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

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INTRODUCTION

- Autoimmune hemolytic anemia (AIHA) is a rare acquired condition caused by autoantibody-mediated decompensated destruction of red blood cells and typically presents as warm (wAIHA; immunoglobulin [Ig] G mediated), cold agglutinin disease (CAD; IgM mediated), or mixed-type AIHA[1]
- There are no approved treatments for AIHA, and primary management typically consists of glucocorticoid regimens (wAIHA) or supportive care (CAD) in the first-line setting and rituximab in the relapsed/refractory setting[2,3]
- Aberrant phosphatidylinositol 3-kinase delta (PI3Kδ) signaling has been implicated in the pathogenesis of several B-cell–mediated autoimmune diseases[4]
- Parsaclisib is a potent and highly selective PI3Kδ inhibitor that has shown efficacy in preclinical models of autoantibody-mediated diseases[5,6]

OBJECTIVE

- To describe preliminary 12-week efficacy and safety from an ongoing, multicenter, open-label phase 2 trial (NCT03538041) of parsaclisib in patients with primary AIHA

METHODS

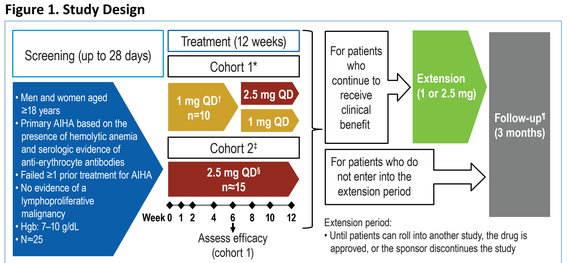
Patients

- Eligible patients were aged ≥18 years; had a diagnosis of primary wAIHA, CAD, or mixed-type AIHA without an underlying lymphoproliferative malignancy or other autoimmune-related underlying conditions; had hemoglobin (Hgb) levels of ≥7–≤10 g/dL; and failed ≥1 standard therapy for AIHA

Study Design and Treatment

- Patients received oral parsaclisib for 12 weeks at a starting dose of 1.0 mg once daily (QD; cohort 1; optional dose increase to 2.5 mg QD after 6 weeks) or 2.5 mg QD (cohort 2; dose reduction to 1.0 mg QD permitted at any time for tolerability; **Figure 1**)
  - Cohort 2 was enrolled after ≥6 patients with wAIHA in cohort 1 completed 6 weeks of treatment
  - Concomitant use of low-dose corticosteroids (≤20 mg/d prednisone equivalent) was permitted
- Patients achieving clinical benefit could continue to receive parsaclisib in an extension period

Figure 1. Study Design



AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; Hgb, hemoglobin; QD, once daily; wAIHA, warm AIHA.
* Cohort 1, n=10, ≤3 patients with CAD or mixed-type AIHA.
† At Week 6, patients who receive 1 mg QD parsaclisib and who fulfill 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]) may have their dose increased to 2.5 mg QD parsaclisib until Week 12.
‡ Cohort 2, n=15, with ~5 patients with CAD and ≤8 with wAIHA; the remainder can be wAIHA, CAD, or mixed-type AIHA.
§ Dose reduction to 1 mg QD permitted for tolerability.
¶ If relapse of AIHA occurs within this period, pharmacodynamic and clinical laboratory markers of hemolysis will be assessed, and the patient will be treated based on investigator's decision.

Endpoints and Assessments

- Primary endpoints
  - Proportion of patients with complete response (CR; Hgb ≥12 g/dL) or partial response (PR; Hgb 10–12 g/dL or ≥2-g/dL increase from baseline) at any visit from Weeks 6 to 12
  - Safety and tolerability (treatment-emergent adverse events [TEAEs])
- Secondary endpoints
  - Proportion 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
  - Proportion of patients who achieve normalization of hemolytic markers

METHODS (continued)

- For this analysis, efficacy assessments (CR, PR, Hgb, and other hemolytic markers) were assessed at baseline and during Week 1, 2, 4, 6, 8, 10, and 12 study visits
- TEAEs were graded for severity using Common Terminology Criteria for Adverse Events v5.0 and were monitored through the safety follow-up period (30–35 days after end of treatment)

Statistical Analyses

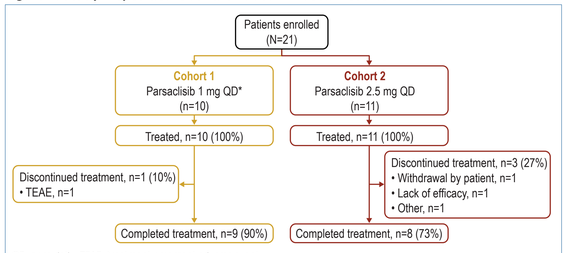
- The full analysis set included all patients enrolled in the study who received ≥1 dose of parsaclisib and was used for all efficacy and safety analyses
- Nonresponder imputation was applied to primary efficacy endpoints
- Data were summarized using descriptive statistics

RESULTS

Patients

- As of the data cutoff (October 12, 2020), 21 patients enrolled and received treatment with parsaclisib (**Figure 2**)

Figure 2. Study Disposition Over the Initial 12-Week Treatment Period



QD, once daily; TEAE, treatment-emergent adverse event.
* Eight patients had a dose increase during the initial 12-week treatment period.

- Patient demographics and baseline clinical characteristics were similar between cohorts (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

Parameter	Parsaclisib 1 mg QD (n=10)	Parsaclisib 2.5 mg QD (n=11)	Total (N=21)
Age, mean (SD), y	63.5 (9.6)	54.5 (20.7)	58.8 (16.6)
Female, n (%)	6 (60.0)	5 (45.5)	11 (52.4)
White/Caucasian, n (%)	9 (90.0)	11 (100.0)	20 (95.2)
Hgb at baseline, mean (SD), g/dL	9.1 (0.8)	9.0 (0.8)	9.0 (0.8)
Type of AIHA, n (%)			
wAIHA	7 (70.0)	7 (63.6)	14 (66.7)
CAD	2 (20.0)	2 (18.2)	4 (19.0)
Mixed	1 (10.0)	2 (18.2)	3 (14.3)
Time since first onset of AIHA, n (%)			
<2 y	4 (40.0)	6 (54.5)	10 (47.6)
2–5 y	1 (10.0)	2 (18.2)	3 (14.3)
>5 y	5 (50.0)	3 (27.3)	8 (38.1)
Previous therapies, n (%)			
Prednisone/rituximab	3 (30.0)	4 (36.4)	7 (33.3)
Prednisone	0	5 (45.5)	5 (23.8)
Rituximab/other	3 (30.0)	1 (9.1)	4 (19.0)
Prednisone/rituximab/other	3 (30.0)	0	3 (14.3)
Rituximab	1 (10.0)	1 (9.1)	2 (9.5)
Received transfusion(s) in the past year, n (%)	3 (30.0)	3 (27.3)	6 (28.6)
Number of hospitalizations due to AIHA in the past year, n (%)			
0	6 (60.0)	10 (90.9)	16 (76.2)
1	3 (30.0)	1 (9.1)	4 (19.0)
≥2	1 (10.0)	0	1 (4.8)
Splenectomy received, n (%)	1 (10.0)	2 (18.2)	3 (14.3)

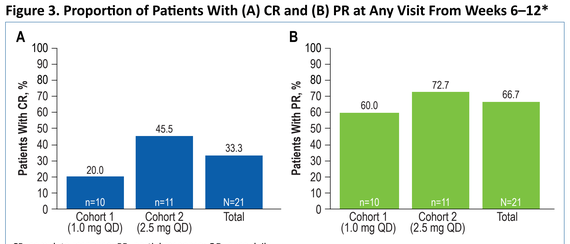
AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; Hgb, hemoglobin; QD, once daily; wAIHA, warm AIHA.

Efficacy Over the Initial 12-Week Treatment Period

- Overall, 7 patients (33%) achieved CR and 14 (67%) had PR at any visit from Weeks 6 to 12 (**Figure 3**)
- The proportion of patients achieving CR increased over time (**Figure 4**)
- Hgb levels increased over time for both treatment cohorts (**Figure 5A**)
- The proportion of patients achieving ≥2-g/dL increase in Hgb also increased over the 12-week treatment period (**Figure 5B**)
- Other hemolytic markers (haptoglobin, reticulocytes, indirect bilirubin, and lactate dehydrogenase) trended toward normalization

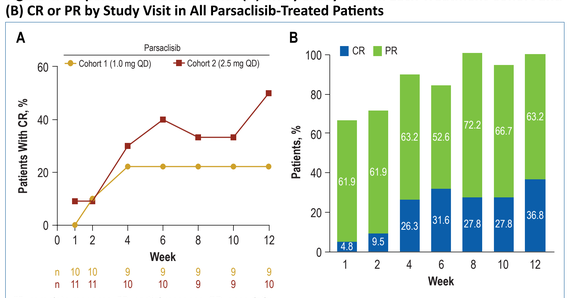
RESULTS (continued)

Figure 3. Proportion of Patients With (A) CR and (B) PR at Any Visit From Weeks 6–12*



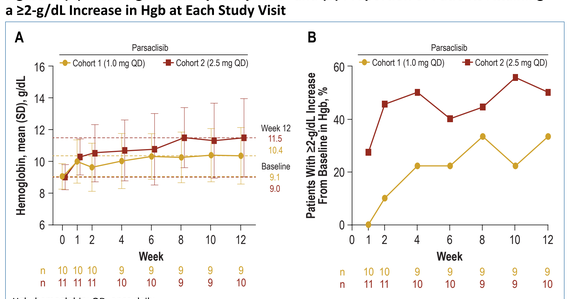
CR, complete response; PR, partial response; QD, once daily.
* Response categories are not mutually exclusive.

Figure 4. Proportion of Patients With (A) CR by Study Visit in Each Treatment Cohort and (B) CR or PR by Study Visit in All Parsaclisib-Treated Patients



CR, complete response; PR, partial response; QD, once daily.

Figure 5. (A) Mean Hgb Levels by Study Visit* and (B) Proportion of Patients Attaining a ≥2-g/dL Increase in Hgb at Each Study Visit



Hgb, hemoglobin; QD, once daily.
* Dashed lines indicate mean Hgb (g/dL) at baseline and Week 12 for each cohort.

Safety

- Overall, 86% of patients receiving parsaclisib experienced ≥1 TEAE, with headache, pyrexia, and diarrhea being the most common (**Table 2**)

Table 2. TEAEs/TRAEs Occurring in >1 Patient Over the Initial 12-Week Treatment Period

Adverse Events, n (%)	Parsaclisib 1 mg QD (n=10)	Parsaclisib 2.5 mg QD (n=11)	Total (N=21)
Any TEAE	8 (80.0)	10 (90.9)	18 (85.7)
Headache	3 (30.0)	2 (18.2)	5 (23.8)
Pyrexia	2 (20.0)	3 (27.3)	5 (23.8)
Diarrhea	2 (20.0)	2 (18.2)	4 (19.0)
Hyperuricemia	0	2 (18.2)	2 (9.5)
Neutropenia	2 (20.0)	0	2 (9.5)
Oedema Peripheral	0	2 (18.2)	2 (9.5)
Rash	1 (10.0)	1 (9.1)	2 (9.5)
Rash pruritic	2 (20.0)	0	2 (9.5)
Any TRAE	4 (40.0)	2 (18.2)	6 (28.6)
Rash pruritic	2 (20.0)	0	2 (9.5)

QD, once daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

RESULTS (continued)

- Five patients (24%) had grade ≥3 TEAEs, with only neutropenia occurring in >1 patient (n=2 [10%])
- One patient (5%) had a serious TEAE (hemolytic anemia; deemed unrelated to treatment)
- One patient (5%) had grade ≥3 treatment-related AEs (neutropenia and thrombocytopenia)
- TEAEs led to dose interruption in 4 patients (19%) and included neutropenia (n=2 [10%]), diarrhea (n=1 [5%]), and hepatotoxicity (n=1 [5%]; deemed unrelated to parsaclisib)
- One patient (5%) in cohort 1 discontinued parsaclisib due to a TEAE (thrombocytopenia)
- There were no fatal TEAEs

CONCLUSIONS

- Orally administered parsaclisib was generally well tolerated and demonstrated preliminary efficacy over the initial 12-week treatment period in this ongoing phase 2 study in patients with AIHA
- Overall, 33% of patients achieved CR and 67% achieved PR at any visit from Weeks 6 to 12
- TEAEs led to treatment discontinuation in 1 patient and dose interruptions in 4 patients
- Treatment resulted in durable normalization of Hgb levels as early as Week 2
- Parsaclisib has the potential to be an effective oral treatment for AIHA and warrants further clinical investigation

DISCLOSURES

WB has served as a consultant for Agios, Alexion, Apellis, Biocryst, Bioverativ, Incyte Corporation, Momenta, and Novartis; and has received lecture fees and/or congress support from Alexion, Incyte Corporation, Novartis, and Sanofi. IM has received research support from Alexion, Incyte Corporation, Kezar, Momenta, Rigel, and Sanofi; and has served as a consultant for Apellis, Momenta, Novartis, and Sanofi. LT has served as a consultant for Alexion and Novartis; and has received lecture fees and/or congress support from Alexion, Novartis, and Sanofi. FP has served as a consultant for Incyte Corporation and Novartis, and has received lecture fees and/or congress support from Incyte Corporation and Novartis. AP has received honoraria from Incyte Corporation, Novartis, Pfizer, Sanofi, and Takeda. KB, SM, and SW are employees and shareholders of Incyte Corporation. UJ has served as a consultant for Incyte Corporation, Janssen, Novartis, Roche, and Sandoz; has served as an advisor to AbbVie, Annexion, BMS/Celgene, Gilead, Incyte Corporation, Janssen, Miltenyi, Novartis, Roche, and Sandoz; has received lecture fees from AbbVie, BMS/Celgene, Gilead, Incyte Corporation, Janssen, Novartis, and Roche; and has received institutional research support from BMS/Celgene, Gilead, Novartis, and Roche. Parsaclisib is in development for AIHA and is not currently approved by any regulatory authorities.

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