Hemophilia

Title: Unmet Needs of Patients With Hemophilia A/B With or Without Inhibitors: Real-World End-of-Study Results From the explorer6 Non-Interventional Study

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Abstract

Background: Unmet needs associated with hemophilia and its treatment persist, including repeated bleeding episodes, reduced physical activity, treatment burden, and the development of antibodies with resultant limited treatment options (Putz P et al. *Haemophilia* 2021; 27(2):e260–e266; Ljung R et al. *Eur J Haematol* 2019;102(2):111–122). Evaluating data from patients with hemophilia prospectively would help better define existing unmet needs and assist in optimizing treatment and improving healthcare outcomes. explorer6 (NCT03741881) was a prospective, multi-national, non-interventional study in patients with hemophilia (hemophilia A or B with inhibitors [HAwI or HBwI] or without inhibitors [HA or HB]).

Aims: To communicate end-of-study data from explorer6 in routine clinical practice, focusing on bleeding episodes and physical activity.

Methods: Male patients aged ≥12 years with severe HA, severe/moderate HB, or HAwI/HBwI of any severity were recruited. Each patient was treated according to their center's standard of care. The primary objective was to investigate the number of bleeding episodes from enrolment up to a maximum of 115 weeks in routine clinical treatment practice. Exploratory objectives included assessment of physical activity, based on data collected by a wrist-worn physical activity tracker, from enrolment for a duration of 3–12 weeks. Haemophilia Joint Health Score (HJHS) measurements were reported if available. All statistics are descriptive and exploratory. Results are presented according to treatment regimen at end of study (on-demand [OnD] or prophylaxis [PPX]), hemophilia type (HA or HB) and inhibitor status (with or without inhibitors). Informed consent/ethics committee approval were obtained.

Results: A total of 231 patients from 109 clinical centers across 33 countries were enrolled. There were 138 patients without inhibitors (HA: 70; HB: 68) and 80 patients with inhibitors (HAwI: 49; HBwI: 31) who completed the study. Most patients (97.8%) had severe hemophilia, and five patients (HB and HAwI) had mild to moderate hemophilia. For treated bleeding episodes, the mean

ABR (SD) for HA and HB for OnD treatment was 21.5 (17.7) and 10.5 (8.6), respectively, and for PPX 4.7 (5.9) and 2.2 (3.0), respectively. The mean ABR (SD) for HAwI and HBwI for OnD treatment was 15.2 (14.8) and 9.3 (13.3), respectively, and for PPX 10.3 (8.5) and 12.4 (14.1), respectively. Physical activity levels (moderate to vigorous), reported as mean percentage of awake time, were similar for patients on PPX (HA: 13.7%; HB: 12.6%; HAwI: 16.3%; HBwI: 11.6%) versus those on OnD treatment (HA: 12.3%; HB: 14.2%; HAwI: 13.9%; HBwI: 10.2%). Physical activity levels were lowest among patients with HBwI. HJHS data were available for 130 (56.3%) patients, and mean HJHS results were numerically lower or similar for PPX (HA: 16.2; HB: 8.8; HAwI: 19.1) compared with OnD (HA: 25.1; HB: 31.0; HAwI: 23.9). Mean HJHS results for HBwI were similar for patients receiving PPX (HBwI: 23.7) and OnD treatment (HBwI: 22.3).
Conclusions: The explorer6 study assessed bleeding episodes and physical activity in routine clinical practice in patients with hemophilia, including a large HBwI population (31/231 patients; 13.4%). The data reported indicate that an unmet need still exists in patients with inhibitors, as evidenced by increased bleeding events and HJHS results, as well as decreased physical activity. This is particularly pertinent for those with HBwI for whom there is no efficacious PPX or subcutaneous treatment regimen available. These unmet needs emphasize the need for new therapeutic options to improve health outcomes; emerging therapy options have the potential to meet these needs.

Title: Annualized Bleeding Rates in Patients with Hemophilia A or B and Inhibitors with and without Target Joints at Baseline: Results from the Concizumab Phase 3 Explorer7 Study
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Abstract
Background: In patients with hemophilia, recurring bleeds into the same joint, known as target joint, cause hemophilic arthropathy and reduce quality of life. Prophylaxis is the current standard of care for severe hemophilia, started early in life to prevent onset and progression of joint damage by reducing recurrent bleeds, allowing patients to participate in physical and social activities, and improve their quality of life. Concizumab is a recombinant anti-tissue factor path-

way inhibitor monoclonal antibody under development as a once-daily subcutaneous prophylaxis for hemophilia A/B with and without inhibitors. Here, we present the annualized bleeding rate (ABR) results in patients with hemophilia A/B with inhibitors (HAwI/HBwI), with or without target joints at baseline, from the prospective, multicenter, open-label, phase 3 explorer7 (NCT04083781) study.
Aim: To assess the ABR in patients with HAwI/HBwI, with or without target joints at baseline, during concizumab prophylaxis *vs* on-demand treatment.
Methods: Target joints were defined as ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period; target joints were deemed resolved when there had been ≤2 bleeds in the joint during the previous 12 months (Blanchette VS et al. *J Thromb Haemost*. 2014;12(11):1935–39). Treated spontaneous and traumatic bleeding episodes were assessed at the 32- and 56-week cut-offs for patients with and without target joints at baseline. The 32- and 56-week cut-offs were defined as when all patients had completed the visit after 32 or 56 weeks respectively, or permanently discontinued treatment. In the explorer7 study, patients with HAwI/HBwI were randomized 1:2 to on-demand treatment (arm 1; ≥24 weeks) or concizumab prophylaxis (arm 2; ≥32 weeks), or assigned to non-randomized concizumab prophylaxis arms 3 and 4. After ≥24 (arm 1) or ≥32 weeks (arm 2–4), all patients were offered entry into the extension part, and patients in arm 1 switched to concizumab prophylaxis. Patients received a 1.0 mg/kg concizumab loading dose on Day 1, followed by an initial 0.20 mg/kg daily dose starting on Day 2, with potential adjustment to 0.15 or 0.25 mg/kg based on measured plasma concizumab concentration after week 4. Results for estimated mean ABRs are presented for arm 2 *vs* arm 1; descriptive results are presented for all patients (arms 1–4). Informed consent/ethics committee approval were obtained.
Results: Male patients (≥12 years) with HAwI/HBwI were recruited (2.3% American Indian/Alaska Native, 27.8% Asian, 6.8% Black/African American, 58.6% White, 4.5% not reported). Of the 133 patients enrolled (HAwI: 80; HBwI: 53), 19 were randomized to on-demand treatment (arm 1), 33 randomized to concizumab prophylaxis (arm 2), and 81 allocated to concizumab prophylaxis (arms 3/4). After the 32-week cut-off, 13 patients from arm 1 switched to concizumab prophylaxis. A total of 104 patients in arms 1–4 completed treatment at the 56-week cut-off.
At the 32-week cut-off, for patients with target joints at baseline, estimated mean ABR (95% confidence interval [CI]) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis (arm 2) was 1.7 (0.55–5.51) *vs* 10.6 (4.18–26.92) on-demand (arm 1); ABR ratio was 0.16 (0.06–0.48; P=0.001), indicating an 84% reduction in bleeding episodes. For patients with no target joints at baseline, estimated mean ABR (95% CI) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis (arm 2) was 0.9 (0.48–1.58) *vs* 9.0 (5.59–14.53) on-demand (arm 1); ABR ratio was 0.10 (0.05–0.19; P<0.001), indicating a 90% reduction in bleeding episodes.
At the 32-week cut-off, overall median ABR (interquartile range [IQR]) during concizumab prophylaxis (arms 1–4) in patients with and without target joints at baseline, for treated spontaneous and traumatic bleeding episodes was 0.9 (0.0–4.3) and 0.0 (0.0–2.8), for joint bleeding episodes 0.0 (0.0–3.9) and 0.0 (0.0–1.5), and for target joint bleeding episodes 0.0 (0.0–1.1) and 0.0 (0.0–0.0), respectively. By the 56-week cut-off, 92% of target joints had resolved (arms 1–4), low median ABRs were maintained on concizumab. Overall safety data showed no new findings.

Conclusion: In the explorer7 study, once-daily, subcutaneous concizumab prophylaxis effectively reduced ABR irrespective of the presence of target joints at baseline at the 32-week cut-off, low ABRs were maintained at the 56-week cut-off.

Title: Mim8 Prophylaxis Beyond Bleeding: Investigating Multifaceted, Patient-reported Outcomes for Hemophilia A in the FRONTIER2 Study

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Abstract

Introduction: Beyond hemostatic efficacy, patient-reported outcomes (PROs) appear critical for evaluating patient experience and disease burden with new hemophilia treatments. Mim8 (denecimig) is a factor VIIIa mimetic bispecific antibody in development for subcutaneous prophylaxis (PPX) of hemophilia A (HA) and HA with inhibitors (HAwI). In the phase 3 FRONTIER2 study (NCT05053139), Mim8 demonstrated hemostatic efficacy by reducing annualized bleeding rate (ABR) for treated bleeds compared with on-demand treatment and vs previous clotting factor concentrate (CFC) PPX (Mancuso et al. ISTH 2024; LB01.5).

Aims: To investigate Mim8 once every week (QW) and once every month (QM) PPX for PROs assessing patient physical functioning, treatment burden and joint pain intensity.
Methods: FRONTIER2 is an open-label, randomized controlled study for male and female patients (aged ≥12 years) with HA/HAwI of any severity. Patients receiving on-demand treatment before enrollment were randomized to continued on-demand treatment or Mim8 PPX QW or QM for 26 weeks. Patients on CFC PPX continued PPX for 26 weeks and were then randomized to Mim8 PPX QW or QM for 26 weeks. The following PROs were prespecified secondary outcomes: physical function domain of the Pediatric Quality of Life Inventory™ (PedsQL; 0–100, higher domain scores denote better physical functioning), Hemophilia Treatment Experience Measure (Hemo-TEM; 0–100, lower scores denote less treatment burden) and Joint Pain Rating Scale (JPRS; 1–10, lower scores denote less intense pain). Supportive PROs included the Hemophilia Patient Preference Questionnaire (HPPQ) and Patient Global Impression (PGI) scales: Change in Pain Intensity, and Severity and Change in Physical Function. Data are reported as mean [SD] scores at baseline (randomization) and mean [SD] change from baseline scores at Week 26. A post hoc ANCOVA model was used to analyze changes from baseline to Week 26 for prior on-demand arms, with treatment, inhibitor status and historical ABR as factors and baseline as a covariate. Estimated treatment differences (ETD) and p-values are provided for two-sided 2.5% tests of no difference.
Results: Of 254 randomized patients (17, 21 and 20 in prior on-demand arms and 98 in each prior CFC PPX arm), 246 completed 26-week treatment. Overall 26% were adolescents, 2% female and 83% had severe HA. HAwI patients represented 47% of prior on-demand arms and 2% of prior CFC PPX arms. Physical functioning (PedsQL) baseline scores for prior on-demand arms were 50.5 [18.6] to 59.2 [22.2]. Scores increased with Mim8 PPX (Mim8 QW 14.2 [22.0], Mim8 QM 20.8 [20.3]) and decreased with on demand (−5.5 [17.8]). ETD (95% CI) vs on demand was 19.9 (4.9, 34.9; p=0.0108) for Mim8 QW and 27.3 (12.6, 41.9; p=0.0006) for Mim8 QM. Baseline scores for prior CFC PPX arms were 71.8 [21.1] and 75.2 [21.5] and increased with Mim8 QW (1.9 [13.1]) and Mim8 QM (2.1 [10.1]). Treatment burden (Hemo-TEM) baseline scores were 29.0 [19.4] for the on-demand arm and 15.3 [12.4] to 18.4 [15.6] for Mim8 arms. Scores for prior on-demand arms decreased by −9.9 [13.4] with Mim8 QW, −11.2 [11.6] with Mim8 QM and −2.2 [14.1] with on demand. ETD (95% CI) vs on demand was −13.0 (−20.2, −5.8; p=0.0009) for Mim8 QW and −16.6 (−23.8, −9.4; p<0.0001) for Mim8 QM. Prior CFC PPX arms had decreases of −10.8 [15.5] with Mim8 QW and −10.0 [10.5] with Mim8 QM. Clinically meaningful score decreases (≥8 points) were reported for 33% (on demand), 38% (Mim8 QW) and 60% (Mim8 QM), and in prior CFC PPX arms for 49% (Mim8 QW) and 48% (Mim8 QM) of patients**.** Joint pain intensity (JPRS) baseline scores were 5.0 [2.4] for the on-demand arm and 2.8 [2.5] to 3.1 [2.4] for Mim8 arms. Scores for prior on-demand arms decreased by −0.5 [3.4] for Mim8 QW, −1.8 [2.8] for Mim8 QM and −0.8 [2.4] for on demand; decreases for prior CFC PPX arms were −0.1 [2.4] for Mim8 QW and −0.3 [1.9] for Mim8 QM. Similar improvements were reported with Mim8 for all PGI scales. HPPQ scores showed a strong patient preference for Mim8.

Conclusion: Mim8 PPX improved physical functioning and reduced treatment burden compared with on-demand treatment and baseline. Among patients previously receiving CFC PPX, physical functioning improved to a lesser extent. Joint pain intensity was not severe at baseline in all arms and did not change notably with Mim8 PPX. These findings demonstrate the holistic benefits of Mim8 beyond bleed protection and provide insights into opportunities for individualized care.

Title: Safety and efficacy of Mim8 prophylaxis administered once every two weeks for patients with hemophilia A with or without inhibitors: Interim analysis of the FRONTIER4 open-label extension study

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Abstract

Introduction: Mim8 (denecimig) is a next-generation, activated factor VIII mimetic, fully human bispecific IgG4 antibody in clinical development as a subcutaneous prophylactic treatment for patients with hemophilia A with or without factor VIII inhibitors. In the phase 2, open label, multiple ascending dose part of the FRONTIER1 study (NCT04204408), Mim8 was well tolerated with no safety concerns and few treated bleeding episodes beyond the lowest dose cohort. Efficacy for reducing annualized bleeding rate (ABR) and safety of weekly (QW) or monthly (QM) prophylaxis were established in the phase 3 FRONTIER2 study (NCT05053139; Mancuso, et al. ISTH 2024; LB01.5). FRONTIER4 (NCT05685238) is an open-label extension study enrolling participants from FRONTIER1 (Arm 1) or several phase 2/3 studies of Mim8 (Arm 2).

Aim: This interim analysis investigates the safety and efficacy of Mim8 prophylaxis once every two weeks (Q2W) in Arm 1 of FRONTIER4 (26 weeks).

Methodology: Adults and adolescents (12–17 years old) with hemophilia A with or without inhibitors who completed the 12-week phase 2 part of FRONTIER1, along with at least 12 weeks of its extension, enrolled in Arm 1 of FRONTIER4. Patients received Mim8 prophylaxis Q2W for 26 weeks (part 1), after which they could remain on Q2W dosing or switch to QW or QM (part 2). The primary endpoint was number of treatment-emergent adverse events and secondary endpoints included number of treated bleeding episodes, subtypes of bleeds, number of injection

site reactions, and occurrence of anti-drug antibodies. In this interim analysis we report safety and efficacy from part 1 of FRONTIER4 (26-week Q2W dosing).
Results: Of 39 patients who completed the FRONTIER1 phase 2 extension study, 37 transferred to FRONTIER4; all completed part 1 of the study. Mean (standard deviation [SD]) age was 35 (12) years (two adolescents and 35 adults; all male). All participants had severe hemophilia A, four of whom were positive for inhibitors. Mean (SD) ABR from the phase 2 FRONTIER1 study (previous 12 months) was 1.76 (5.34) and mean (SD) exposure time on Mim8 prophylaxis during the extension was 1.73 (0.33) years. Of the 60 adverse events (AEs) reported by 20 patients, none were AEs of special interest (thromboembolic and thrombotic microangiopathy events) or hypersensitivity reactions. All AEs were non-serious, except three (two patients), which were considered unlikely to be related to Mim8 and resolved. Two participants reported 14 mild, transient injection site reactions (mainly erythema). One participant, who had zero bleeding episodes, had one low-titer positive anti-drug antibody result at one visit, which did not impact Mim8 concentration (measured by Meso Scale Discovery immunoassay) or activity (measured by modified FVIII chromogenic assay). Values for laboratory parameters, including coagulation parameters (D-dimer, fibrinogen, Factor IX, and X antigens), were generally within the normal range and remained stable over time. No trend was observed with prothrombin fragments 1 and 2; outlying values were observed from a single site, which may be attributed to technical issues. Six participants had seven treated bleeding episodes (four spontaneous and three traumatic), five of which were joint bleeds. This resulted in an estimated mean ABR of 0.4 (95% confidence interval [CI] 0.17, 0.82) for treated bleeding episodes with Mim8 Q2W dosing. Median ABR was 0 and 31/37 (84%) participants had zero treated bleeding episodes. Estimated mean ABR (95% CI) for treated spontaneous, traumatic, and joint bleeds were 0.2 (0.07, 0.60), 0.2 (0.03, 0.81), and 0.3 (0.11, 0.65), respectively. Mim8 plasma concentration was stable at steady state with Q2W dosing (C_{max} 5.0 µg/mL and C_{trough} 4.8 µg/mL).
Conclusions: This interim analysis of FRONTIER4 showed that Mim8 Q2W prophylaxis was well tolerated with no participants discontinuing treatment, and no safety concerns were observed. Few participants experienced treated bleeding episodes with Mim8 Q2W dosing and a large proportion had zero treated bleeding episodes. These data are consistent with the findings from FRONTIER2, which reported no safety concerns and a low number of treated bleeding episodes with either QW or QM prophylaxis. Further data from this ongoing arm of FRONTIER4, as well as data for participants enrolled from other studies in the FRONTIER program, will provide valuable long-term data for different Mim8 dosing regimens.

Title: Burden of Treatment on People with Hemophilia: Global Real-World Data
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Abstract

Background: Prophylaxis lowers bleed risk and facilitates individualized treatment for people with hemophilia (PWH). Prior real-world data from the United States (US) show that treatment burden persists, although is lower with newer therapies (Garcia VC et al. *Haemophilia*. 2024;30(2):375–387).

Aims: The study investigated the remaining clinical needs of people with hemophilia A (HA) and B (HB) receiving prophylaxis, from a global perspective. The current analysis assessed the burden of treatment reported by PWH.

Methods: This cross-sectional real-world survey captured patient-reported outcomes, experiences, and clinical data from PWH and parents/guardians of PWH (PPWH) in eight countries (Canada, France, Germany, India, Italy, Saudi Arabia, Spain and the US). Participants were recruited via interaction with treating healthcare professionals, social media, online panels and patient groups. Eligible participants were ≥1 year of age, with HA and ≥6 months of prophylaxis, or HB who were on prophylactic and/or on-demand treatment. Exclusions included mental incapacity, language barriers, clinical trial participation, or receipt of investigative/compassionate treatments.

Between December 2023 and March 2024, participants completed a 30-minute online survey. Treatment burden was measured using the adult Hemophilia Treatment Experience Measure (Hemo-TEM), a validated questionnaire covering five domains (injection difficulties, physical impact, treatment bother, interference, and emotional impact). Scores range from 0 to 100 with higher scores indicating greater burden. Here we report treatment burden for people with severe hemophilia at diagnosis without inhibitors (woI) by treatment class: standard half-life (SHL) and extended half-life (EHL) for factor VIII in HA or factor IX in HB, and non-factor therapy (NFT) in HA.

Results: Of 495 PWH/PPWH who completed the survey, most were self-completing PWH (n=323, 65%). Mean (standard deviation) age of PWH was 27.1 (17.1) years. Of the 229 people with severe HAwoI 26% (n=59) received SHL, 28% (n=64) EHL, 40% (n=91) NFT and 6% (n=15) unknown. Of the 46 people with severe HBwoI 20% (n=9) received SHL, 78% EHL (n=36) and 2% (n=1) unknown.

Across the five Hemo-TEM domains, people with severe HAwoI (n=144) experienced similar degrees of treatment burden regardless of therapy class, with a trend towards reduced burden in PWH from SHL to EHL to NFT. Median scores (interquartile range [IQR]) by treatment class, SHL (n=46)/EHL (n=36)/NFT (n=62) were 17 (0–35)/8 (0–25)/4 (0–17) for injection difficulties, 29 (4–42)/17 (4–35)/8 (0–18) for physical impact, 29 (14–44)/21 (7–36)/13 (4–29) for treatment bother, 44 (13–63)/25 (2–44)/9 (0–25) for interference, and 38 (21–50)/29 (2–46)/21 (7–38) for emotional impact. For people with severe HBwoI (n=26), Hemo-TEM results indicated comparable treatment burden across the five domains. Median scores (IQR) by treatment class, SHL (n=5)/EHL (n=21), were 8 (0–38)/17 (0–42) for injection difficulties, 17 (6–38)/8 (0–31) for physical impact, 14 (9–39/21 (7–39) for treatment bother, 50 (28–66)/19 (6–28) for interference, and 17(13–58)/17 (8–33) for emotional impact.

In the Hemo-TEM physical impact domain, of people with severe HAwoI on SHL/EHL/NFT, 43%/22%/19% experienced soreness and 35%/33%/18% reported pain due to their treatment (while injecting or after) at least sometimes (sometimes/often/always). Responses for people

with severe HBwoI on SHL/EHL were 40%/19% for soreness and 20%/14% for pain. In the treatment bother domain 33%/11%/6% of people with severe HAwoI reported at least some level of bother (somewhat/very/extremely bothered) for time taken to prepare and administer treatment, 30%/14%/26% for the need to store medication and supplies and 35%/3%/6% for the number of steps it takes to administer treatment. Responses for people with severe HBwoI were 20%/33% for time taken to prepare and administer treatment, 20%/24% for the need to store medication and supplies and 20%/14% for the number of steps it takes to administer treatment.
Conclusion: Although current therapies can improve bleed prevention outcomes for PWH, treatment burden remains, manifesting as pain due to therapies and administrative aspects that may negatively affect patient experience. Assessing treatment burden using standard tools is an important part of comprehensive care to individually optimize care and outcomes.

Title: Physical and Psychological Burden on People with Hemophilia: Global Real-World Data
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Abstract
Background: Although current and emerging prophylactic treatments can reduce bleeding risk for people with hemophilia (PWH), a residual physical and psychological burden associated with treatment may persist (Barry V et al. *Haemophilia*. 2021;27(3):375–382).
Aims: This study investigated the remaining clinical needs of people with hemophilia A (HA) and B (HB) receiving prophylaxis, from a global perspective. The current analysis assessed the physical and psychological burden reported by PWH.
Methods: This cross-sectional real-world survey captured patient-reported outcomes, experiences, and clinical data from PWH and parents/guardians of PWH (PPWH) in eight countries (Canada, France, Germany, India, Italy, Saudi Arabia, Spain and the US). Participants were recruited via interaction with treating healthcare professionals, social media, online panels and patient groups. Eligible participants were ≥1 year of age with HA and ≥6 months of prophylaxis or HB who were on prophylactic and/or on-demand treatment. Exclusions included mental incapacity, language barriers, clinical trial participation, or receipt of investigative/compassionate treatments.
Between December 2023 and March 2024, participants completed a 30-minute online survey. Disease impact on physical and psychological health was measured using the Patient-Reported Outcomes Measurement Information System 29+2 version 2.1 (PROMIS®-29+2 Profile v2.1 [PROMIS-29]), a validated questionnaire covering eight domains (physical functioning, ability to participate in social roles and activities, cognitive function, fatigue, sleep disturbance, pain interference, anxiety, and depressive symptoms). PROMIS-29 scores were transformed into T-scores using a reference sample from the general population with a mean of 50. Lower scores for

physical, social, and cognitive domains reflect higher burden, while higher scores for the other domains indicate greater burden. This analysis focuses on results for people with severe hemophilia without inhibitors (woI) by treatment class: standard half-life (SHL) and extended half-life (EHL) for factor VIII in HA or factor IX in HB, and non-factor therapy (NFT) in HA.
Results: Of 495 PWH/PPWH who completed the survey, most were self-completing PWH (n=323, 65%). Mean age (standard deviation, SD) of PWH was 27.1 (17.1) years. Of the 229 people with severe HAwoI 26% (n=59) received SHL, 28% (n=64) EHL, 40% (n=91) NFT and 6% (n=15) unknown. Of the 46 people with severe HBwoI 20% (n=9) received SHL, 78% EHL (n=36), and 2% (n=1) unknown.
Adult PROMIS-29 scores indicated that burden of disease for people with severe HAwoI in all domains was similar regardless of treatment class. Median scores (interquartile range) by treatment class, SHL (n=46)/EHL (n=36)/NFT (n=62), were 44 (38–57)/46 (41–57)/44 (39–57) for physical functioning, 48 (44–56)/52 (49–64)/52 (46–58) for social roles and activities, 56 (54–58)/56 (54–58)/58 (54–60) for sleep disturbance, and 59 (52–64)/56 (50–60)/56 (42–61) for pain interference. Similar results were observed for people with severe HBwoI, SHL (n=5)/EHL (n=21), at 46 (42–51)/48 (39–57) for physical functioning, 54 (50–60)/56 (46–64) for social roles and activities, 58 (57–60)/56 (54–58) for sleep disturbance, and 56 (53–57)/52 (42–61) for pain interference.
In response to two independent survey questions, people with severe HAwol (SHL [n=59]/EHL [n=64]/NFT [n=91]) reported feeling anxious (39%/38%/30%) or worried (34%/34%/26%), at least sometimes, that their treatment might not adequately protect them from bleeds. Corresponding responses for 45 people with severe HBwoI (SHL [n= 9]/EHL [n=36]) were 22%/22% (anxious) and 33%/31% (worried). The mean [SD] number of self-reported bleeds from people with severe HAwoI in the 12 months before the survey or since therapy switch was 6.8 [6.1] (SHL, n=59), 6.6 [9.7] (EHL, n=64), and 2.3 [4.2] (NFT, n=91). Corresponding mean [SD] self-reported bleeds from people with severe HBwoI were 3.2 [2.8] (SHL, n=9) and 4.8 [5.8] (EHL, n=36).
Conclusion: Assessing treatment burden using standard tools is an important part of comprehensive care to individually optimize care and outcomes. Irrespective of treatment class, individuals with severe hemophilia woI continue to experience physical burden from the disease, manifested as pain, sleep disturbances and psychological burden of anxiety, and worry about breakthrough bleeds.

Sickle Cell Disease

Title: Motivators and Barriers for People with Sickle Cell Disease Participating in Clinical Trials: United States Findings from the LISTEN Survey

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Abstract

Introduction: Recruitment and retention of a large and broad group of participants is imperative for the success of clinical trials and the development of new therapies for sickle cell disease (SCD). The Learnings and Insights into Sickle Cell Trial Experiences (LISTEN) Survey was developed to deepen understanding of the motivators and barriers in the recruitment of people with SCD (PwS) for clinical trials. This sub-analysis focuses on the results from the US.

Methods: A diverse group of adults (≥18 years) with SCD and health care professionals (HCPs) involved in the treatment and/or clinical research of SCD from 17 countries completed a quantitative survey between Oct 2022 and June 2023. PwS rated and ranked the importance of specified factors to consider when deciding whether to participate in a clinical trial, and HCPs rated and ranked their perceptions of PwS beliefs on those factors. Factors were grouped into 5 categories (impact on daily life, treatment impact, trial outcomes, trial information, and other sources of information and influence), rated on a 7-point scale from "not at all" to "extremely important," and ranked from most to least important. The perspectives of PwS and HCPs were compared, and the results presented include the total proportion of respondents who rated factors as "very" or "extremely" important and the factors that were ranked within the top two in each category.

Results: Of 1145 PwS who completed the global LISTEN survey, 193 were from the US (USPwS). Of 193 USPwS, 67% were female with a mean age of 33 years. Almost all USPwS expressed being negatively impacted by SCD, and only 5% reported the disease does not limit them at all. Of USPwS, 40% had taken part in clinical trials for SCD, and the majority had a positive experience. Of 361 global HCP respondents, 76 were from the US (USHCP) with an average of 21 years of experience treating PwS. Of USHCPs, 43% had taken part in clinical trials for SCD, and the majority had a positive experience. For factors relating to impacts on daily life, both USPwS and USHCPs ranked highly the "potential to miss school/work or lose income" (44% USPwS, 45% USHCPs) and "additional travel requirements" (40% USPwS, 49% USHCPs); however, a significant difference was noted on the importance of the "potential to see a SCD specialist more often" (41% USPwS v 29% USHCPs, P=0.067) as "very" or "extremely" important. For factors relating to treatment impact, both USPwS and USHCPs rated the "potential to better manage their symptoms" (56% USPwS, 55% USHCPs) and "opportunity to try a therapy that might work better" (53% USPwS, 51% USHCPs) as "very" or "extremely" important. However, USHCPs significantly underestimated "the trial treatment might have different side effects than their current treatment" (54% USPwS v 32% USHCPs, P=0.001), which was the second most important factor for patients in absolute terms. For factors relating to wider clinical trial outcomes, compared to USPwS responses, USHCPs significantly underestimated the importance of all 5 categories: "feeling that

they are supporting new treatment developments that may benefit them" (62% v 22%) "or benefit others" (62% v 22%), "to increase self-knowledge about SCD" (63% v 22%), "the opportunity to receive their own data" (51% v 21%), and "the possibility of receiving treatment regularly after the trial" (47% v 33%). For sources of information, USPwS identified that "HCPs" were the most common channel through which they learn about clinical trials; however, "other PwS" (52%) was their most trusted source. USHCPs also reported referring patients mainly to the "pharmaceutical company sponsoring the trial" (54%) or to "hospitals/medical centers" for SCD trial information (47%), as opposed to referring patients to "other PwS" (18%), whom USPwS trust the most.
Conclusions: Findings from the US sub-analysis of the LISTEN Survey highlighted not only areas of absolute and relative importance of different barriers and motivators, but also areas of significant disconnect between the perspectives of USPwS and USHCPs. USPwS responses suggested USHCPs should place greater emphasis on wider clinical trial outcomes and more deeply discuss potential side effects, travel requirements, and time missed from school/work. These insights can be used to improve the delivery of clinical trial information to enhance patient recruitment and ensure that future clinical research outcomes benefit the needs of the SCD community.

Title: How People with Sickle Cell Disease Rate Motivators Is Associated with the Likelihood of Wanting to Participate in a Clinical Trial: Findings from the Global Listen Survey
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Abstract
Background: The success of clinical trials for sickle cell disease (SCD) and global generalizability of the results rely on securing a sufficiently large and diverse participant pool. The global Learnings and Insights into Sickle Cell Trial Experiences (LISTEN) Survey investigated the attitudes towards SCD clinical trial participation among people with SCD (PwSCD). The survey identified several motivators and barriers affecting decisions to participate in clinical trials. The importance of individualized communication to improve clinical trial access and recruitment was a key finding of the LISTEN Survey (James J *et al. Blood* 2023;142[Suppl 1]:2498).
Aim: In this LISTEN Survey analysis, we investigate how demographics, characteristics, and factors representing the experiences and attitudes of PwSCD may impact the likelihood of wanting to participate in an SCD clinical trial.
Methods: Between October 2022 and August 2023, adults with SCD (≥18 years old) from 17 countries completed a quantitative survey. The survey assessed the importance of motivators (e.g., better manage symptoms or increase knowledge of SCD) and barriers (e.g., different side effects or missing work/school) that affect decisions to participate in a clinical trial by rating them on a 7-point scale. Using regression analysis, we investigated the association between

contextual factors and responses to the survey question, “In general, how likely do you think you are to want to take part in a clinical trial for SCD?” (rated on a 5-point scale from very unlikely to very likely). Contextual factors included demographics and characteristics such as gender, living location, having dependents, life satisfaction, financial situation, and treatment preferences. Additional contextual factors were derived from factor analysis, grouping responses to multiple questions into categories including importance of motivators, importance of barriers, impact of symptoms on daily life, frequency of receiving SCD care and information, frequency of pain management, trust and relationship with
healthcare professionals (HCPs), frequency of interaction with the SCD community, and usefulness of SCD information. Key contextual factors identified from the regression analysis were analyzed further.
Results: A total of 1,145 PwSCD (58% female) with a median age of 30 years(interquartile range: 24–38) participated in the LISTEN Survey. Of these, 67% (n=772)had never been invited to participate in an SCD clinical trial. When PwSCD were asked how likely they would be to want to participate in a clinical trial, 13% of respondents(n=146) were very unlikely, 10% (n=118) were unlikely, 23% (n=269) were neither likely nor unlikely, 36% (n=408) were likely, and 18% were (n=204) very likely. Regression analysis revealed that how PwSCD rated the importance of motivators had the greatest association with the likelihood of wanting to participate in a clinical trial (standardized regression coefficient [β]=0.38; $p<0.01$). Other positively associated contextual factors were frequent interaction with the SCD community (β=0.12), living ina rural location (β=0.11), preferring to receive a different treatment (β=0.09), and frequently receiving SCD care and information (β=0.08; all $p<0.01$). How PwSCD rated the importance of barriers was not associated. Reporting a comfortable financial situation was negatively associated with the likelihood of wanting to participate in a clinical trial (β=−0.08; $p<0.05$). Further analysis indicated that the importance of certain motivators was higher among those educated to at least university degree level than those not educated to university degree level. Few differences in the importance of motivators were observed based on household income and rural living location.
Conclusions: HCPs, industry and patient organizations should be aware that individuals’ perceptions of the positive aspects of clinical trials in SCD may affect their decision to participate. This awareness is crucial, as 23% of PwSCD who responded to the LISTEN Survey were undecided about participating in a clinical trial, highlighting a need to raise awareness and understanding of clinical trials. Ensuring clinical trial opportunities are accessible to all PwSCD and understanding the reasons that motivate individuals may improve participation in SCD clinical trials.

Title: Large Scale Analysis of the Real-World Association between Fetal Hemoglobin and Vaso-Occlusive Crises in Sickle Cell Disease

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Abstract

Background: Fetal hemoglobin (HbF) attenuates the rate of vaso-occlusive crises (VOCs) in sickle cell disease (SCD), but exact quantification is lacking.

Methods: We analyzed two large historic datasets with contemporary statistical methods. Data, acquired through BioLINCC, were the Cooperative Study of SCD (CSSCD; USA, 1979-1988) and the Multicenter Study on Hydroxyurea (MSH; USA and Canada, 1992-1995).

The CSSCD had 3 planned HbF assessments: baseline, 1 stannual visit, 2 ndannual visit.We included those aged ≥12 years with at least one HbF measurement at baseline, 1st,or 2 ndannual visit (1395 unique individuals, median age 22 years). Follow-up was up to8 years post baseline. We analyzed the data using one of three approaches: baseline HbF and all follow-up; three HbF readings and one year of follow-up after each visit; three HbF readings and all follow-up up to next visit or follow-up end. For the MSH (HbSS genotype, age ≥18 years, ≥3 VOCs within the pre-trial year, 299 unique individuals, median age 29 years), we used HbF at randomization in the placebo arm and after titration in the hydroxyurea (HU) arm. Placebo participants were offered HU after early trial termination and their follow-up was censored then. HbF was analyzed as a percentage of total hemoglobin. In the MSH data, F-cells (as a percentage of red blood cells [RBC]) were additionally analyzed. F-cells were averaged over follow-up.

We used directed acyclic graphs for confounder identification and negative binomial generalized additive models to allow the data to suggest the functional relationship between HbF and the VOC rate. A straight line suggests a linear effect of HbF% on logVOC rate and implies that each percentage point (%pt) increase in HbF or F-cells reduces the VOC rate by a fixed percentage.

We regressed VOC rate during follow-up on HbF and adjusted models for age at baseline, sex, ethnicity, and when applicable for β-globin haplotype, assigned treatment (HU/placebo) and received HU dose.

Results: HbF showed a linear protective effect on log VOC rate in two of the CSSCD analyses and a non-linear progressive effect for the remaining analysis: each additional %pt increase in HbF reduced the VOC rate by a slightly larger percentage. When fitting linear models, each %pt increase in HbF was associated with a 4% (95% CI**:** 2-6%) to6% (95% CI**:** 3-8%) reduction in VOC rate.

For MSH data, each %pt increase in HbF was associated with an 8% (95% CI: 4-11%) reduction in VOC rate. The model suggested that the reduction per %pt increase in HbF depended on the level of HbF%, with a larger reduction in VOC rate the higher the HbF%. We found no evidence of change in VOC rate up to 35% F-cells. Above 35% F-cells, there was increasing protection against VOCs. Individuals with ≥70% F-cells had less than half the VOC rate of those with 35% F-cells.

Results did not change when the models were adjusted for total hemoglobin.
Interpretation: The results show that each %pt increase in HbF has a protective effect on VOC rate, which was larger for higher HbF% in two analyses. Since HbF intercalates in HbS polymerization, VOC rate may be driven by HbF/HbS ratio. Hence, increasing HbF% would be progressively more effective through the numerator effect in HbS (like odds).
These data further highlight the importance of HbF distribution across RBC, as VOCs occurred at a progressively lower rate for F-cells >35%. HbF content varies also among RBC that fail the F-cell threshold (6pg), and a small number of sickle RBC may suffice to cause a VOC.
Translation of these data from its geographic reach to a current, global setting may be limited. However, data from a recent small study on HU in India suggested an upper limit of 9% VOC reduction for every %pt increase in HbF, if all protective effect of HU comes from HbF induction. This corresponds well with the 4-8% reduction in VOC rate found here. The CSSCD remains the largest real-world study on SCD, which contributes pre-treatment data, and the MSH yielded comparable results.
Conclusion: This large real-world study on prospectively collected data confirms the direct relationship between HbF and VOC occurrence. Further, our results suggest that one %pt increase in HbF% may be more beneficial for patients with a higher starting HbF%. These results highlight the importance of HbF distribution across the RBC population with a focus on HbF as an important SCD therapy target. Repeating the study on data of greater geographic reach would strengthen the interpretation.

Title: Etavopivat Reduces Incidence of Vaso-Occlusive Crises in Patients with Sickle Cell Disease: Hibiscus Trial Phase 2 Results through 52 Weeks
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Abstract
Background: Etavopivat is a potent, selective, once-daily, orally bioavailable activator of the red blood cell (RBC) pyruvate kinase isozyme, decreasing 2,3DPG levels and increasing ATP levels in RBCs. In a phase 1 study, treatment with etavopivat in patients with sickle cell disease (SCD) resulted in a rapid and sustained increase of hemoglobin (Hb) levels and decreased markers of hemolysis over 12 weeks (Saraf S et al*. Blood Adv* 2024). HIBISCUS(NCT04624659) is a multi-cen-

ter, phase 2/3, randomized, double-blind, placebo (PBO)-controlled trial investigating the efficacy and safety of etavopivat in SCD. Here we report 52-week data from the phase 2 part of the trial.

Methods: Participants were aged 12–65 years, with any SCD genotype, Hb level ≥5.5 to ≤10.5 g/dL at screening, and 2–10 vaso-occlusive crises (VOC)
requiring a medical setting visit in the previous 12 months. Participants were randomized 1:1:1 to blinded oral etavopivat 200 mg, etavopivat 400 mg, or PBO, once daily for 52 weeks. Permitted standard of care included stable dosing with hydroxyurea (HU; ≥90 days prior), crizanlizumab, or L-glutamine (≥12 months prior). Primary study endpoints were annualized, independently adjudicated VOC rate over 52 weeks and Hb response (>1 g/dL increase from baseline [BL]) at Week 24. The primary efficacy analysis is reported for the intent-to-treat (ITT) population. We also report the analysis for the per-protocol (PP) population, defined as ≥80% protocol compliance and completion of the double-blind period with no major protocol deviations. Hemolysis biomarkers (absolute reticulocyte count, indirect bilirubin and lactate dehydrogenase [LDH]), and patient-reported outcome measures (PROMIS Fatigue Scale) were assessed.

Results: Sixty participants (19 male [32%], 7 adolescents [12%], 54 HbSS genotype [90%]) were randomized to receive etavopivat 200 mg (n=21), etavopivat 400 mg (n=20), or PBO (n=19). Mean (SD) age was 33.5 (13.7) years and BL Hb level was 8.4 (1.16) g/dL. Mean (SD) number of VOCs in the previous 12 months was 3.3 (1.78). Concomitant HU was used by 16 (76%),13 (65%) and 14 (74%) participants in the etavopivat 200 mg, 400 mg, and PBO groups, respectively. Six participants in each etavopivat group and 3 in the PBO group discontinued the study drug early (2 in the 200 mg group secondary to an adverse event [AE]).

In the ITT population, annualized VOC rates were 1.07 for the etavopivat 200mg group, 1.06 for the 400 mg group and 1.97 for PBO. VOC rate ratios for etavopivat:PBO (95% CI; % reduction) were 0.55 (0.24, 1.26; 45.7%) for the 200mg group and 0.54 (0.23, 1.26; 46.2%) for the 400 mg group. Median time to first VOC was 33.6 weeks for each etavopivat group and 16.9 weeks for PBO. Hb response at Week 24 was 38% (n=8/21) in the 200 mg group, 25%(n=5/20) in the 400 mg group and 11% (n=2/19) in the PBO group. Hb response with etavopivat was seen early by Week 2 and was maintained over52 weeks.

In the PP population, annualized VOC rates were 0.66 (n=13) for the 200 mg group, 0.7 (n=12) for the 400 mg group and 1.77 (n=15) for PBO. VOC rate ratios (95% CI; % reduction) were 0.37 (0.16, 0.85; 62.7%) for the 200 mg group and 0.39 (0.17, 0.90; 60.5%) for the 400 mg group. Hb response at Week 24 was 46% (n=6/13) in the 200 mg group, 33% (n=4/12) in the 400 mg group and 13% (n=2/15) in the PBO group. Mean change from BL Hb levels at Week 24 were 1.11 g/dL (n=8) for the 200 mg group, 0.73 g/dL (n=10) for the400 mg group and 0.15 g/dL (n=14) for PBO. In the ITT population, all hemolysis biomarkers decreased from BL in both etavopivat groups at Week 24; with the LDH decrease sustained through Week52. PROMIS Fatigue Scale showed improvements for participants receiving
etavopivat. Most reported AEs in any group were mild to moderate and resolved without action. Serious AEs, all of which resolved, were reported by 5participants in the etavopivat 200 mg group (1 hepatic enzyme increase possibly drug related), 4 in the 400 mg group (1 Hb decrease possibly drug related) and 3 in the PBO group; 1 cerebrovascular accident unrelated to therapy occurred in the 200 mg group. Insomnia was reported by 3participants in the 400 mg group.

Conclusions: Compared with PBO, etavopivat reduced annualized VOC rate through Week 52, increased Hb levels at Week 24, and improved hemolysis markers and patient-reported fatigue, consistent with potential clinical benefit. Etavopivat was well tolerated. Based on the totality of data, proof of concept was established for etavopivat in SCD.

Title: Characterizing People with Sickle Cell Disease Who Share Attitudes Regarding Clinical Trial Participation: Findings from the Global Listen Survey

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Abstract
Background: Recruiting a sufficiently large and diverse pool of participants is critical to the success and global generalizability of clinical trials for sickle cell disease (SCD). The Learning and Insights into Sickle Cell Trial Experiences (LISTEN) Survey was a large international survey that investigated the global attitudes of people with SCD toward clinical trial participation. The survey identified several motivators and barriers that may affect a person's decision to participate in a clinical trial and highlighted the importance of individualized communication to improve access and recruitment. To understand survey responses, participants with similar attitudes were grouped into five distinct groups (archetypes) defined by their responses to questions about motivators and barriers to trial participation (James J *et al. Blood* 2023;142[Suppl 1]:2498).
Aim: To further characterize the five patient archetypes identified from the LISTEN Survey, to understand how a person's situation, impact of SCD on their lives and relationship with the healthcare system may affect their attitudes to clinical research participation.
Methods: Between October 2022 and August 2023, people with SCD (≥18 years old) from 17 countries completed the global LISTEN Survey. The survey included general background questions and assessed the perceived importance of factors that affect decisions to participate in a clinical trial. A hierarchical cluster analysis was used to identify patterns in responses to survey questions and organize into archetypes of people with SCD who shared similar attitudes. Five archetypes were identified and based on the responses could be described as treatment motivated (TM, primarily motivated by the opportunity to try a new treatment and less concerned about most barriers), practical minded (PM, primarily motivated by potential to better manage symptoms but concerned about practical barriers), care motivated (CM, primarily motivated by access to SCD specialists and investigational treatment after the trial),uncertain (UN, concerned about most barriers, in particular the risk that trial treatment
may be inferior), and risk averse (RA, highly concerned about the risk of side effects). These archetypes were further characterized according to respondent demographics, regional distribution and treatment received. Differences in the distribution across the archetypes were assessed using a chi-squared test.

Results: A total of 1,145 adults with SCD (58% female) with a median age of 30 years completed the survey. Of these, 980 could be defined in an archetype: 22% TM, 14%PM, 6% CM, 23% UN and 20% RA.
Demographically, the five archetypes were well balanced for mean age (30–33 years), proportion living in rural areas (15–18%), burden of SCD (13–19% with high burden) and education level (33–37% completing higher education). Differences across the archetypes were observed for household income (65% TM, 64% PM, 78% CM, 53% UN and 53% RA had income in the lowest three brackets per country; $p<0.05$) and gender (61% TM, 63% PM, 45% CM, 61% UN and 53% RA were female; $p<0.05$).
The distribution of archetypes differed across geographical regions. Each archetype was represented in every region and no single archetype was dominant in a specific region. The archetype distributions by region were as follows: North America (n=222)31% TM, 17% PM, 2% CM, 23% UN and 27% RA; South America (n=113) 25% TM, 19%PM, 7% CM, 33% UN and 16% RA; Europe (n=213) 23% TM, 12% PM, 4% CM, 34% UN and 28% RA; Sub-Saharan Africa (n=262) 25% TM, 20% PM, 10% CM, 28% UN and 17%RA; India (n=58) 43% TM, 16% PM, 3% CM, 2% UN and 36% RA; Middle East and North Africa (n=112) 16% TM, 15% PM, 15% CM, 32% UN and 21% RA.
The archetypes were well balanced for trust in healthcare professionals (60–66%) and whether respondents received blood transfusions (27–40%) or no treatment at all (1–4%). The proportion of respondents who received treatment to reduce or alleviate SCD symptoms differed across archetypes (64% TM, 73% PM, 82% CM, 68% UN and 67%RA; $p<0.05$).
Conclusions: Few differences in demographic and other characteristics were observed between groups of people with SCD defined by shared attitudes to clinical trial participation. This suggests that determining a person's attitude is complex and underscores the importance of adopting personalized approaches to understand what factors may motivate or discourage an individual to participate in a clinical trial.

Title: Noninvasive, Accessible, Smartphone App for at-Home Hemoglobin Monitoring in Sickle Cell Disease

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Abstract

Background: Anemia is a widespread health issue impacting more than 2 billion people worldwide. In sickle cell disease (SCD), which impacts more than 100k individuals in the USA, severity of anemia is associated with development of complications, end organ damage, and poor quality of life. The gold standard test for hemoglobin (Hgb) monitoring is the complete blood count, which is invasive and costly. Therefore, we developed and launched a smartphone app that

measures Hgb levels using fingernail pictures. This app is noninvasive, inexpensive, patient-supported, easy to use, and accessible, having been downloaded more than 200,000 times across the USA with thousands of active users per month and more than 1.4 million tests taken since launch in Dec 2021. Here we investigated its utility as a Hgb monitoring tool for people with SCD. This investigational app has not been reviewed or approved for SCD by the FDA.
Methods: We enrolled 35 participants (26 Female/8 Male, 35 years old ±7 years) diagnosed with SCD (26 Hgb SS, 6 Hgb SC, 2 Hgb Sb + thalassemia, 1 unknown) in 3 cities (Atlanta, Houston, and Washington D.C) for this investigational study. No participants were excluded from the study due to presence of nailbed discoloration or limited technological competence regarding smartphone use. The study consisted of up to 4 site visits across a total of 8 weeks. At each visit, participants took an app test and received a fingerstick Hgb test for calibration. In between visits, participants took app tests every other day and recorded their symptoms and medications in the app. Finally, participants took usability and acceptance surveys upon completion of the study.
Results: In this study, we found the mean absolute error (MAE) of the test to be ±0.9 g/dL (R= 0.6, root mean squared error = ± 1.2 g/dL, 95% limits of agreement = ±2.3 g/dL), which is within the range of accuracy accepted by the FDA. Despite the variability introduced by a significantly anemic population and self-testing in a variety of locations and background lighting conditions, these results are similar to our previously published results obtained in clinical settings (Mannino *et. al.*, *Nature Communications*, 2018). 10 participants took hydroxyurea (HU) throughout the study, which can cause fingernail discoloration, and 3more participants took disease modifying drugs that do not discolor fingernails (Voxelotor, Crizanlizumab, L-glutamine). The MAE in the participants who took HU was 0.2g/dL greater (±1.0 g/dL) than in those not taking any disease-modifying drug (±0.8 g/dL). However, the MAE of the HU group was still within the accepted deviation range. Furthermore, the MAE of the 3 participants who took the non-nail discoloring drugs was±0.7 g/dL, which coupled with low sample size, does not suggest a significant impact of these drugs on app results. In addition to accuracy, we noticed that app Hgb levels correlated with presence of anemia related symptoms. In tests where users reported symptoms in the app, Hgb levels were significantly different on average 8.3 g/dL, compared to 8.7 g/dL when participants did not report any symptoms (P = 0.04). This suggests that the app was able to pick up small changes in Hgb level when participants felt worse. Study participants were eager to use the app, with 100% of participants taking more than 11 test over the duration of the study, and 91% of participants taking more than21 tests. Moreover, these participants indicated that they had a positive experience with the app, with 13 indicating they took action based on Hgb measurements resulting in better management of their health. 97% of the participants indicated that they would like to incorporate the app as part of their daily routine after completion of the study. Despite these overall positive results, this study was limited by reliance on self-reporting of symptoms as well as unsupervised app use. This resulted in some protocol deviations that likely introduced variability into the data and forced the exclusion of 2 participants from data analysis.
Conclusion: The correlation between symptoms and Hgb levels calls for future research to better understand the relation of reported symptoms, including vaso-occlusive pain events and Hgb. Overall, the degree of accuracy reported and the correlations between SCD symptoms and Hgb

suggest that this noninvasive app is a useful tool for individuals suffering from SCD including users of HU to frequently monitor their Hgb levels, empowering them to better self-manage their condition.

Title: Etavopivat Increases Arterial Hemoglobin-Oxygen Saturation during Moderate and Severe Hypoxia: A Mechanistic Phase 1 Trial in Healthy Volunteers

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Abstract
Background: Maintaining oxygen delivery during conditions of hypoxia is important, particularly for patients with hemoglobinopathies. Evidence in comparative physiology indicates that high hemoglobin-oxygen (Hb-O2) affinity serves as a beneficial hematological adaptation to chronic hypoxia exposure. The improved hypoxia tolerance is likely due to an increase in arterial oxygen saturation with high Hb-O 2affinity. However, the relationship between high Hb-O 2affinity and hypoxia tolerance in humans is not well understood. Etavopivat is a potent, selective, once-daily, oral activator of the red blood cell (RBC) pyruvate kinase isozyme (PKR), with a half-life of ~13hours, under investigation for the treatment of sickle cell disease (SCD) and other hematological conditions. Etavopivat has a multimodal mechanism of action in RBCs by decreasing 2,3-diphosphoglycerate (2,3-DPG) levels to increase Hb-O 2affinity and increasing adenosine triphosphate (ATP) levels to improve RBC health. In Phase 1 trials etavopivat increased Hb-O 2affinity in healthy volunteers (HVs; Forsyth et al. *Clin Pharmacol Drug Dev* 2022) and patients with SCD (Saraf et al. *Blood Adv* 2024) in room air.
Aim: To investigate arterial oxygenation changes with etavopivat under conditions of moderate and severe hypoxia in HVs.
Methods: HVs visited the laboratory for assessments at baseline and following 7 days of etavopivat exposure (400 mg once daily). Participants completed rhythmic handgrip exercises (rest, 10% and 20% maximum voluntary contraction [MVC]) during graded hypoxic exposure, breathing room air (21% O2), moderate hypoxic gas (15% O2), and severe hypoxic gas (10%O2), resulting in acute duration (~12 minutes) of exposure to each level of hypoxia. Hb-O 2affinity was assessed by partial pressure of oxygen at 50% Hb saturation (P50), measured using dual-wavelength spectrophotometry at a standardized pH (~7.4) and temperature (37 ºC). Arterial catheterization was used to collect samples for fractional oxygen saturation (FO2Hb) and Hb and to measure arterial blood pressure. Blood gases were analyzed after 5minutes of resting exposure to each inspirate, then ~2.5 minutes after commencing each of the 3-minute handgrip exercises (10% followed by 20%MVC). Liquid chromatography-tandem mass spectrometry was used to evaluate 2,3-DPG and ATP levels in whole blood. Data for FO2Hb and heartrate were analyzed using separate repeated measures 2 (treatment) x 3(intensity) ANOVA for each inspirate and all other hematological data pre vs post etavopivat were analyzed using paired-sample t-tests. Statistical significance was set at $P<0.05$. Data presented are mean ± standard deviation.

Results: Sixteen HVs (five women) aged 32 ±8 years were enrolled. After 7days of oral once-daily 400 mg etavopivat, P 50decreased from 28.6 ±1.6 at baseline to 24.8 ±1.3 mmHg (P<0.001). Hb concentration remained unchanged from baseline (14.6 ±1.1 g/dL), post etavopivat (14.5 ±1.1 g/dL;P>0.05). FO2Hb at rest decreased from 96.0% ±0.6 under normal oxygen conditions to 74.6% ±6.7 during severe hypoxic exposure; however, this decrease in FO2Hb was mitigated post etavopivat exposure (79.7% ±5.2,P<0.001). A similar mitigation of the FO2Hb decrease was observed during the handgrip exercise (20% MVC, P<0.001). Concentrations of 2,3-DPG decreased, and RBC ATP increased following etavopivat exposure during both normoxia and moderate hypoxia (P<0.001). Mean arterial pressure was lower post etavopivat exposure under normoxia, but not during moderate or severe hypoxia. Heart rate showed no change post etavopivat exposure during normoxia and hypoxia (P>0.50). Etavopivat was well tolerated with no unexpected adverse events reported.
Conclusions: Etavopivat enhanced FO2Hb during brief hypoxic episodes with an apparent relationship to hypoxia severity for which the greatest improvements were observed at more severe hypoxic exposure. In SCD, high Hb-O 2affinity is beneficial for maintaining Hb 'R' state, thereby reducing the risk of polymerization and associated sickling. Increased Hb-O2 affinity, together with maintenance of a high FO2Hb under hypoxic conditions, demonstrates etavopivat's ability to promote oxygen exchange and subsequent delivery. Together with projected improvement of RBC health, also achieved via PKR activation, this indicates a potential clinical benefit with etavopivat for hemoglobinopathies and beyond.