SUPPLEMENTARY MATERIALS

Evaluation of Longitudinal Pain Study in Sickle Cell Disease (ELIPSIS) by Electronic Patient-Reported Outcomes, Actigraphy, and Biomarkers

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SUPPLEMENTARY METHODS

Study Design

Exclusion Criteria

Volunteers with any of the following characteristics/conditions were not eligible to be included in the study:

1. Marked bone marrow suppression as evidenced by any of the following: severe anemia, neutropenia (ANC <2000 mm^3 WBC), thrombocytopenia (platelet count <100,000 mm^3) within the prior 6 months to Visit 1 (Day 0).
2. History of major surgery within past 3 months.
3. Subjects on chronic exchange transfusion therapy at the time of enrollment
4. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation.
5. Expectation that the subject will not be able to be followed for the duration of the study.

6. Active use of illicit drugs and/or alcohol dependence, as determined by the investigator. Opioid use beyond the amount necessary for pain related to the underlying sickle cell disease as determined by the investigator.
7. Pregnant females.
8. Adult subjects who lack the capacity to consent/assent for themselves.
9. Other severe acute or chronic medical or psychiatric condition, including cognitive impairment that prevents with accurate reporting of pain and/or assessment of Sickle Cell Disease (SCD) symptoms, or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
10. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

Biomarkers and Clinical Laboratories

Blood was collected for biomarkers, clinical and cellular chemistries at home using mobile phlebotomy (Sanquine Biosciences, Inc) or in the hospital if the patient chose medical utilization for a VOC. When a patient reported onset of a VOC pain crisis on the ePRO device, a series of VOC blood collections were scheduled: the first within 24 hours (VOC1), a second the following day (VOC2), and a third sample collection after the VOC had resolved (patient reported 2 consecutive days of not having a VOC,

VOC3). Baseline, non-VOC samples were interrupted and restarted 2 weeks after resolution of the VOC (if blood volumes limits were not exceeded). For every 2-month period, no more than 180 mL of blood was collected from a study participant, which meant that some VOCs blood draws could not be captured. Additionally, there were blood draws that we were unable to obtain due to issues of venous access/poor veins and a small number that were missed because we were not able to arrange the home visit in the window of time allotted. Serum was collected for analysis in a multiplex panel of protein analytes (Myriad RBM, Austin TX). Analytes included: alpha-2-macroglobulin, CD163, E-selectin, granulocyte- macrophage colony-stimulating factor, intercellular adhesion molecule 1, interferon gamma, interferon gamma induced protein 10, interleukin-1 alpha, interleukin-1 beta, interleukin-1 receptor antagonist, interleukin-2, interleukin-3, interleukin-4, interleukin-5, Interleukin-6, Interleukin-6 receptor, interleukin-7, interleukin-8, interleukin-10, interleukin-17, interleukin-18, monocyte chemotactic protein 1, monocyte chemotactic protein 2, monocyte chemotactic protein 4, myoglobin, P-selectin, ST2, T-cell–specific protein RANTES, tumor necrosis factor alpha, vascular cell adhesion molecule-1, and vascular endothelial growth factor. Blood for neutrophil-platelet and monocyte-platelet aggregate number and size was processed and measured as previously described.[1,2] Neutrophil-platelet and monocyte-platelet aggregate number and size were measured as previously described.[1,2] Briefly, within 30 minutes of sample collection, 0.3 mL of citrate-anticoagulated blood was added to 1.2 mL FACSLysing™ solution (Becton Dickinson, San Diego, CA), mixed gently, then refrigerated until analysis. Samples were centrifuged (5 min, 500 x g), and the cells resuspended in 300 µL 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 0.15 M NaCl, 0.5% bovine

serum albumin, pH 7.4. Samples were stained with a mixture of R Phycoerythrin-Cyanin 5.1 (PC5)-conjugated antihuman CD14 monoclonal antibody (directed against the lipopolysaccharide receptor, a monocyte identifier; Beckman Coulter, Carlsbad, CA, USA) and phycoerythrin-conjugated CD42a monoclonal antibody (directed against glycoprotein IX, a platelet identifier; Pharmingen, San Jose, CA, USA) or IgG1kappa (isotype control; Pharmingen). Sample analysis was performed in a FACSCalibur flow cytometer with CellQuest software (Becton Dickinson), as previously described.[1,2] Whole blood was collected in sodium citrate for microfluidic flow-adhesion assays to P-selectin or VCAM-1(Functional Fluidics, Detroit, MI).[3] Whole blood was collected in sodium citrate and the plasma was analyzed for a number of coagulation markers (thrombin-antithrombin complexes, prothrombin fragment 1+2, D-dimer, and clinical laboratory measurements were performed at Detroit Medical Center.

Electronic Report Outcome (ePRO) Device

The e-diary was developed to characterize the patient's VOC experience based in part on previous research conducted in PiSCES and other studies.[4-6] The e-diary also included a pain severity scale, functionality, and fatigue (sample screen shots supplemental Figure 1).[7] Development followed standard qualitative approaches consistent with the U.S. Food and Drug Administration (FDA) regulations for electronic records guidance and input from regulators[7,8] The content for the eDiary was formatted for use on an ePRO device (TrialMax Touch® HTC Touch Desire 320 programmed by CRF Health, Inc) [7]. The device was designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records. The ePRO was a separate device provided to the study participants. Study

participants were trained on the use of both the ePRO devices at the first home visit. Study participants charged the device as needed. Participants or a designated authorized caregiver reporter securely completed the eDiary daily on the ePRO device on the ePRO, without assistance, and data was transmitted to a centralized database. Three consecutive days of non-compliance by either non-use of the Actigraphy or ePRO device resulting in notification of the PI and retraining was provided as needed. Further testing of the eDiary's operating characteristics and construct validation is ongoing.

Actigraphy

Actigraphy monitors continuously measured movement frequency to determine the longitudinal changes activity. Study participants were provided and ActiWatch 2 (Philips Respironics, Bend, OR, USA) and trained on the use on the first home visit. Participants used the ActiWatch 2 device for the entire study duration on a wrist band on the non-dominant hand, excluding periods of charging the device. A new watch was provided every two weeks at non-VOC home visits and the data from the previous watch was uploaded to the data base. The following measures were obtained via a Philips' Rapid Actigraphy Data Analyzer (RADA) proprietary scoring algorithm[9]: average activity counts during active state (average of any valid activity counts in a given interval), peak activity counts during active state (largest of any valid activity counts in a given interval), total rest time during active state (total number of epochs per interval scored as sleep multiplied by epoch length), total sleep time (total number of epochs per interval scored as sleep multiplied by epoch length), sleep onset latency (time required for sleep to start after initiating intent to sleep), sleep efficiency (percent time spent in bed sleeping),wake time after sleep onset or WTASO (total number of

epochs between start and end time of sleep interval scored as wake multiplied by epoch length), fragmentation index or MFI (sum of percent mobile and percent one-minute immobile bouts divided by number of immobile bouts per interval). The raw activity counts were used to evaluate 24-hour activity profile.

Statistical Methods

Statistical methods were defined prospectively and took into consideration the repeated measures within patients. Sample demographics, overall and by SCD (SCD, SC trait, and non-SCD), were summarized using counts and percentages for categorized variables. For all analyses, due to skewed distribution shape, all biomarker and algorithmically derived actigraphy measures were log-transformed. For all ePRO, actigraphy, and biomarker measures the baseline levels were calculated for each subject as mean (for ePRO) or geometric mean (for actigraphy measures and biomarkers) value across all days when a subject did not report having a VOC. The baseline biomarker levels were presented by SCD as geometric means with corresponding 95% confidence intervals (CIs) and were compared between SCD groups using repeated measures ANOVA.

Distribution of crisis occurrence and their characteristics (duration, acuity) were presented using counts and percentages, and graphically. Repeated measures mixed models were used to evaluate change from baseline in ePRO, actigraphy and biomarker measures during crisis, adjusting for subject's baseline value for each measure. For all models, AR(1)[10] variance covariance structure was assumed between observations for each subject, and degrees of freedom were estimated by Kenward- Roger algorithm. Separate models were used to compare any crises and

self-treated crises with non-crisis state. The results of the analyses were presented as an estimate of change from baseline (for ePRO) or percent change from baseline (for actigraphy measures and biomarkers), corresponding 95% CI and p value. Generalized additive models were used to evaluate raw actigraphy counts during 24-hour day cycle in order to compare non-VOC days to days with any crisis, self-treated crisis and crisis with health care utilization. The estimated 24-hour activity profiles were presented graphically.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) or R 3.5.0.[10] In all analyses $P<0.05$ was considered significant and no correction for multiplicity was done.

Supplementary Table 1. Baseline Biomarkers by SCD Status

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Functional Cellular Adhesion							
Monocyte-platelet aggregates, %	32.56 (27.62, 38.38)	23.33 (16.78, 32.44)	19.65 (11.67, 33.09)	0.060			
Monocyte-platelet aggregates, MFI	128.47 (114.91, 143.64)	87.49 (69.16, 110.67)	79.34 (54.71, 115.06)	0.002	0.659	0.016	0.004
Neutrophil-platelet aggregates, %	12.35 (10.38, 14.68)	10.37 (7.32, 14.69)	9.00 (5.19, 15.61)	0.418			
Neutrophil-platelet aggregates, MFI	63.78 (58.59, 69.42)	44.40 (37.10, 53.14)	38.04 (28.64, 50.53)	<0.001	0.362	0.001	0.001
Whole blood adhesion to vascular cell adhesion molecule-1, adherent cells/mm^2	287.68 (236.84, 349.44)	57.01 (39.12, 83.09)	65.35 (36.06, 118.41)	<0.001	0.699	<0.001	<0.001

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
White blood cell adhesion to vascular cell adhesion molecule-1, adherent cells/mm^2	404.17 (377.14, 433.14)	438.65 (376.09, 511.62)	510.24 (400.05, 650.78)	0.145			
Whole blood adhesion to P-selectin, adherent cells/mm^2	28.61 (24.35, 33.62)	13.37 (9.54, 18.72)	21.79 (12.83, 37.01)	0.001	0.125	0.329	<0.001
White blood cell adhesion to P-selectin, adherent cells/mm^2	110.51 (95.09, 128.42)	88.44 (64.16, 121.89)	99.20 (59.73, 164.76)	0.443			
Cellular Blood Counts							
Platelets, k/cumm	337.53 (305.72, 372.65)	290.79 (240.36, 351.79)	213.77 (158.15, 288.94)	0.014	0.089	0.006	0.169
Mean platelet volume, fl	10.17 (9.90, 10.46)	11.03 (10.48, 11.61)	11.88 (10.95, 12.88)	<0.001	0.127	0.001	0.007
Eosinophil, %	2.52 (1.81, 3.52)	1.46 (0.77, 2.78)	3.72 (1.34, 10.35)	0.213			

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Absolute eosinophil count, k/cumm	0.25 (0.18, 0.35)	0.11 (0.06, 0.22)	0.12 (0.04, 0.35)	0.072			
Absolute lymphocyte count, k/cumm	3.33 (2.96, 3.75)	2.28 (1.82, 2.86)	2.54 (1.78, 3.63)	0.011	0.607	0.155	0.004
Lymphocyte, %	33.33 (30.58, 36.33)	35.06 (29.71, 41.38)	45.69 (35.16, 59.38)	0.080			
Absolute monocyte count, k/cumm	1.00 (0.87, 1.14)	0.40 (0.31, 0.52)	0.35 (0.23, 0.52)	<0.001	0.529	<0.001	<0.001
Monocyte, %	10.11 (9.14, 11.19)	5.94 (4.90, 7.20)	6.33 (4.66, 8.58)	<0.001	0.725	0.005	<0.001
Absolute neutrophil count, k/cumm	4.73 (4.23, 5.29)	3.57 (2.88, 4.44)	2.28 (1.62, 3.22)	<0.001	0.031	<0.001	0.025
Neutrophil, %	47.83 (44.69, 51.18)	54.32 (47.69, 61.86)	40.87 (33.27, 50.22)	0.059			
White blood cell, k/cumm	9.95 (9.08, 10.90)	6.54 (5.49, 7.79)	5.59 (4.24, 7.37)	<0.001	0.341	<0.001	<0.001
Red blood cell, m/cumm	2.69 (2.52, 2.88)	4.31 (3.79, 4.90)	4.80 (3.91, 5.88)	<0.001	0.378	<0.001	<0.001
Red cell distribution width, %	20.33 (19.38, 21.32)	14.03 (12.82, 15.36)	13.23 (11.47, 15.27)	<0.001	0.487	<0.001	<0.001

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Nucleated red blood cell, k/cumm	0.09 (0.05, 0.16)	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)	<0.001	0.928	<0.001	<0.001
Immature reticulocyte, %	28.62 (25.58, 32.02)	8.41 (6.76, 10.46)	3.88 (2.75, 5.47)	<0.001	<0.001	<0.001	<0.001
Reticulocyte, %	11.49 (10.02, 13.17)	1.38 (1.07, 1.80)	0.89 (0.59, 1.34)	<0.001	0.074	<0.001	<0.001
Reticulocytes, 1,000/cumm	305.96 (269.77, 346.99)	59.642 (46.84, 75.94)	42.08 28.75, 61.59)	<0.001	0.127	<0.001	<0.001
Hematocrit, %	23.92 (22.68, 25.23)	36.35 (32.89, 40.19)	41.84 (35.71, 49.03)	<0.001	0.138	<0.001	<0.001
Hemoglobin, gm/dL	8.27 (7.83, 8.74)	12.19 (11.00, 13.51)	13.75 (11.69, 16.18)	<0.001	0.215	<0.001	<0.001
Hemoglobin F, %	8.16 (5.81, 11.47)	0.10 (0.05, 0.19)	0.23 (0.08, 0.62)	<0.001	0.168	<0.001	<0.001
Clinical chemistries							
Aspartate aminotransferase, units/L	43.97 (37.75, 51.21)	14.81 (11.10, 19.76)	15.91 (10.09, 25.10)	<0.001	0.791	<0.001	<0.001

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Bilirubin, total, mg/dL	2.44 (2.01, 2.96)	0.31 (0.21, 0.44)	0.34 (0.19, 0.60)	<0.001	0.788	<0.001	<0.001
Lactate dehydrogenase, units/L	528.95 (473.89, 590.40)	206.11 (167.38, 253.80)	202.69 (145.83, 281.71)	<0.001	0.932	<0.001	<0.001
C-reactive protein, mg/L	3.87 (2.97, 5.05)	4.63 (2.77, 7.72)	1.45 (0.64, 3.26)	0.053			
Urea nitrogen, mg/dL	7.52 (6.62, 8.55)	10.25 (8.04, 13.07)	9.89 (6.73, 14.52)	0.054			
Albumin, gm/dL	4.00 (3.88, 4.13)	3.69 (3.48, 3.90)	3.81 (3.48, 4.18)	0.038	0.531	0.311	0.014
Total protein, gm/dL	7.90 (7.75, 8.06)	7.78 (7.49, 8.08)	7.30 (6.88, 7.75)	0.046	0.078	0.015	0.455
Soluble Inflammatory/Cytokines/ Markers							
Soluble E-selectin, ng/mL	20.07 17.10, 23.56)	9.29 (6.88, 12.56)	5.79 (3.59, 9.31)	<0.001	0.097	<0.001	<0.001
Soluble P-selectin, ng/mL	110.05 (99.64, 121.56)	81.02 (67.04, 97.92)	74.76 (55.43, 100.83)	0.004	0.650	0.017	0.006

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Soluble intercellular adhesion molecule 1, ng/mL	92.05 (70.35, 120.44)	73.59 (44.47, 121.78)	59.70 (26.92, 132.36)	0.481			
Soluble vascular cell adhesion molecule-1, ng/mL	947.2 (826.9, 1084.9)	461.4 (357.1, 596.1)	551.0 (367.6, 826.0)	<0.001	0.460	0.014	<0.001
Interleukin-6 receptor, ng/mL	17.28 (15.67, 19.06)	11.71 (9.49, 14.46)	9.57 (6.87, 13.32)	<0.001	0.308	0.001	0.001
Interleukin-10, pg/mL	1.72 (1.56, 1.89)	0.70 (0.58, 0.85)	0.65 (0.48, 0.88)	<0.001	0.684	<0.001	<0.001
Interleukin-18, pg/mL	472.55 (382.25, 584.18)	121.00 (81.21, 180.28)	62.97 (33.53, 118.26)	<0.001	0.085	<0.001	<0.001
ST2, ng/mL	9.79 (8.28, 11.57)	4.02 (2.93, 5.52)	4.45 (2.70, 7.35)	<0.001	0.732	0.004	<0.001
Tumor necrosis factor-alpha, pg/mL	1.78 (1.60, 1.99)	0.93 (0.75, 1.16)	0.93 (0.66, 1.31)	<0.001	0.992	0.001	<0.001
Interferon gamma induced protein 10, pg/mL	258.14 (219.74, 303.25)	121.88 (89.56, 165.87)	93.00 (57.17, 151.29)	<0.001	0.350	<0.001	<0.001

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Monocyte chemotactic protein 4, pg/mL	1383.7 (1097.1, 1745.1)	480.5 (301.3, 766.2)	350.8 (168.2, 731.6)	<0.001	0.473	0.001	<0.001
Interleukin-6, pg/mL	3.39 (2.24, 5.13)	2.20 (1.00, 4.80)	0.92 (0.27, 3.18)	0.116			
Interleukin-1 beta, pg/mL	0.09 (0.08, 0.10)	0.08 (0.06, 0.10)	0.06 (0.04, 0.09)	0.054			
Interleukin-1 receptor antagonist, pg/mL	57.36 (53.07, 61.99)	49.03 (41.63, 57.74)	49.99 (38.65, 64.64)	0.168			
Myoglobin, ng/mL	17.01 (14.65, 19.75)	23.62 (17.73, 31.46)	29.17 (18.55, 45.86)	0.023	0.433	0.027	0.047
Vascular endothelial growth factor, pg/mL	224.20 (173.71, 289.36)	152.14 (93.85, 246.64)	47.91 (22.33, 102.79)	0.001	0.013	<0.001	0.160
Coagulation Markers							
D-dimer, µg/L	1.26 (0.98, 1.61)	0.42 (0.26, 0.66)	0.25 0.12, 0.53)	<0.001	0.259	<0.001	<0.001
Prothrombin fragment 1+2, pmol/L	300.53 (256.56, 352.03)	193.51 (142.81, 262.22)	112.31 (69.51, 181.45)	<0.001	0.060	<0.001	0.013

Biomarker	SCD Geometric Mean (95%CI)	SC Trait Geometric Mean (95%CI)	Non-SCD Geometric Mean (95%CI)	Overall p-value	SC Trait vs. Non-SCD	SCD vs. Non-SCD	SCD vs. SC Trait
Thrombin-antithrombin complex, µg/L	7.11 (6.20, 8.16)	3.11 (2.35, 4.11)	2.40 (1.55, 3.73)	<0.001	0.329	<0.001	<0.001
Tissue factor, pg/mL	29.42 (26.15, 33.10)	36.28 (29.08, 45.27)	22.03 (15.53, 31.25)	0.053			

MFI, mean fluorescence intensity; SC, sickle cell; SCD, sickle cell disease.
SCD (HBSS, HBS-B^0), SC Trait (HbAS) and Non-SCD (HbA)
Changes were not observed in other biomarkers analyzed.

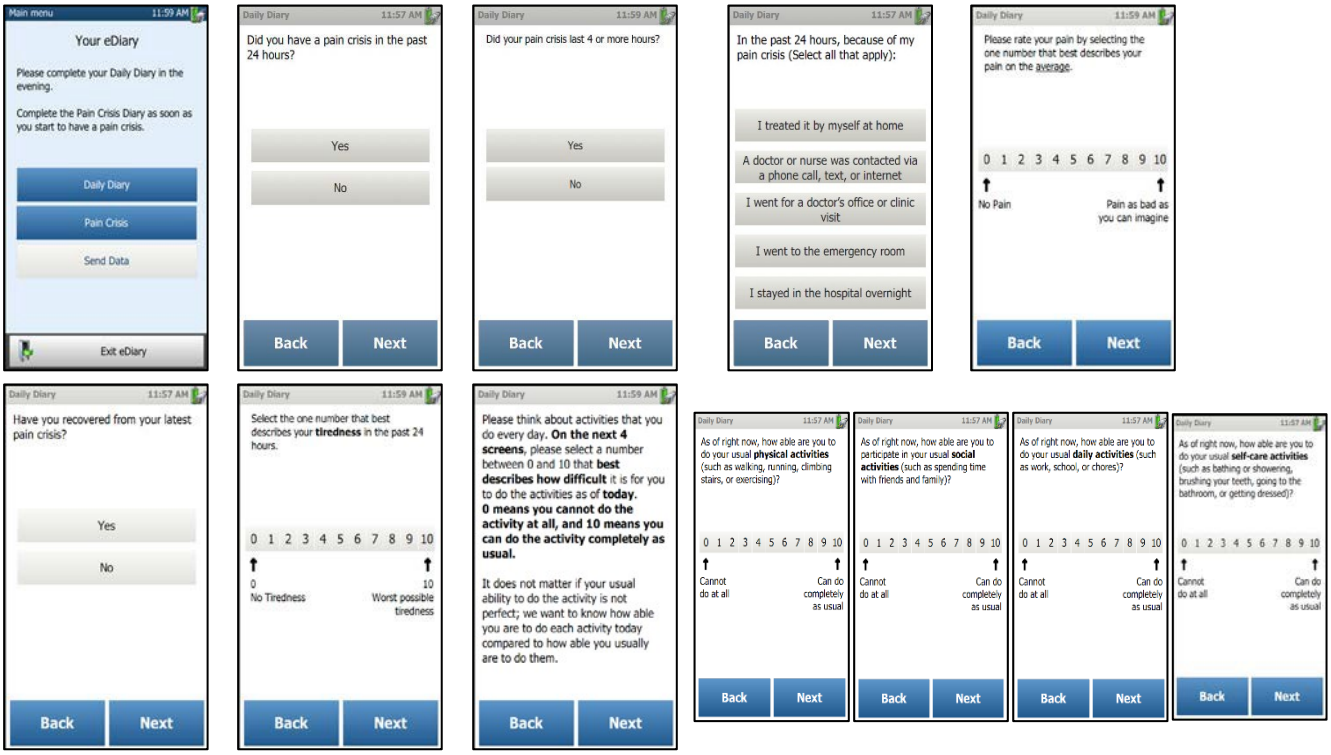
Supplementary Table 2: Actigraphy Measures

Actigraphy Measure	Non-VOC Percent Change (95%CI) Patients = 35, Days = 2265	VOC Percent Change (95%CI) Patients = 15, Days = 159	Change Difference
Active: Duration	0.0 (-1.0,1.1), p=0.923	0.2 (-3.5,4.0), p=0.914	0.2 (-3.7,4.1), p=0.937
Active: Peak Activity Counts	-0.0 (-1.2,1.2), p=0.970	-1.6 (-6.0,2.9), p=0.470	-1.6 (-6.1,3.1), p=0.491
Active: Average Activity Counts	0.2 (-1.5,1.9), p=0.849	-7.1 (-12.5, -1.3), p=0.016	-7.2 (-12.8, -1.3), p=0.017
Active: Total Rest Time	-0.5 (-4.0,3.2), p=0.798	22.2 (7.7,38.7), p=0.002	22.8 (7.8,39.9), p=0.002
Active: Total Active Time	-0.0 (-1.3,1.3), p=0.962	-6.9 (-11.3, -2.3), p=0.004	-6.9 (-11.4, -2.1), p=0.005
Rest: Duration	-0.0 (-1.6,1.6), p=0.996	-6.0 (-11.4, -0.2), p=0.042	-6.0 (-11.6, -0.0), p=0.050
Rest: Peak Activity Counts	-0.0 (-2.1,2.0), p=0.970	-1.4 (-8.7,6.5), p=0.723	-1.3 (-8.9,6.8), p=0.739
Rest: Average Activity Counts	0.0 (-2.8,2.8), p=1.000	7.1 (-3.4,18.9), p=0.193	7.1 (-3.7,19.3), p=0.207

Actigraphy Measure	**Non-VOC Percent Change (95%CI) Patients = 35, Days = 2265**	**VOC Percent Change (95%CI) Patients = 15, Days = 159**	**Change Difference**
Rest: Onset Latency	0.1 (-6.0,6.6), p=0.981	-7.2 (-26.6,17.3), p=0.532	-7.3 (-27.2,18.2), p=0.541
Rest: Efficiency	-0.1 (-0.8,0.7), p=0.886	-0.2 (-2.9,2.6), p=0.908	-0.1 (-2.9,2.8), p=0.941
Rest: Wake Time After Sleep Onset	0.0 (-3.0,3.1), p=0.987	1.0 (-9.8,13.2), p=0.859	1.0 (-10.2,13.6), p=0.867
Rest: Awakenings	0.0 (-2.3,2.4), p=0.995	-7.1 (-14.9,1.4), p=0.100	-7.1 (-15.2,1.7), p=0.111
Rest: Total Sleep Time	-0.0 (-1.6,1.6), p=0.991	-6.7 (-12.1, -0.9), p=0.024	-6.7 (-12.3, -0.7), p=0.029
Rest: Fragmentation Index	-0.1 (-2.4,2.3), p=0.946	-0.1 (-8.2,8.6), p=0.972	-0.1 (-8.4,9.0), p=0.988

VOC, vaso-occlusive crisis.

Supplementary Figure 1. Example ePRO Screen Shots of the E-Diary



The e-Diary questions were asked in 2 different modules. The Daily Diary which included the following 5 forms that were completed daily in the evening in the following order: Daily Diary (VOC/VOCD); Severity Scale for Pain; Tiredness/Fatigue; Functional Activity (RNAQ; Physical, social, daily and self-care activities); and Medication Diary (not shown).

The second module was for an acute onset of a Pain Crisis (sickle cell pain crisis), which was completed once every time the patient started to experience a pain crisis. The eDiary also captured how the subject managed the pain crisis (indirect medical contact, unplanned clinic visit, emergency room visit, overnight hospitalization, or at home).

REFERENCES

1. Charnigo RJ, Beidler D, Rybin D, et al. PF-04447943, a phosphodiesterase 9a inhibitor, in stable sickle cell disease patients: a phase Ib randomized, placebo-controlled study. *Clin Transl Sci.* 2019;12(2):180-188.
2. Gerrits AJ, Frelinger AL, 3rd, Michelson AD. Whole blood analysis of leukocyte-platelet aggregates. *Curr Protoc Cytom.* 2016;78:6 15 11-16 15 10.
3. White J, Lancelot M, Sarnaik S, Hines P. Increased erythrocyte adhesion to VCAM-1 during pulsatile flow: Application of a microfluidic flow adhesion bioassay. *Clin Hemorheol Microcirc.* 2015;60(2):201-213.
4. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med.* 2008;148(2):94-101.
5. Smith WR, Bovbjerg VE, Penberthy LT, et al. Understanding pain and improving management of sickle cell disease: the PiSCES study. *J Natl Med Assoc.* 2005;97(2):183-193.
6. Bakshi N, Stinson JN, Ross D, et al. Development, content validity, and user review of a Webbased multidimensional pain diary for adolescent and young adults with sickle cell disease. *Clin J Pain.* 2015a;31(6):580-90.
7. Andreas M Pleil AM, Barsdorf A, Callaghan, MU et al. Defining vaso-occlusive crises in sickle cell disease from the perspective of the patient: development of a new toolbox to measure treatment outcomes. *Blood.* 2017; 130:3415.

8. Food Drug Administration (FDA). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. *Fed Regist.* 2009;74(235):65132-3.

9. Peterson BT, Anderer P, Moreau A, et al. A novel actigraphy data analysis tool and its application to identifying the optimal threshold value in three subject populations. *Physiol Meas.* 2016;37(7):N49-61.

10. The R Project for Statistical Computing. 2018. Available at: www.R-project.org. Accessed: October 3, 2019.