A Patient-Centric Approach to Sickle Cell Disease Clinical Trials: Integrating Patient Perspectives in the RISE UP Phase 2/3 Trial of Mitapivat for Informed Protocol Design and Associated Patient Community Benefit

2376

Charles Jonassaint, PhD[1], Blaze Armon Eppinger[2], Dominique Friend[3], Golie Lorenzo Green[4], Mia Robinson[5], Teonna Woolford[6], DeMitrious Wyant[7], Janie Davis[8], Abdulafeez Oluyadi[8], PharmD, Ahmar U Zaidi, MD[8], Holly John[8], Wally R Smith, MD[9]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA; [2]Independent Contributor, Eatonton, GA; [3]Independent Contributor, Orlando, FL; [4]Independent Contributor, Houston, TX; [5]Sickle Cell Awareness 365, Atlanta, GA; [6]Sickle Cell Reproductive Health Education Directive, Owings Mills, MD; [7]Independent Contributor, Washington, DC; [8]Agios Pharmaceuticals, Cambridge, MA; [9]Virginia Commonwealth University, Richmond, VA

BACKGROUND

- Sickle cell disease (SCD) is an inherited blood disorder characterized by mutations in the β-globin chain of hemoglobin, leading to red blood cell sickling, hemolytic anemia, pain events, and end-organ damage in cardiopulmonary, central nervous, and renal systems[1]
- SCD affects >3 million people worldwide and ~100,000 people in the United States[1]
- There are limited treatment options and a need remains for additional disease modifying therapies
- Clinical trials remain essential for identifying new, safe, and effective therapies; however, patient involvement in clinical trial design is often late or absent[2]
- Although patients with SCD have benefited from past clinical trials, there are barriers to trial awareness and enrollment (e.g., mistrust of research studies, emotional issues, practical considerations)[3]
- RISE UP, a randomized, double-blind, placebo-controlled, multicenter phase 2/3 clinical trial of mitapivat, a pyruvate kinase activator under investigation for treatment of patients with SCD (NCT05031780)[4], utilized an innovative, patient-forward approach to clinical trial design, awareness, and recruitment that considered patient preferences wherever possible

OBJECTIVE

- **Using Agios' RISE UP Phase 2/3 trial, redefine best practices in clinical trial design by:**
  1. **Asking patients with SCD to describe what matters most to them in a trial setting**
  2. **Involving patients in decision making processes and trial awareness communications**

METHODS

Protocol Design

- 9 patients with SCD (>16 years of age) and advocates (Bahrain n=1, France n=1, United Kingdom n=2, United States n=5) took part in a series of clinical trial design workshops
- 4 remote patient advisory board interviews were held with patients and advocates to consult on the RISE UP Phase 2/3 clinical trial design
- Patient perspectives were sought in the following areas:
  - Meaningful trial parameters
  - Study duration
  - Post-study access to treatment
  - Study endpoints
  - Eligibility criteria
  - Assessments and procedures
  - Operational support needs (e.g., visit frequency and locations)
  - Compensation considerations
  - Pain reporting
- Insights gained from these consultations were incorporated into the proposed trial protocol design that was subsequently shared with Health Authorities (HAs) for their comment from a regulatory perspective
- Once finalized, key patient-related feedback from HAs was presented to the patient advisory board to determine whether changes requested by HAs met the needs and barriers-to-uptake expressed during partner consultations

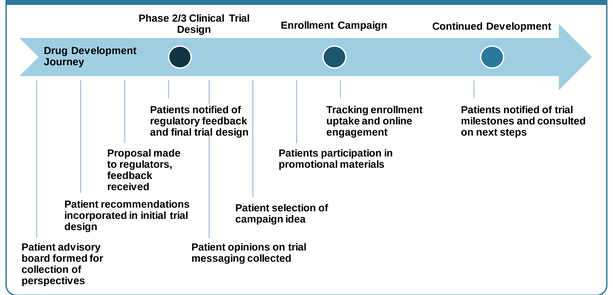
Awareness Campaign

- In addition, a group of 7 patients (5 US patients from the clinical trial design workshops and 2 additional US patient advocates) co-created the RISE UP phase 2/3 clinical trial awareness campaign, which sought to educate the community about the RISE UP clinical trial and value of patient participation
- It also sought to provide insights, build trust, and improve engagement of patients with SCD with respect to clinical trial awareness and enrollment in the RISE UP study
- A combination of communication approaches focused on:
  - Reaching/engaging individuals and local community groups, fostering relationships, and building trust to gain support
  - Connecting with decision-makers and influential individuals who could advance the campaign's objectives
- The campaign launched a YouTube advertisement during World Sickle Cell Day 2022 (June 19) and monitored site traffic to the video, as well as to clinicaltrials.gov, Twitter, and the RISE UP clinical trial website
- Media metrics, including views, clicks, and webpage visits, as well as other key performance indicators were used to measure campaign success as well as infer insights for future trial design or awareness campaigns

RESULTS

- Patient contributions were considered at appropriate points throughout the drug development process (**Figure 1**)

Figure 1. Patient engagement process



Protocol Design

- Patient contributions to the protocol design included modified inclusion/exclusion criteria and the addition of pain (beyond pain crises) and fatigue as study outcomes; an overview is shown in **Table 1**
  - As per patient input, the trial was adjusted to include a recommendation for tailored management of SCD pain crises using a daily diary; the trial also approved reimbursement for study-related travel, lodging, and specific non-study assessments

Table 1. RISE UP trial design, summary of community feedback on different aspects of the study design

Study Aspects	Community Feedback	Protocol Design Elements
Study Duration	• 12-month study duration may hamper participation and/or compromise compliance	• Approximately monthly study visits for 7 months, followed by visits every 3 months
Post-study access	• Important to provide patients access to treatment after completion of the clinical trial	• An open label extension period was also added with visits on the 2nd, 4th, 8th, and 12th weeks of the extension period, followed by every 3 months up to 1.5 years and every 6 months thereafter
Study endpoints	• Evaluate effect as assessed by high quality patient-reported outcomes (PROs) • Evaluate pain and fatigue • Provide flexibility with questionnaire and minimize questionnaire burden	• Key secondary and other secondary endpoints in the study include Health-Related Quality of Life and Performance Outcome Assessments
Eligibility criteria	• Assessing effect in patients with Hb <8 g/dL could be beneficial • Prohibiting concomitant therapies (e.g., hydroxyurea or exchange transfusion) may preclude patient participation	• Subgroup analyses specified in the protocol based on baseline Hb (<8 g/dL, >=8 g/dL)

Hb, hemoglobin; PRO, patient reported outcome.

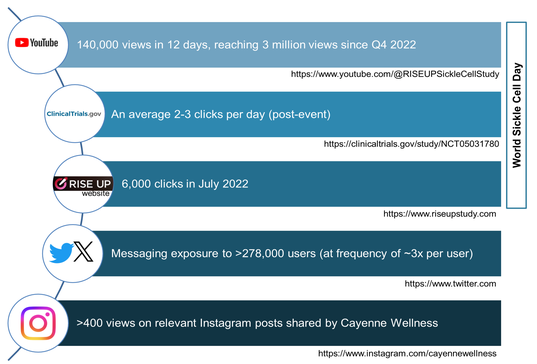
Campaign

- An example of a campaign that was co-created with the sickle cell warriors can be seen in **Figure 2**

Figure 2. Campaign co-created with sickle cell warriors

- The RISE UP campaign heightened interest within the community for clinical trial participation (**Figure 3**)
  - Strong social media engagement and digital efforts resulted in increased trial website views
  - Community education and awareness efforts resulted in increased clinicaltrials.gov views to an average of 2-3 clicks per day

Figure 3. Media metrics following RISE Up campaign launch during World Sickle Cell Day



Key Learnings and Recommendations for Future Patient Engagement

- Patient engagement for clinical trial design for the RISE UP study yielded important insights relating to trial design, endpoint selection, trial awareness, and effective use of communication channels (**Table 2**)

Table 2. Key learnings and recommendations for patient involvement in trial design and recruitment

Action	Learnings	Recommendations
Trial design	• Prioritizing patient input and involvement can enhance the clinical trial design process and help address patient concerns	• Create patient advisory board to guide decision-making processes • Take action on recommendations and keep patients informed of continued developments • Ensure trial protocol meets both regulatory requirements and patient needs
Patient relevant endpoints	• Including patient-centered outcomes and endpoints improves data collection methods	• Prioritize the development of the most convenient protocol possible for patients based on their lived experience
Trial awareness	• Patient involvement can create a uniquely impactful and differentiated awareness approach	• Build relationships and trust with patients, families, and patient advocacy groups • Engage local and national decisionmakers and influencers • Provide information to patients in a comprehensive manner, tailored to common questions and potential concerns
Communications channels	• Meeting patients where they are, using familiar language and engaging with their priorities drives engagement and action	• Leverage social media platforms for campaign reach and engagement • Allow patients to guide the process to generate authenticity and trust among peers • Monitor traffic to trial websites and clinical trial registration platforms to assess impact and course correct, as needed

CONCLUSIONS

- By partnering with patients with SCD to gather their contribution to protocol design, Agios integrated feedback from patients into the design and implementation of the study
- The campaign succeeded in building awareness and engagement with patients, families, and advocacy groups, as well as local and national decision-makers and influencers
  - The Phase 2 portion of the RISE UP clinical trial was launched on time and fully enrolled, a notable result given that 80% of clinical trials globally are delayed due to missed enrollment targets[5]
- Learnings and recommendations from this innovative patient-forward approach may be applied further throughout the drug development process

By engaging with patient communities, the RISE UP campaign was able to build trust, engage with local and national decisionmakers, and provide timely information to patients, allowing them to make informed decisions about trial participation

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References: 1. Brandow AM, Liem RI. J *Hematol Oncol*. 2022;15(1):20; **2.** Geißler et al. *Commun Med* 2022;2,94; **3.** Lebensburger JD et al. *Pediatr Blood Cancer*. 2013;60(8):1333–1337; **4.** ClinicalTrials.gov. A Study Evaluating the Efficacy and Safety of Mitapivat (AG-348) in Participants With Sickle Cell Disease (RISE UP). https://classic.clinicaltrials.gov/ct2/show/NCT05031780. Accessed Oct 27, 2023; **5.** Desai M. *Perspect Clin Res*. 2020;11(2):51–53.

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