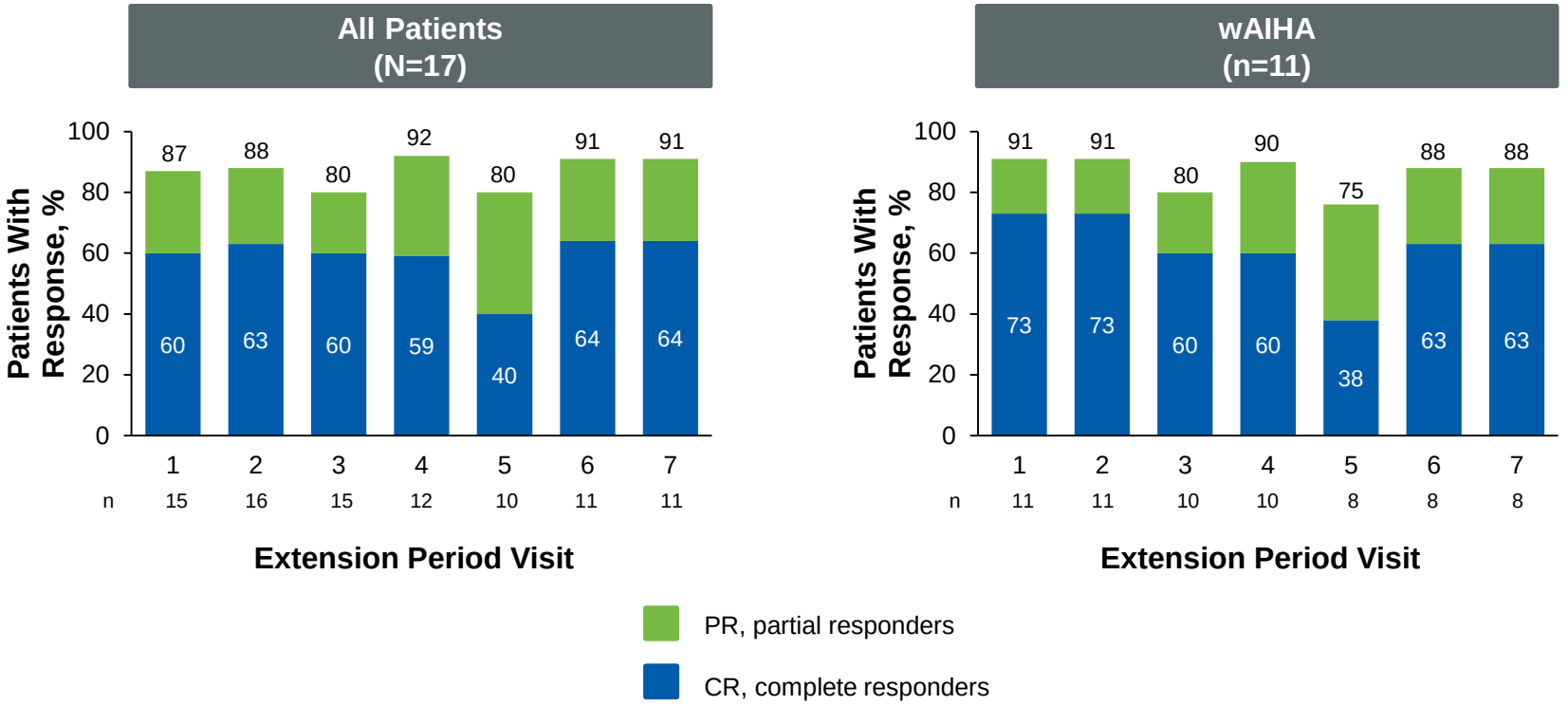


Response by Study Visit

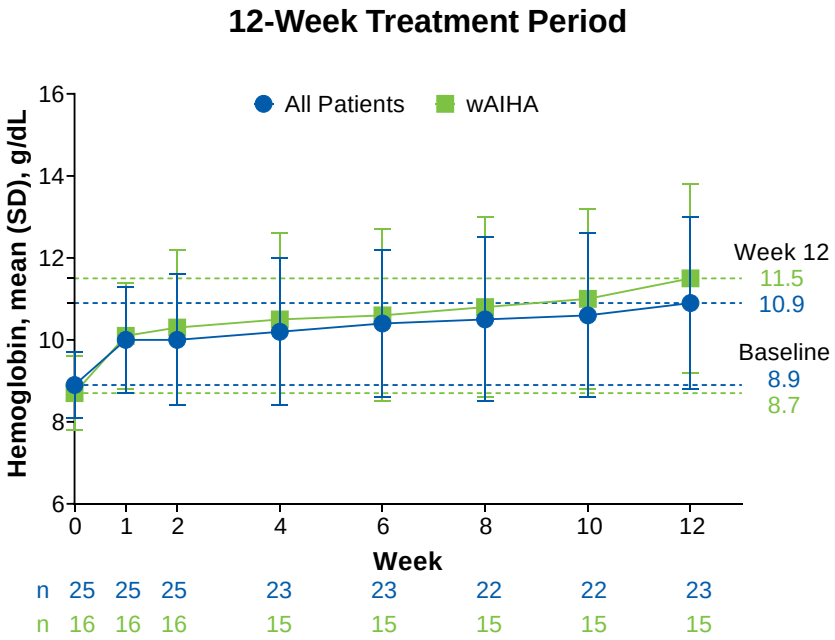


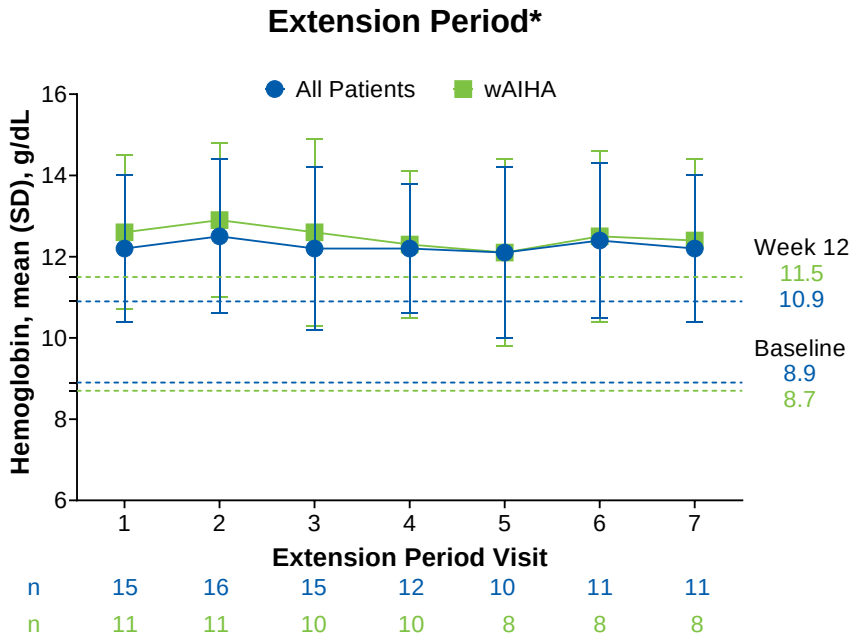
Response

Extension Period



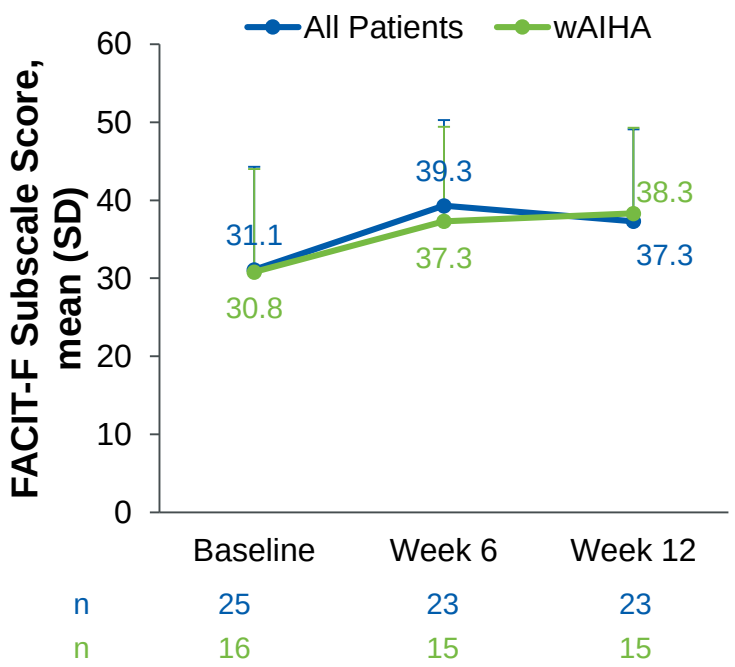
Hemoglobin Levels

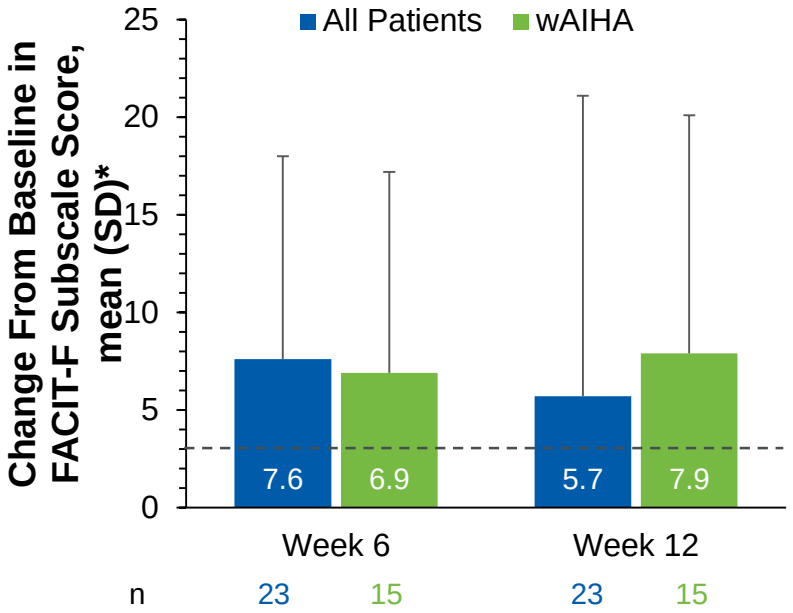




* Visits during the extension period were conducted every 8–12 weeks.

FACIT-F





Higher FACIT-F scores indicate less fatigue.
* Dashed line indicates a clinically meaningful improvement from baseline (≥3-point increase in FACIT-F score).

Safety

12-Week Initial Treatment Period

- Six patients (24%) had grade ≥3 TEAEs
  - Neutropenia was the only grade ≥3 TEAE reported in >1 patient (n=2)
- Two patients (8%) had SAEs
  - None were deemed related to treatment
- Seven patients (28%) had TRAEs
  - Rash pruritic was the only TRAE reported in >1 patient (n=2)
- No fatal TEAEs were reported
- TEAEs led to parsaclisib dose interruptions and discontinuations in 5 (20%) and 2 (8%) patients, respectively
  - There were no dose reductions due to TEAEs

TEAEs Reported in >1 Patient

Event	All Patients (N=25)
Any TEAE, n (%)	22 (88.0)
Diarrhea	5 (20.0)
Headache	5 (20.0)
Pyrexia	5 (20.0)
Neutropenia	3 (12.0)
Rash	3 (12.0)
Dizziness	2 (8.0)
Edema peripheral	2 (8.0)
Hyperuricemia	2 (8.0)
Pain in extremity	2 (8.0)
Rash pruritic	2 (8.0)
Vomiting	2 (8.0)

SAE, serious adverse event; TRAE, treatment-related adverse event.

Safety
Extension Period

- Eight patients (47%) had grade ≥3 TEAEs
  - AIHA was the only grade ≥3 TEAE reported in >1 patient (n=2)
- Eight patients (47%) had SAEs
  - Hypernatremia was the only SAE reported in >1 patient (n=2)
  - Three SAEs (diarrhea [grade 2], CMV reactivation [grade 2], and psoriasis [grade 3]) were deemed related to treatment
- Six patients (35%) had TRAEs
  - Diarrhea and rash were the only TRAEs reported in >1 patient (n=2 each)
  - Psoriasis was the only grade ≥3 TRAE (n=1)
- No fatal TEAEs were reported
  - There was 1 fatal AE overall (COVID-19 infection)
- TEAEs led to parsaclisib dose interruptions and discontinuations in 6 (35%) and 4 (24%) patients, respectively
  - There were no dose reductions due to TEAEs

CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TEAEs Reported in >1 Patient

Event	All Patients (N=17)
Any TEAE, n (%)	16 (94.1)
Diarrhea	4 (23.5)
Rash	3 (17.6)
Asthenia	2 (11.8)
AIHA	2 (11.8)
Cough	2 (11.8)
Edema peripheral	2 (11.8)
Hypernatremia	2 (11.8)
Nausea	2 (11.8)
Psoriasis	2 (11.8)
Pyrexia	2 (11.8)
SARS-CoV-2 test positive	2 (11.8)

Conclusions

- Parsaclisib resulted in Hgb improvements as early as Week 2 that increased over 12 weeks of treatment and were sustained through the extension period
- Parsaclisib resulted in a 64% response rate (32% CR) at any visit from Weeks 6–12, which was higher among patients with wAIHA (75% response; 50% CR); responses were sustained during the extension period
- Parsaclisib resulted in clinically meaningful improvements in the FACIT-F subscale
- Treatment was generally well tolerated and had a manageable safety profile
- Parsaclisib may be an effective and durable oral treatment for AIHA
- A randomized, controlled phase 3 trial in wAIHA is now recruiting (NCT05073458)