FACIT-Fatigue Subscale Outcomes From an Ongoing Phase 2, Open-Label Study of the PI3Kδ Inhibitor Parsaclisib in Patients With Autoimmune Hemolytic Anemia

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

[1]University of Naples "Federico II," Naples, 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]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, 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

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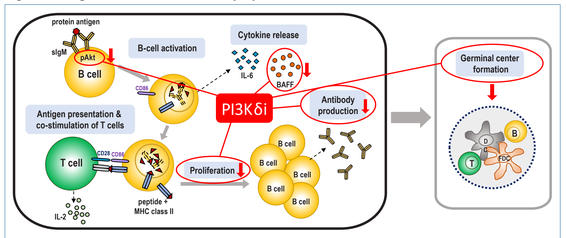
INTRODUCTION

- Autoimmune hemolytic anemia (AIHA) is a rare acquired condition resulting from decompensated autoantibody-mediated hemolysis of red blood cells[1]
- Although the precise etiology of primary AIHA is unclear, aberrant signaling of phosphatidylinositol 3-kinase delta (PI3Kδ) has been associated with B-cell–mediated autoimmunity[2] and may be implicated in AIHA
- There are currently no US Food and Drug Administration– or European Medicines Agency–approved therapies for AIHA[3]
- Fatigue resulting from low hemoglobin (Hgb) levels (anemia) is one of the most common patient-reported symptoms of AIHA,[4] and has been associated with reduced quality of life (QoL) in anemia[5]
- PI3Kδ is a critical regulator of B-cell biology (**Figure 1**); the PI3Kδ inhibitor parsaclisib has shown clinical antitumor activity in B-cell malignancies[6] and ameliorated pathology in preclinical models of autoantibody-mediated disease[7,8]

Figure 1. Regulation of B-Cell Activity by PI3Kδ



BAFF, B-cell activating factor; DC, dendritic cell; FDC, follicular dendritic cell; IL, interleukin; MHC, major histocompatibility complex; pAkt, phosphorylated protein kinase B; PI3Kδ, phosphatidylinositol 3-kinase delta; PI3Kδi, PI3Kδ inhibitor; sIgM, surface immunoglobulin M.

- A reduction in anemia-related fatigue with parsaclisib treatment may improve QoL in patients with AIHA
  - A ≥3-point increase in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) subscale, a 13-item instrument designed to assess fatigue and its impact on daily activities and functioning,[9] is considered clinically meaningful
- We hypothesized that patients treated with parsaclisib for AIHA may report less anemia-related fatigue

OBJECTIVE

- To describe FACIT-F outcomes 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; were diagnosed with primary warm AIHA, cold agglutinin disease, or mixed-type AIHA, without an underlying lymphoproliferative malignancy or other autoimmune-related underlying conditions; had Hgb levels of ≥7–≤10 g/dL; and failed ≥1 prior treatment for AIHA
- Patients were enrolled from study centers in the United States, France, Italy, and Austria

Study Design and Treatment

- Patients were enrolled into 1 of 2 successive cohorts and received parsaclisib for 12 weeks (**Figure 2**)
  - Cohort 1 (n=10): 1.0 mg once-daily (QD) parsaclisib, with an option for a dose increase (2.5 mg QD) at Week 6 based on protocol-defined dose increase criteria
  - Cohort 2 (n≈15): 2.5 mg QD parsaclisib; a dose reduction to 1.0 mg QD was permitted for tolerability at any time during the 12-week treatment period
- Following completion of the initial 12-week treatment period, eligible patients achieving clinical benefit could continue into an extension period

Assessments

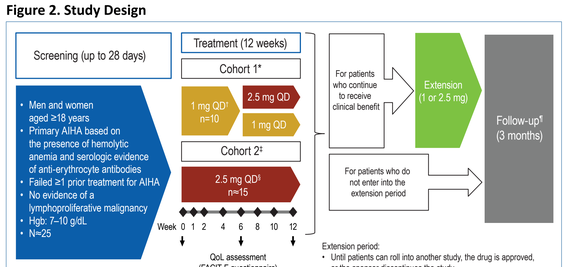
- For the QoL assessment, the FACIT-F paper questionnaire was administered at baseline, Week 6, and Week 12
  - A higher summary FACIT-F score indicates less fatigue and better QoL

METHODS (continued)

Statistical Analyses

- All patients enrolled in the study who received ≥1 dose of parsaclisib were included in the analysis
- Data were summarized using descriptive statistics

Figure 2. Study Design



AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; Hgb, hemoglobin; QD, once daily; QoL, quality of life; 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.

RESULTS

Patients

- By data cutoff (October 12, 2020), 21 patients were enrolled and received parsaclisib (**Table 1**)
  - Cohort 1, n=10 (dose increase, n=8)
  - Cohort 2, n=11

Table 1. Patient Disposition

Parameter	Parsaclisib 1 mg QD (n=10)	Parsaclisib 2.5 mg QD (n=11)	Total (N=21)
Patients treated in the 12-week period, n (%)	10 (100.0)	11 (100.0)	21 (100.0)
Patients who completed the 12-week treatment period, n (%)	9 (90.0)	8 (72.7)	17 (81.0)
Patients who discontinued treatment during the 12-week period, n (%)	1 (10.0)	3 (27.3)	4 (19.0)
Adverse event	1 (10.0)	0	1 (4.8)
Withdrawal by patient	0	1 (9.1)	1 (4.8)
Lack of efficacy	0	1 (9.1)	1 (4.8)
Other	0	1 (9.1)	1 (4.8)

QD, once daily.

- Demographics and baseline clinical characteristics were similar between cohorts (**Table 2**)

Table 2. Patient Demographics and Baseline Clinical Characteristics

Parameter	Parsaclisib 1 mg QD (n=10)	Parsaclisib 2.5 mg QD (n=11)	Total (N=21)
Age, median (range), y	62.0 (46–77)	60.0 (22–80)	62.0 (22–80)
Female, n (%)	6 (60.0)	5 (45.5)	11 (52.4)
Race, n (%)			
White/Caucasian	9 (90.0)	11 (100.0)	20 (95.2)
Black/African American	1 (10.0)	0	1 (4.8)
Type of AIHA, n (%)			
Warm	7 (70.0)	7 (63.6)	14 (66.7)
Cold	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)
Received transfusion(s) in the past year, n (%)	3 (30.0)	3 (27.3)	6 (28.6)
Hgb at baseline, g/dL, mean (SD)	9.1 (0.8)	9.0 (0.8)	9.0 (0.8)
FACIT-F score at baseline,* mean (SD)	32.6 (12.8)	34.8 (11.7)	33.8 (12.0)

AIHA, autoimmune hemolytic anemia; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; Hgb, hemoglobin; QD, once daily.
* FACIT-F score ranges from 0–52 points.[9]

RESULTS (continued)

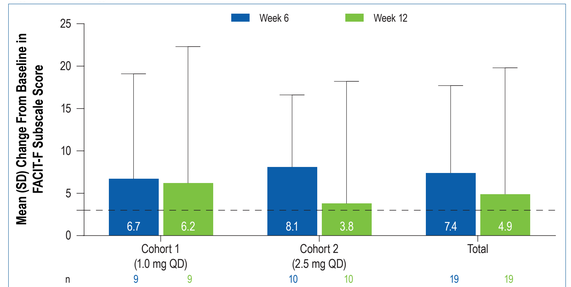
Change From Baseline in FACIT-F Score Over the Initial 12-Week Treatment Period

- Both cohorts showed an increase in FACIT-F subscale score compared with baseline at Weeks 6 and 12 (**Figures 3** and **4**)
- Mean percentage change from baseline in FACIT-F score was 40% for all patients (cohort 1, 52%; cohort 2, 29%) at Week 6 and 35% for all patients (cohort 1, 55%; cohort 2, 17%) at Week 12
- A corresponding increase in Hgb levels was seen over time (presented in EP685)

Patients Achieving a Clinically Meaningful Increase in FACIT-F Score Over the Initial 12-Week Treatment Period

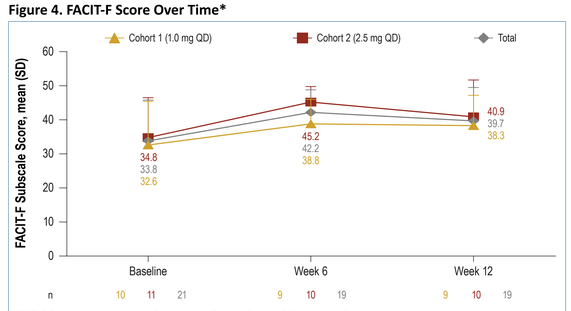
- By Week 6, nearly half of all patients had a clinically meaningful (ie, ≥3-point) increase in FACIT-F score (**Figure 5**)
- The improvement was maintained through Week 12

Figure 3. Change From Baseline in FACIT-F Score*



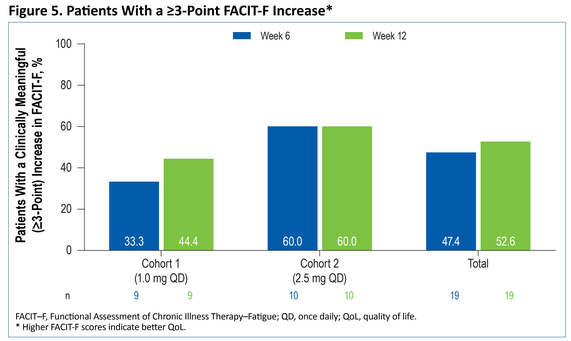
FACIT–F, Functional Assessment of Chronic Illness Therapy–Fatigue; QD, once daily; QoL, quality of life.
* Higher FACIT-F scores indicate better QoL. Dashed line indicates a clinically meaningful improvement from baseline (≥3-point increase in FACIT-F score).

Figure 4. FACIT-F Score Over Time*



FACIT–F, Functional Assessment of Chronic Illness Therapy–Fatigue; QD, once daily; QoL, quality of life.
* Higher FACIT-F scores indicate better QoL.

Figure 5. Patients With a ≥3-Point FACIT-F Increase*



FACIT–F, Functional Assessment of Chronic Illness Therapy–Fatigue; QD, once daily; QoL, quality of life.
* Higher FACIT-F scores indicate better QoL.

CONCLUSIONS

- FACIT-F scores improved from baseline at Weeks 6 and 12 of parsaclisib administration
- Parsaclisib treatment was associated with a clinically meaningful (ie, ≥3-point) improvement in fatigue-related QoL in patients with primary AIHA
  - This benefit was seen as early as Week 6 and persisted throughout the treatment period, with more than half of patients overall achieving a clinically meaningful improvement at Week 12
- Additional clinical studies of parsaclisib for patients with primary AIHA to further investigate the potential clinical benefit, including effects on QoL, are warranted

DISCLOSURES

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. 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. 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. AP has received honoraria from Incyte Corporation, Novartis, Pfizer, Sanofi, and Takeda. KBibeau, KButler, 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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CONTACT INFORMATION

Fabrizio Pane, MD, PhD • E-mail address: fabrizio.pane@unina.it

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