2nd Sickle Cell & Thalassaemia Virtual Conference

ABSTRACT BOOK

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ABSTRACT BOOK
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The European Hematology Association (EHA), British Society of Haematology (BSH) & Annual Academy of Sickle Cell and Thalassaemia Conference (ASCAT) joined forces again to organize the 2nd Sickle Cell & Thalassaemia Virtual Conference.

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**Word of welcome**

On behalf of the Annual Scientific Conference on Sickle Cell and Thalassaemia (ASCAT), the European Hematology Association (EHA), and the British Society for Haematology (BSH), we are pleased to present our 2022 Abstract Book. This year's theme is ‘Improving the lives of people living with Sickle Cell Disease and Thalassaemia’.

The Annual Scientific Conference on Sickle Cell and Thalassaemia is one of the must attend events of the year for consultants and specialist psychologists, nurses, scientists and all relevant experts. The event is an ideal opportunity to see the latest advances in diagnosis, treatment and emerging fields in haemoglobinopathies. It is an opportunity to interact on the latest advances in clinical care, transition services and emerging new therapies including updates for curative treatment options. Abstract and poster presentations will take place during the three days of this year’s scientific meeting covering key areas in Sickle Cell and Thalassaemia. The accepted abstracts are published in this official HemaSphere supplement.

On behalf of the joint leadership of ASCAT, EHA, BSH, and the esteemed Steering Committee and abstract reviewers, we would like to welcome you to this year’s momentous conference, bringing to you a comprehensive programme on Sickle Cell Disease and Thalassemia; have a pleasant experience.

**Professor Baba Inusa**  
ASCAT President

**Professor Marianne de Montalembert**  
EHA Chair

**Katy Amberley**  
BSH CEO
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S102 OBLIGATE N-TERMINAL BUT NOT C-TERMINAL MONOFERRIC TRANSFERRIN AMELIORATES ANEMIA IN β-THALASSEMIA MICE

Guerra, A.1; Parrow, N.L.2; McVeigh, P.1; Fleming, R.E.2; Ginzburg, Y.Z.2; Rivella, S.4
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Transferrin (TF) is a bilobed 80kD glycoprotein with N- and C-lobe iron binding sites. TF circulates as four forms: unbound to iron (apo-TF), iron bound to the N-lobe (monoferric N-TF), the C-lobe (monoferric C-TF), or to both lobes (diferric-TF). Most circulating TF under physiological conditions is monoferric. The iron-bound TF forms interact with TF receptor-1 (TFR1), which is ubiquitously expressed and serves as the main mechanism for cellular iron delivery. Iron-bound TF also interacts with TF receptor-2 (TFR2) which is expressed on hepatocytes, erythroblasts, and bone cells. Whereas TFRI serves primarily as a cargo receptor, TFRII serves primarily to influence cellular signaling events regulating hepatic iron expression, erythropoiesis, and bone formation. We proposed that different transferrin forms provide differential signaling properties in this regulation. We thus generated TF mutant mice in which all iron-containing TF was either monoferric N (TfmonoN) or monoferric C (TfmonoC). Compared with TfmonoN mice, the TfmonoC mice demonstrated increased RBC production and increased hepcidin expression relative to iron status (Parrow et al. Blood). Based on observations in β-thalassemic mice treated with exogenous TF (Li et al. Nat Med), we hypothesized that β-thalassemic mice obligate for monoN TF would demonstrate improved erythropoietic and iron parameters compared with β-thalassemic mice obligate for monoC TF.

To address this hypothesis, we crossed Hbbth3/+ mice, a mouse model of β-thalassemia intermedia (BT), with TfmonoN and TfmonoC mice. Compared with Hbbth3/+TfmonoN mice, in Hbbth3/+TfmonoC mice demonstrated significantly increased RBC counts, elevated hemoglobin, improved erythrocyte morphology (Figure 1A-B), decreased splenomegaly, fewer bone marrow erythroblasts, and improvement of ineffective erythropoiesis (as measured by the ratio of progenitors to RBC in the bone marrow). Additionally, serum erythroferrone (ERFE) was significantly reduced and hepcidin levels were increased in Hbbth3/+TfmonoN relative to Hbbth3/+TfmonoC controls. Conversely, hematological parameters from Hbbth3/+TfmonoN mice were comparable to Hbbth3/+TfmonoC mice. Similarly, Hbbth3/+TfmonoC mice had no improvements in markers of ineffective erythropoiesis in the bone marrow compared with Hbbth3/+TfmonoN mice.

In summary, we demonstrate that the differential regulatory effects of monoN and monoC TF on erythropoiesis are relevant not only in steady-state, but also in the ineffective erythropoiesis that is characteristic of β-thalassemia. Because both monoN and monoC TF forms can deliver only one iron atom per TF-TFR1 binding event, our findings suggest that the improvements observed only in the Hbbth3/+TfmonoN mice were not due to iron restriction alone. We are now elucidating the mechanisms by which the two TF lobes exert their differential effects on ineffective erythropoiesis and exploring the translational potential of obligate monoN TF in the treatment of β-thalassemia.

References
1. Li et al, Nat Med 2010; 16:177
2. Parrow et al, Blood 2019; 134:1373
**Table. Key eligibility criteria for pts 12-65 y of age**

| Cohort | Key Inclusion Criteria                                                                 |
|--------|---------------------------------------------------------------------------------------|
| A/B    | • >8 RBC units in the 24 hrs before the first etavopivat dose, without a ~35-day transfusion-free period |
|        | • >3 weeks of iron chelation therapy before enrollment                                   |
|        | • Significant infection, hepatic/renal dysfunction                                        |
|        | • History of malignancy/cardiovascular disease, or a drug malabsorption disorder         |
|        | •  Prior/concurrent therapies ≥3 months before the first dose (eg, chronic systemic glucocorticoids, new chelation therapy) |
|        | • Exchange RBC transfusion within the previous 3 months (group A)                        |
| C      | • Hb <10.0 g/dL                                                                       |

| Homologous: RBC/Red blood cell |

**Figure. Study design**

*Table: Etaetopivat 400 mg once-daily orally*

48-wk treatment period

**Primary endpoints**

| Cohort A: Pts with SCD on chronic transfusions (12–20 pts will be enrolled)* |
|---|---|
| Cohort B: Pts with TDT (12–20 pts will be enrolled)* |
| Cohort C: Pts with NTDT (12–20 pts will be enrolled)* |

| Cohort A | Cohort B | Cohort C |
|---|---|---|
| 48-wk treatment period | 12-wk treatment period versus baseline | Hb response at Wk 12: an increase in Hb of ≥1.0 g/dL from baseline |

*A minimum of 12 evaluable pts provides 84% power to detect a significantly greater response rate than 20%, assuming the true response rate is 63%.

*A minimum of 12 evaluable pts provides 80% power to detect a significantly greater response rate than 10%, assuming the true response rate is 55%.

**Novel therapies, gene therapies, bone marrow transplant and emerging diagnostics**

**S104 A SEVERE MOUSE MODEL OF ALPHA-TALASSEMIA SHOWS ABNORMAL IRON METABOLISM, ERETHROPOIESIS AND COAGULATION, AND CAN BE RESCUED BY A NOVEL GENE THERAPY APPROACH**

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**Background:** Clinical presentation of deletional α-thal varies from an asymptomatic condition (one inactivated α-globin gene) to a complete knockout (Hb Bart’s Hydrops Fetalis). In patients with severe α-thal, a blood transfusion independent state is achievable through allogeneic bone marrow transplantation.

**Aims:** The aims of this study are to develop a novel adult mouse model of α-thal and a gene therapy approach for this disease.

**Methods:** We generated adult animals that do not produce α-globin chains (α-KO) through transplantation of homozygous B6.129S7-Hbamtm1Paz/J fetal liver cells (FLC; isolated at E14.5) into WT recipient mice. To generate a gene therapy tool, we screened multiple lentiviral vectors for this purpose.

**Results:** We identified ALS20a, a vector where α-globin is under control of the α-KO promoter and its locus control region, as the most efficient vector.

**Conclusion:** The α-KO animals demonstrate a worsening phenotype, paradoxically showing elevated hematocrit, high reticulocyte count and a high number of red blood cells (RBC) which expressed only β-globin chains. RBC show aberrant morphology and aggregation of β-globin tetramers on RBC membranes. Due to severe inability of these RBC to deliver oxygen, the mice eventually succumb to anemia, showing splenomegaly and other organ pathologies, including vaso-occlusive events, associated with neutrophil infiltration, fibrinogen staining, von Willebrand factor (vWF) release, platelet recruitment and activation. These animals also show iron deposition in the liver and kidney, in agreement with very low levels of hepcidin expression in the liver, and elevated erythropoietin (EPO) in the kidney.

We identified ALS20a, a vector where a-globin is under control of the β-globin promoter and its locus control region, as the most efficient vector. One copy of ALS20a produces exogenous a-globin at a level comparable to that produced by one endogenous a-globin gene. These results suggest that a relatively low VCN could result in dramatic therapeutic benefits.
benefits. Use of ALS20a resulted in correction of the disease phenotype in a dose-dependent manner in a KO mice. At VCN<1 we observe a delay in death proportional to the VCN value, while at VCN>1 we observe phenotypic normalization, including Hb, hepcidin and EPO levels. We tested ALS20a in CD34 cells isolated from four patients with both deletional and non-deletional HbH disease. We measured the change of a/b-globin mRNA ratio (a/bAR) and protein level by HPLC in erythroblasts derived from these cultures. For the specimen with mutational HbH, the initial a/bAR matches that of healthy controls, as the mutations do not eliminate the ability for the gene to produce aberrant mRNA transcripts, and decreased with increasing VCN. Erythroblasts with deletional HbH have a a/bAR approximately 3x higher than normal cells, decreasing in a dose dependent manner with increasing VCN. HPLC detection of HbH (β4), a hallmark of HbH disease, is observed in hemo-
lysis products from all non-transduced a-thal erythroblasts. A ~50% reduction of HbH is detected in the very same specimens upon integra-
tion of ALS20a (VCN between 1 and 2).

Conclusion: We generated an adult mouse model of lethal a-thal and, in preliminary experiments, we rescue it with ALS20a. Furthermore, ALS20a successfully improves a-globin levels in patient cells.

References
1. Harteveld et al, Orphanet J Rare Dis. 2010; 5:13.
2. Mettananda et al, Blood. 2015; 125(24):3694–701
3. Higgs, Cold Spring Harb Perspect Med. 2013; Jan 1;3(1)

S105 ADINNG AZATHIOPRINE/HYDROXYUREA PRECONDITIONING TO ALEMTUZUMAB/TBI CONDITIONING IMPROVES DONOR CHIMERISM IN MATCHED SIBLING DONOR STEM CELL TRANSPLANTATION IN ADULT SICKLE CELL DISEASE PATIENTS

dovren, E1; Aydin, M1; Tang, M1; Suik, L1; van Tuin, C1; Zeerleder, S1; Haizenberg, M1; Biemond, B1; Nur, E1

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only established curative treatment option for sickle cell disease (SCD). In adults, myeloablative conditioning is associated with significant toxicity, primarily due to cumulative organ damage. Matched sibling donor (MSD) transplantation with non-myeloablative conditioning (alemtuzumab/TBI) has shown promising results in adult SCD patients.1,2 Patients treated with this regimen had their sickle cell phenotype corrected with only mild complications and no reports of graft-versus-host disease (GvHD). However, most of the described patients did not reach complete donor chimerism with graft failure rates of 13%. Furthermore, in almost 10% of patients, immunosuppressives could not be withdrawn because of too low T cell chimerism (<50%).3 We hypothesized that adding azathioprine and hydroxyurea as preconditioning to the altemzumab/TBI regimen might improve donor chimerism, reduce the risk of graft failure and improve successful withdrawal of immunosuppressives.

Aims: In this study we prospectively investigate the effects of azathio-
prine/hydroxyurea preconditioning on donor chimerism and graft failure in patients receiving non-myeloablative MSD HSCT for SCD.

Methods: Adult SCD patients who had an HLA-identical sibling donor were eligible for this treatment. After 3 months of azathioprine 150mg qd and hydroxyurea 25mg/kg qd, erythrocyte exchange transfusion was performed on day ~30% with no adverse events related to the investigational product. No severe infectious-related adverse events were reported, except for those related to neutropenia as expected after myeloablative conditioning. Polyclonal vector integrations profile with no evidence of clonal dominance have been detected in all patients with the expected genomic distribution for lentiviral vectors.

Clinical outcome showed a reduction of transfusion requirement both in frequency and volume in adult patients up to more than 50%. Among the pediatric patients, 4 out of 6 discontinued transfusions shortly after gene therapy and are transfusion-independent at the last follow-up (up to 75 months).

A robust and persistent engraftment was observed in 7 out of 9 patients, with a marking of BM progenitors that, in engrafted patients, ranged to 75 months.

Summary and Conclusions: A longer follow-up will provide further results on long-term clinical efficacy and safety of this approach.

References
1. Marktel et al, Nat Med 2019; 25(2):234
endothelial P-Selectin from Weibel–Palade bodies to the cell surface, a process promoting sickle Red Blood Cell (SS RBC) adhesion to vessel walls. Up-regulation of P-selectin contributes to cell–cell interactions, as activated platelets bind to neutrophils to form aggregates in a P-selectin–dependent manner. Previous studies have shown that anti-P-selectin agents decrease SBC RBC adhesion in vivo, increasing microvascular flow, and reducing adhesion of the leukocyte to endothelium, showing the potential of P-selectin as a therapeutic target. In November 2019, the FDA approved the first P-selectin inhibitor, crizanlizumab-tmca (Adakveo, Novartis), to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients with SCD. Different types of P-selectin inhibitors can offer physicians and patients new treatment options enhancing the arsenal of drugs to combat SCD. Inclacumab (Global Blood Therapeutics) is a fully human monoclonal antibody designed to bind to and selectively inhibit P-selectin. Differences in static cell adhesion to P-selectin substrate due to inclucumab were shown previously. The present study aimed to validate the dose-dependence of inclucumab in blocking P-selectin cell adhesion in samples from SCD patients using in-vitro Whole Blood (WB) and Isolated White Blood Cell (I-WBC) assays.

Methods: Five deidentified samples from SCD patients undergoing phlebotomy prior to blood exchange had been collected at the Children’s Hospital of Michigan with Flow Adhesion on P-selectin measured using proprietary assays in both Whole Blood (WB) and in Isolated White Blood Cells (I-WBC), with and without Inclucumab after 5 minutes incubation at room temperature. Microfluidic channels were coated with P-selectin, and I-WBC (5x10⁶/mL) suspension or WB sample diluted 1:1 with phosphate buffer was passed through the channel for 6 (I-WBC) or 10 (WB) minutes at a shear rate of 1 dyne/cm² and pulsatility of 1.67 Hz. The channel was washed for 5 minutes with the same buffer, and the number of cells adhering to the channel surface was quantified.

Results: Incubation of either WB or I-WBC with inclucumab significantly reduced flow adhesion to P-Selectin with the overall inhibition being stronger when assessed on isolated white cells (ab. 35% inhibition on WB vs. ab. 55% on I-WBC after incubation with 40 mM Inclucumab as compared to baseline Flow Adhesion values, Fig. 1). Adhesion on P-selectin showed a pronounced dose response that followed logarithmic response curve, with changes in adhesion with I-WBC better correlated with inclucumab dose, than those measured using WB. Decrease in adhesion on P-selectin was reliably detected at 2 μg/mL treatment dose for 3 out of 5 samples, with dose-dependent decrease in adhesion in all samples at 10 and 40 μg/mL treatment doses (for I-WBC; and similar for WB). For flow adhesion with both WB and I-WBC elevated adhesion at lower doses was observed in some samples.

Conclusions: Both WB and I-WBC adhesion to P-Selectin show a dose dependent inhibition by inclucumab, with clinically relevant doses likely demonstrating greater inhibition. P-selectin adhesion assays described in this study may serve as potential surrogate biomarkers of clinical response tp p-selectin inhibitors, like inclucumab.
SICKLE CELL DISEASE TREATED FOR UP TO 12 WEEKS
DECREASES INTRAVASCULAR HEMOLYSIS IN PATIENTS WITH
S109 ACTIVATION OF PYRUVATE KINASE-R WITH ETAVOPIVAT
Methods: A custom search of the Novartis safety database (comprising PM
and a 12-wk open-label (OL) study to characterize safety and clinical
activity at the maximum pharmacodynamic (PD) dose.
Methods: Completed MD cohorts: 20 pts with SCD were randomized
8:2 to etavopivat (300 mg, then 600 mg) or placebo (PBO) QD for 2
wk. Ongoing OL study: ≤20 pts will receive etavopivat 400mg QD for
12 wks. Assessments: safety, PK, PD, and RBC health. All pts provided
written informed consent.
Results: MD cohorts: (n=17 HbSS, n=2 HbSβthalassemia, n=1 HbSC)
completed enrollment and data unblinded (300 and 600mg etavopivat,
≥12 wks of etavopivat (Table)). These initial findings were sustained in
pts receiving etavopivat for ≥1 wk. AEs were reported in 1/4 (25%) MD PBO pts, most were grade (Gr) ≤3, with 1
Gr4 blood creatinine phosphokinase (CPK) increase. AEs were reported
in 13/16 (81%) etavopivat MD pts, most were Gr1/2 and commonly (n=2)
scluded sickle cell pain (n=6[38%]), headache (n=5[31%]), and
nausea (n=3[19%]). One pt had a serious AE (SAE) of Gr3 vaso-occlusive
(VOC, unrelated) after completing etavopivat. In the OL cohort, AEs were
reported in 7/11 (64%) pts on etavopivat for ≤1 wk. AEs reported in >1
pt were headache and VOC (n=2[18%] each). Most AEs were Gr1/2; 1
pt had SAES of Gr3 acute chest syndrome and VOC (unrelated), 1 pt had
an SAE of Gr3 deep vein thrombosis (possibly related), and 1 pt had an
AE of Gr4 transient blood CPK increase (unrelated). Hematologic and
hemolytic parameters significantly improved at end of Trt (MD and OL
cohorts); 11/15 (73%) evaluable MD pts had a hemoglobin (Hb)
increase ≥1 g/dL over baseline (mean 1.1 g/dL, P<0.004) and markers of hemolysis
decreased (Table). These initial findings were sustained in pts receiving
≤12 wks of etavopivat (Table, Fig.). Of 6 pts who completed 12 wks of
etavopivat, 5 (83%) had >1 g/dL Hb increase over baseline (mean 1.39 g/dL).
Markers of hemolysis decreased. Of 9 pts on etavopivat for >2 wks, 8
(89%) had an Hb increase >1 g/dL, highest mean Hb increase was 1.81 g/dL
during Trt. Etavopivat-treated RBCs from MD pts (n=14) exhibited
improved health, including point of sickling and deformability. Improved
def ormability persisted up to 1 wk after etavopivat in 36% of pts. Results in
initial OL pts were similar. Data on additional pts will be presented.
Summary: Etavopivat 400 mg QD for ≤12 wks was well tolerated, with
a safety profile consistent with underlying SCD. Etavopivat increased sickle
RBC lifespan and significantly improved severe anemia associated
with SCD. These early Phase 1 data show longer-living sickle RBCs
have improved health, which may further reduce the risk of VOCS and
end-organ damage, and support further evaluation of etavopivat in the
Hibiscus Study (NCT04624659).

References
1. Kalfa et al, Blood 2019;134(suppl 1):616
2. Brown et al, Blood 2020;136(suppl 1):19

---

Table: Hemoglobin and Hemodynamic Parameters in Pts With SCD in the MD Cohorts. PBO or Etavopivat 300–600 mg QD for 2 Mths or OL Cohort.

| Parameter | Baseline OL | Change PBO | Change Etavopivat 300 | Change Etavopivat 600 |
|-----------|-------------|-------------|-----------------------|-----------------------|
| Hemoglobin | 8.1 | 1.1 | 1.3 | 1.8 |
| CPK | 177 | 98 | 55 | 43 |
| lactate | 3.4 | 2.7 | 2.3 | 2.4 |

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S109 ACTIVATION OF PYRUVATE KINASE-R WITH ETAVOPIVAT (FT-4202) IS WELL TOLERATED, IMPROVES ANEMIA, AND DECREASES INTRAVASCULAR HEMOLYSIS IN PATIENTS WITH SICKLE CELL DISEASE TREATED FOR UP TO 12 WEEKS

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Background: Etavopivat, an investigational, once daily (QD), selective, erythrocyte pyruvate kinase (PKR) activator, increases PKR activity, resulting in 2,3-DPG and ATP in RBCs of healthy volunteers (HV) and patients (pts) with sickle cell disease (SCD) [1,2].

Aims: Multiple-dose studies in pts with SCD (NCT03815695): 2-wk multiple ascending dose (MD) cohorts to identify the etavopivat QD dose providing maximum PD activity with an acceptable safety profile and

pain events, such as back pain, chest pain and myalgia. Pain events are known adverse drug reactions in the crizanlizumab label, however, pain events occurring during/within 24 hours of crizanlizumab infusion in SUSTAIN were not identified as potential IRRs. For SCD patients, IRR-related pain events may differ in location, severity and/or nature from their usual SCD/VOC pain.

Aims: We reviewed PM data on IRRs presenting as pain events in SCD patients treated with crizanlizumab.

Methods: A custom search of the Novartis safety database (comprising PM reports [spontaneous] and managed access/patient orientation program reports) was performed for reports received in November 2019–June 2021, using ~111 MedDRA terms associated with potential signs/symptoms of IRRs presenting as pain events. IRRs must have occurred during/within 24 hours of the most recent crizanlizumab infusion, and pain could differ from a patient’s usual SCD/VOC. As reports were not gathered via a uniform data collection system, potential limitations include underreporting, incompletely documented cases, or bias towards reporting severe events.

Results: IRRs presenting as pain events were experienced by 28 patients (Table), and most commonly presented as back pain, pain in extremity, arthralgia, musculoskeletal chest pain and headache. Reporting rate was 1.67 cases per 100 patient-years (95% CI 1.11–2.42). Most patients (n=24) initially experienced IRR at the first or second infusion. IRR recurred on subsequent infusion(s) in six patients. Twenty patients (71%) were hospitalized for treatment, including anagliesis, anhitistamines, IV fluids and/or steroids. Nine patients (32%) reported known complications of SCD following IRR (Table). Crizanlizumab was discontinued in 23 patients (82%) after their most recent IRR, including all who experienced secondary SCD complications.

All patients recovered (the majority within 3 days; one with sequelae), except one who died following SCD complications and refusal of blood transfusions for personal reasons. Resolution time was prolonged for patients who reported SCD complications following IRR. Causal analysis of complications was confounded by the underlying disease and use of steroids to treat IRR (systemic corticosteroid exposure in SCD patients has been associated with pain, complications [including severe VOCs and hemorrhagic stroke] and death). We do not know whether the 28 patients had an active VOC or other SCD complications before receiving crizanlizumab.

Summary – Conclusion: Although rare, based on review of PM data, healthcare professionals should be aware of the possibility of IRRs presenting as pain events during/after crizanlizumab infusion. Crizanlizumab label has been updated to reflect this information. Novartis will continue to monitor, manage and prevent IRRs, including a statement recommending caution when using corticosteroids. Given the limited data available regarding IRRs, Novartis is committed to further understanding these events.

References
1. Kang & Saff. J Support Oncol 2007; 5:451–7
2. Rombouts et al, Anticancer Res 2020; 40:1201–18
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S110 ACUTE AND CHRONIC PAIN MANAGEMENT IN SICKLE CELL DISEASE: OUTCOMES OF AN ENGLISH NATIONAL AUDIT.

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Background: Acute pain is the most common complication of sickle cell disease (SCD). Patients suffering severe pain often seek treatment in an acute hospital setting. Feedback from service users indicates a lack of satisfaction with quality of care. NHS England specialised commissioning recommended forming a National Sickle Pain Group (NSPG) consisting of multi-professional stakeholders and patient representatives, to understand the range of practices and challenges in providing high-quality acute pain care.

Aims: The objective was to develop national guidelines for acute and chronic pain management which will improve quality of care, patient experience and outcomes. The aim was to understand the variety of acute and chronic pain management policies and protocols used across England, identify aspects of care where there was unacceptable variation and evaluate the outcomes in scenarios of best practices identified here.

Methods: A questionnaire was developed through discussion meetings with members of the NSPG. This was sent to haemoglobinopathy co-ordinating centre (HCC) leads, to be distributed to all specialist haemoglobinopathy teams (SHTs) and local haemoglobinopathy centres (LHTs) in their network, inclusive of adult and paediatric services.

Results: In total, 56 services (26 paediatric and 30 adult departments), in 39 centres completed the questionnaire (75% response rate). Of these, 51% were LHTs, 15% SHTs and 33% HCCs. The size of services varied between 0 and 808 patients for adult services and 0 and 439 patients for paediatric services. Hospital admissions with vaso-occlusive episode in the year April 2020 to March 2021 for adult services varied between 0 and 754. Admission rates in paediatric services are generally lower. For both adult and paediatric acute pain presentations, the majority of centres provided care in their hospital emergency department (ED), and only a small number offered direct access to a ward (5%) or an ambulatory facility (12%). Ambulatory facilities’ opening days ranged from 5 – 7, with 64% only operating during standard hours. Access to an acute pain service (APS) was available in 83% and 65% for adult and paediatric departments respectively. Generic pain protocols were available in 56 services. The protocols vary, but the most common analgesia prescribed in adults was morphine (oral or subcutaneous or). In children, morphine (oral or intranasal) was widely used. Individual pain protocols were used in 61% of responding centres. The NICE standard ‘<30 minutes time to first analgesia’ were not met in the majority of centres (range 30–60, outliers 80–128min). Overall, the time to first analgesia was lower in services with ambulatory care facilities. The length of stay ranged between 3–5 days. Between 1–5% of the patients experienced a prolonged admission (>21 days). Frequent re-admissions occurred in 2–10% of the patient population (≥3 admissions/year). Education and teaching sessions were infrequently delivered for ED consultants, ED nurses, Acute Medicine consultants and pharmacists (30%, 40%, 21% and 5%).

Summary: Hospital management of acute sickle pain is a significant challenge to NHS services and needs to be re-evaluated.

Conclusion: The questionnaire results will inform the objectives and work plans of four working groups within the NSPG (acute pain, chronic pain, education and research). In order to develop national policies, it will be necessary to generate evidence through a more detailed audit of outcomes in scenarios of best practices identified here.

No references, but a more detailed summary is available.

Summary: Hospital management of acute sickle pain is a significant challenge to NHS services and needs to be re-evaluated at local and national level. Despite publication of NICE guidelines in 2012, few services in the UK currently provide timely pain relief. The range of policies for analgesia management is surprisingly broad.

The availability of ambulatory care in some centres could function as an exemplar for national practice. There may be alternative models of care which could be effective. Patients with frequent attendance and prolonged hospital stay are present in most centres and, although relatively small as a proportion of the service, are especially challenging to manage. The management of these patients requires a multidisciplinary approach and the development of national guidance, as often this is outside the expertise of haematologists. This may be helpful in improving outcomes in this patient cohort.

The infrequent delivery of teaching reveals the need for regular local and national mandatory educational training of all ED staff providing care to SCD patients during acute presentations.

S111 BRAIN PERFUSION CHANGES IN BETA-THALASSEMIA

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Background: Brain involvement in hereditary hemoglobinopathies (e.g. sickle cell disease, beta-thalassemia, spherocytosis) is commonly attributed to anemia-related relative hyperperfusion. Supratentorial and infratentorial vascular watershed regions seem to be especially vulnerable, but data are very scarce.

Aims: We investigated a large beta-thalassemia sample with arterial spin labelling in order to characterise regional perfusion changes and their correlation with phenotype and anemia severity.

Methods: We performed a multicenter single-scan cross-sectional MRI study analyzing non-invasively in 71 beta-thalassemia patients and 56 healthy controls the brain perfusion changes. Clinical phenotype, age, hemoglobin levels, cognitive functioning and parenchymal lesions were also recorded.

Results: Brain perfusion was globally increased in beta-thalassemia patients compared to healthy controls; using age and sex as covariates and scaling the perfusion maps for the global cerebral blood flow, beta-thalassemia patients showed: hyperperfusion in the white matter of the centrum semiovale bilaterally, located in the watershed regions between the vascular territories of the main cerebral arteries (Fig-1a) and in the cerebellar white matter corresponding to the cerebellar watershed regions. Subdividing patients according to anemia severity (hemoglobin level < or > 9.5g/dL), the hyperperfusion clusters persisted exclusively in the subgroup with lower hemoglobin levels.

Summary and Conclusion: The relative hyperperfusion observed in vascular watershed territories does not support the previous hypothesis of a selective parenchymal hypoperfusion in the pathogenesis of brain injury in hereditary hemoglobinopathies. A careful management of anemia severity seems to be pivotal for preventing perfusion dysfunction, at least in beta-thalassemia.

Fig-1. Analysis of brain perfusion correcting for global rCBF. Upper row (panels a,b,c) shows t-maps of significantly globally increased perfusion in patients vs healthy controls (HC). Panel a. contains T-maps of the statistical contrast HC vs. thalassemia patients. Panel b. contains T-maps of the statistical contrast HC vs. transfusion dependent (TDT) thalassemia patients. Panel c. contains T-maps of the statistical contrast HC vs. non-transfusion dependent (NTDT) thalassemia patients.

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Among SCA-children, 138 were transplanted with matched sibling donor, the present study encourages to propose partial vs total splenectomy just before stem cell transplantation in order to preserve splenic function.

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many patients lack a matched donor. Haploidentical (haplo) SCT with post-transplant cyclophosphamide (Cy) has improved the access to SCT. Mitapivat has shown promise in improving hemoglobin (Hb) levels and reducing transfusion burden in patients with sickle cell disease (SCD) and other transfusion-dependent anemias. In FIRST, patients who completed FIRST could enter FIRST-EXT for up to 2 years. Patients previously treated with DFP continued on DFP (DFP-DFP), while those previously treated with DFO were switched to DFP (DFO-DFP). Baseline was defined as the start of FIRST for DFP-DFP patients, and the start of FIRST-EXT for DFO-DFP patients. Efficacy endpoints were yearly changes from baseline in liver iron concentration (LIC), cardiac MRI T2+, and serum ferritin (SF). We also report adverse drug reactions (ADRs), defined as adverse events at least possibly related to DFP. All patients provided informed consent or assent.

Results: Patients (N=134; 89 DFP-DFP; 45 DFP-DFO) were 60.4% male, with a mean (SD) age of 16.2 (8.6) years. Most (85.8%) had SCD; 14.2% had other anemias. At baseline, all patients had elevated (≥1.8 mg/g dry weight [dw]) LIC; all but one had elevated (≥300 µg/L) SF; and all had cardiac MRT2+ in the normal range (≤20 ms). A significant, progressive decline was seen in LIC, with mean (SD) changes from baseline to years 1, 2, and 3 of -2.64 (4.64), -3.91 (6.38), and -6.64 (7.72) mg/g dw, respectively (P<0.01 for all). A decline was also seen in SF, with mean (SD) changes from baseline to years 1, 2, and 3 of -1 (1986), -771 (2171), and -1016 (3617) µg/L, respectively (P<0.05 for years 2 and 3). Cardiac MRT2+ values changed little from baseline. Of 343 ADRs, 212 were neutrophil count (9.0%), and abdominal pain (7.5%); 2 patients (1.5%) experienced agranulocytosis. One patient withdrew due to ADRs of thrombocytopenia and neutropenia, which resolved. Another patient withdrew due to generalized edema and died for reasons unknown 17 days after withdrawal from the study.

Conclusion: DFP-DFP (up to 2 years) was effective in controlling body iron load in patients with SCD and other anemias. There were no new safety concerns.

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S116 LONG-TERM EFFICACY AND SAFETY OF THE ORAL PYRUVATE KINASE ACTIVATOR MITAPIVAT IN ADULTS WITH NON–TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

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Background: Thalassemia is characterized by ineffective erythropoiesis and hemolysis that occur due to imbalanced production and precipitation of globin chains.α β Thalassemic red blood cells (RBCs) have increased levels of ATP to meet increased energy demands associated with globin chain imbalance, protein degradation, and cellular oxidative stress responses. Mitapivat is an oral activator of RBC pyruvate kinase (PKR), a key glycolytic enzyme regulating ATP production. In a phase (ph) 2, open-label trial of mitapivat in adults with α- or β-non–transfusion-dependent (NDT) thalassemia (NCT03692052), 80% of patients (pts) met the primary endpoint of a hemoglobin (Hb) response (≥1 g/dL increase from baseline [BL] at ≥1 assessment between Weeks [Wks] 4–12, inclusive). Improvements in markers of hemolysis and ineffective erythropoiesis were also observed and mitapivat was generally well tolerated. Aims: To report data from the ongoing long-term extension (LTE) period (up to Wk 72; data cutoff 27Mar21).

Methods: Pts aged ≥18 y with a known medical history of α- or β-thalassemia, Hb concentration ≤10.0 g/dL, and ≤5 RBC units transfused in 4–12, inclusive). Improvements in markers of hemolysis and ineffective erythropoiesis were also observed and mitapivat was generally well tolerated. Aims: To report data from the ongoing long-term extension (LTE) period (up to Wk 72; data cutoff 27Mar21).

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SCD genotype, occurrence of major disease-related events (hospitalization for vaso-occlusive crisis (VOC), acute chest syndrome/pneumonia, severe infections and neurological complications) are presented. Overall survival and survival without specific SCD-related complications were analyzed by Kaplan-Meier curves.

**Results:** Up until now, 98 (56%) out of 174 eligible subjects from this institution were included, with a total follow-up of 805 patient-years. This concern approximately 53% of the national number. The majority (57%) had the severe genotype (HbSS or beta0-thalassemia), the remainder had the milder genotype (HbSC or HbS-beta+--thalassemia). Survival by the age of 14 was 98.9%, with 1 death at the age of 1 years due to sepsis. Seven patients (7.1%) had a severe infection (meningitis, sepsis, osteomyelitis) caused by Streptococcus Pneumoniae in 3/7 cases. Two patients experienced a symptomatic cerebral infarction at the age of 11 months and 1.5 years. At the age of 10 years the survival without hospitalization for vaso-occlusive crisis was 27% (95% CI: 12.7 – 43.14%) and 51% (25.3 – 72.0%) for the SS/S0 and SS/S0+ genotype respectively.

**Conclusion:** In this cohort of neonatally screened patients with SCD, the SCD-related mortality and morbidity is still impressive with 1% mortality, 3 severe infections caused by Streptococcus Pneumoniae, and 2 patients with neurological complications. A final analysis of the effect of neonatal screening for SCD will follow after completion of data collection in all participating centers in the Netherlands.

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**S118 LONG-TERM SAFETY AND EFFICACY OF VOLEXOR FOR PATIENTS WITH SICKLE CELL DISEASE: RESULTS FROM AN OPEN-LABEL EXTENSION OF THE PHASE 3 HOPE TRIAL**

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**Background:** Sickle cell disease (SCD), a lifelong, inherited blood disorder, leads to sickle hemoglobin (HbS) formation. HbS polymerization causes red blood cell sickling, leading to hemolysis, chronic anemia, and vaso-occlusive crises (VOCs). Patients with SCD are at higher risk of end-organ damage, increased morbidity, and early mortality due to low hemoglobin (Hb) and increased hemolysis. Voxelotor, a HbS polymerization inhibitor, is approved in the US for SCD treatment in adults and adolescent patients aged ≥12 years. The randomized, placebo-controlled HOPE trial showed that significantly more patients on voxelotor 1500 mg had a >1 g/dL Hb increase than those on placebo at any time to week 72. These Hb increases were associated with reduced hemolysis markers. Here we report an interim analysis of an ongoing open-label extension (OLE) of the HOPE trial.

**Methods:** Patients who completed the phase 3 HOPE trial were eligible to enroll in the multicenter OLE study and receive treatment as long as they continued to receive clinical benefit and/or until they had access to voxelotor through commercialization or a managed access program. All patients received voxelotor 1500 mg as ongoing treatment. Adverse event data were collected from the date of informed consent through 28 days after voxelotor discontinuation. Measurements of Hb and clinical markers of hemolysis are ongoing and summarized here for 48 weeks of the OLE. Data presented are based on an interim data cut (December 31, 2020).

**Results:** Of the 199 patients who completed the HOPE trial, 178 (89.4%) were enrolled and dosed in the OLE. Median age at enrollment was 25 years (15.7% adolescents, 84.3% adults). At the cutoff date, the median voxelotor exposure duration in the OLE was 69.9 weeks (range:
Methods: Healthy adult subjects over 18 years of age without significant signs, laboratory findings, or ECGs were observed. The most common nor dose-limiting toxicities were reported. Across the duration of the cohorts, no treatment-emergent adverse events (AEs) > grade 1 (mild) were grade 1 or 2. Eleven patients (6.2%) had an adverse event that led to treatment discontinuation. No TEAEs consistent with lack of tissue oxygenation were observed.

Conclusions: In this OLE study, treatment with voxelotor 1500 mg led to improvements in Hb and clinical measures of hemolysis at 48 weeks in patients who received placebo in the HOPE trial and showed durability of response in patients previously treated with voxelotor of any dosage in the HOPE trial. No new safety signals were identified with exposure through a combined 144 weeks of treatment. For these results, long-term voxelotor treatment is safe, well tolerated, and effective in reducing anemia and hemolysis, with a low rate of VOCs, in patients with SCD.

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S119 PRELIMINARY RESULTS OF A PHASE 1 STUDY IN HEALTHY SUBJECTS ADMINISTERED INCLACUMAB, A FULLY HUMAN IgG4 ANTI-P-SELECTIN MONOCLONAL ANTIBODY IN DEVELOPMENT FOR TREATMENT OF SICKLE CELL DISEASE

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Background: Inclacumab, a fully human IgG4 anti-P-selectin monoclonal antibody, is being developed for the reduction of vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD). P-selectin-mediated platelet-leukocyte aggregate (PLA) formation has been shown to contribute to vaso-occlusion. Safety and pharmacology of inclacumab have been previously well characterized in over 700 subjects (healthy volunteers and patients with cardiovascular disease), at doses up to 20 mg/kg every 4 weeks for up to 9 months. The current Phase 1 study was initiated to evaluate the safety and pharmacology of inclacumab at doses of 20 mg/kg and 40 mg/kg in healthy subjects in support of a target Phase 3 dose of 30 mg/kg administered every 12 weeks to patients with SCD.

Methods: Healthy adult subjects over 18 years of age without significant current or prior health conditions received a single intravenous (IV) dose of 20 mg/kg inclacumab infused over approximately one hour (Cohort 1). Following a review of safety, a second cohort received a single IV dose of 40 mg/kg infused over approximately one hour (Cohort 2). The total study duration and sample collection period was 29 weeks. Final safety and preliminary pharmacokinetics (PK), anti-drug antibody (ADA), and ex vivo thrombin receptor-activating peptide (TRAP)-activated PLA formation data are reported.

Results: Fifteen subjects received a single dose of inclacumab 20 mg/kg (n=9) or 40 mg/kg (n=9). Median age was 42 years (range 22–52 years); median body weight was 73.6 kg (range 63.7–89.3 kg). Through the prespecified 72-hour post-infusion safety assessment period in both cohorts, no treatment-emergent adverse events (AEs) > grade 1 (mild) nor dose-limiting toxicities were reported. Across the duration of the study, there were no serious AEs, infusion-related reactions, or hypersensitivity reactions. Additionally, no clinically significant changes in vital signs, laboratory findings, or ECGs were observed. The most common AEs were upper respiratory tract infections, headache, myalgia, back pain, and contact dermatitis. The only events assessed by the investigator as potentially related to inclacumab were headache and dizziness, which were reported by 1 patient (20 mg/kg) and occurred 4 hours following the end of infusion. In healthy subjects, inclacumab demonstrated dose-proportional PK over the dose range tested; PK parameter estimates were consistent with those reported for monoclonal antibodies. Geometric mean Cmax following single doses of 20 and 40 mg/kg were 402 and 970 mg/mL, respectively. Mean TRAP-activated pre-dose PLA formation was 33–39% across cohorts and decreased to 9–14% at 2 hours following end of infusion. PLA inhibition was sustained up to 23 weeks for both the 20 and 40 mg/kg doses. Two subjects in the 40 mg/kg cohort were ADA-positive on Week 12 and thereafter; a preliminary analysis demonstrated no apparent impact on PK or safety in these subjects.

Inclacumab displayed a well-tolerated safety profile for up to 29 weeks following a single dose of 20 or 40 mg/kg in healthy subjects. Durable inhibition of TRAP-activated PLA formation was observed up to 23 weeks. Overall, the results support a Phase 3 dose of 30 mg/kg every 12 weeks in patients with SCD-related VOCs.

Funding: This study was supported by Global Blood Therapeutics.

S120 RANDOMIZED CONTROLLED TRIAL OF THE EFFICACY AND SAFETY OF DEFERIPRONE: SUBGROUP ANALYSIS OF PEDIATRIC PATIENTS IN IRON-OVERLOADED PATIENTS WITH SICKLE CELL DISEASE AND OTHER ANEMIAS

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Background: Children with sickle cell disease (SCD) managed with blood transfusions often require iron chelation therapy to prevent iron overload.1 Deferoxamine (DFO) is an iron chelator approved for pediatrics that is often infused; however, adherence is a key challenge due to the burdensome route of administration.2 Deferiprone (DFP), an oral iron chelator, is a first-line treatment for transfusional iron overload in children and adults with SCD and other anemias.3 DFP is noninferior to DFO in SCD with iron overload (evaluated by liver iron concentration [LIC]) and has an acceptable safety profile.4 This subgroup analysis of FIRST (NCT02041299) assessed whether efficacy and safety of DFP were comparable to DFO in children with SCD.

Methods: In this phase 4 open-label study, patients were randomized 2:1 to DFP or DFO for 12 months. The subgroup analysis included children (2–16 years of age) with SCD or another rare anemia treated for transfusional iron overload. Children received either oral DFP three times a day or subcutaneous DFO infusion 5–7 days a week. Iron load was monitored and dosage adjustments were allowed. The primary endpoint was change in LIC from baseline to month 12. Data were analyzed for all patients with a baseline and a follow-up LIC assessment (efficacy population). Safety assessments were done for all patients who received at least 1 dose of study drug (safety population). All patients provided informed consent or assent.

Results: Of 228 patients in the safety population, 128 (DFP, n=86; DFO, n=42) were children. Most children (DFP, 75.6%; DFO, 80.9%) had a primary diagnosis of SCD (HbS). Mean ages (SD) in the DFP and DFO groups were 9.9 (3.7) and 10.9 (3.0) years (P=0.09), respectively. There were no significant differences between the DFP and DFO groups in sex (males, 59.3% vs 57.1%; P=0.85), ethnicity (P=0.68), or race (P=0.34). 5 children withdrew due to AEs (all DFP) and 19 withdrew for other reasons (DFP, n=14; DFO, n=5). There was not a significant difference in number of withdrawals between groups (P=0.23). Children treated with DFP or DFO showed no significant differences in overall incidence of AEs (P=0.77; including neutropenias [P=0.30]), severe AEs (P=0.10), serious AEs (P=0.16), or withdrawals due to AEs (P=0.17). A difference in overall incidence of nonserious AEs considered at least possibly related to DFP (59.3% vs 33.3%; P=0.01) was found. For AEs ≥5%: see Table 1. The only AE with a significantly higher rate with DFP
vs DFO was elevated liver enzymes ($P=0.03$)—a known transient reaction to DFP typically resolving with continued DFP. There were no AEs observed with DFP that had not been previously reported. One child developed agranulocytosis during parvovirus infection, which resolved the following day; and children <6 years of age receiving DFP had a comparable safety profile to older children (6–16 years of age) receiving DFP. In the efficacy population, after 12 months, there was no significant difference in mean (SD) LIC change from baseline with DFP vs DFO ($-3.39\pm4.24 \text{mg/g vs } -2.99\pm3.16 \text{mg/g}$, respectively; $P=0.57$).

**Conclusions:** This subgroup analysis of children receiving chronic transfusions for SCD or other anemias corroborates previous findings that DFP is comparable to DFO in reducing LIC. No new safety concerns were observed. These findings may benefit children and healthcare providers when considering effective iron chelation therapy that may also address treatment-adherence concerns.

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healthcare-managed VOCs after ≥12 months of crizanlizumab treatment were −4.0 (−6.0 to −2.0) and −3.0 (−4.0 to −1.0), respectively. The lower rates of VOCs post-vs pre-crizanlizumab were also observed when stratifying the data by SCD genotype/prior HU use (Figure). Of note, a small number of pts are included in some groups when stratifying the data. Opioids were taken for VOC management by 95% of pts (n=35/37) in the 12 months before crizanlizumab initiation and by 68% (n=25/37) in the 12 months after; the most common opioid taken was morphine (74% [n=26/35] and 56% [n=14/25], respectively).

Summary – Conclusion: Pts participating in the crizanlizumab MAP had a high burden of home- and healthcare-managed VOCs, as well as SCD-related complications at baseline, despite many pts reporting a history of HU use. Most pts reported using opioids for VOC management. Crizanlizumab substantially reduced the median annualized rates of home- and healthcare-managed VOCs and use of opioids from baseline in this real-world setting, consistent with results from SUSTAIN.6

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Table 1, AESI

| Age 12 to <18 years (n=95) |
|---------------------------|
| **AEs irrespective of relationship to study drug** | **AEs suspected to be related to study drug** |
| All grades | Grade ≥3 | All grades | Grade ≥3 |
|---|---|---|---|
| Effect on hemostasis – hemorrhage | 5 (10) | 0 | 0 |
| Infections (all) | 23 (46) | 2 (4) | 1 (2) |
| Potential severe IRIs at any time | 6 (12) | 0 | 4 (9) |
| Signs/symptoms indicative of possible IRR on day of infusion | 15 (30) | 5 (10) | 11 (23) |
| Potential IRIs presenting as pain events on day of infusion | 8 (16.0) | 1 (2) | 3 (6) |
| Anti-drug antibodies to crizanlizumab | 0 | 0 | 0 |

Numbers (n) represent counts of participants.
*Individual preferred terms from the different search strategies overlap; hence, the same patient may be included in more than one category.
1Search intended to identify events more likely to be caused by the infusion and to have a potentially more severe clinical course occurring any time after infusion (regardless of grade and causality).
2Search excluded infusion-site reaction and overlapped the common, non-specific, potential signs and symptoms indicative of IRIs occurring on the day of infusion.
3Two Grade 3 events reported in the same patient (back pain and pain in extremity), both of which resolved on the day of onset.
4AD: adverse event; AESI: adverse event of special interest; IRR: infusion-related reaction

S122 SAFETY AND EFFICACY OF CRIZANLIZUMAB IN ADOLESCENTS WITH SICKLE CELL DISEASE (SCD): INITIAL DATA FROM THE PHASE II, MULTICENTER, OPEN-LABEL SOLACE-KIDS TRIAL

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Background: Vaso-occlusive crises (VOCs) are the hallmark of SCD. P-selectin, a cell adhesion molecule, plays a key role in the multiscellular interactions leading to VOCs. In the SUSTAIN trial, crizanlizumab 5 mg/kg, a first-in-class humanized monoclonal antibody that blocks P-selectin, significantly reduced the annualized rate of VOCs versus placebo and had a favorable safety profile in adults with SCD.

Aims: To describe the initial safety and efficacy results for patients with SCD aged 12–18 years. Most pts reported using opioids for VOC management. VOCs in this real-world setting, consistent with results from SUSTAIN.6

Summary – Conclusion: In this initial analysis, crizanlizumab 5 mg/kg was safe and well tolerated in patients with SCD aged 12–18 years, consistent with the established profile of crizanlizumab in adults. No new safety signals were identified. Crizanlizumab 5 mg/kg led to a clinically relevant reduction in VOCs in this patient population compared with baseline.

S123 SAFETY AND EFFICACY OF EARLY-START DEFERIPRONE IN INFANTS AND YOUNG CHILDREN WITH BETA-TALASSEMIA (START STUDY)

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Background: Patients with beta-thalassemia may need regular red blood cell transfusions in infancy. In the absence of iron chelation therapy, frequent transfusions cause iron to accumulate, which can lead to morbidity, organ damage, and death. However, in very young children, current practice is to delay chelation therapy until receipt of 10–20 transfusions or until serum ferritin (SF) has reached 1000 μg/L, due to concerns over excessive iron depletion with deferoxamine.13 Unfortunately, this delay may increase the risk of iron accumulation in endocrine glands where toxicities could later manifest.1

Aims: START (NCT03591575) evaluated the safety and efficacy of the oral iron chelator deferiprone (DFP) in children with transfusion-dependent beta-thalassemia who did not yet meet the criteria for starting chelation therapy per standard practice.

Methods: Infants and children receiving regular blood transfusions (2 minimum) and whose SF level was between 200–600 μg/L were randomly assigned 1:1 to DFP oral solution or placebo until SF exceeded 1000 μg/L at 2 consecutive visits or 12 months of therapy. DFP was initiated at 2.5 mg/kg/d and increased to 50 mg/kg/d after 2 weeks; based on iron load, DFP was increased to 75 mg/kg/d. Efficacy was assessed by
monthly SF measurements to monitor iron load. The primary endpoint was the percentage of patients in each group with SF <1000 μg/L. All patients provided informed consent or assent.

Results: The study enrolled 64 patients; 32 per group. The mean (SD) age was 3.03 (2.42) years in the DFP group and 2.63 (1.70) years in the placebo group; participants were 62.5% and 65.6% male in the DFP and placebo groups, respectively. There were no group statistical differences in the baseline demographics. The primary reason for withdrawal was SF levels that exceeded 1000 μg/L at 2 consecutive visits, which occurred in 25% of patients receiving DFP vs 63% of patients receiving placebo (P=0.0051). After completing 12 months of treatment, 65.6% of patients receiving DFP had a SF level <1000μg/L vs 37.5% receiving placebo (P=0.0446). The percentage of patients who reached the 1000μg/L SF threshold increased more rapidly in the placebo group vs the DFP group, and the difference in rates between the 2 groups was significant (P=0.0407). A summary of adverse events (AEs) is shown in Table 1. There were no significant group differences in the number of overall AEs (P=1.0000), serious AEs (P=0.4258), or the number of AEs that were considered to be at least possibly related to the study treatment (P=1.0000). Two patients receiving DFP withdrew from the study due to AEs: 1 patient experienced agranulocytosis and 1 patient experienced neutropenia of moderate severity and both patients recovered.

Conclusions: Initiation of DFP chelation therapy at a lower threshold of SF values than currently recommended was safe and efficacious in preventing iron overload in most transfusion-dependent children. After 12 months of treatment, the number of patients with a SF level <1000 μg/L was significantly higher in the DFP group vs the placebo group. Moreover, there were significantly more patients who withdrew due to elevated SF levels in the placebo group compared to the DFP group (25%). The safety and tolerability profile of DFP administered for up to 12 months in infants and young children was comparable to the profile established in Table 1. There were no significant group differences in the number of overall AEs (P=1.0000), serious AEs (P=0.4258), or the number of AEs that were considered to be at least possibly related to the study treatment (P=1.0000). Two patients receiving DFP withdrew from the study due to AEs: 1 patient experienced agranulocytosis and 1 patient experienced neutropenia of moderate severity and both patients recovered.

Conclusions: Initiation of DFP chelation therapy at a lower threshold of SF values than currently recommended was safe and efficacious in preventing iron overload in most transfusion-dependent children. After 12 months of treatment, the number of patients with a SF level <1000 μg/L was significantly higher in the DFP group vs the placebo group. Moreover, there were significantly more patients who withdrew due to elevated SF levels in the placebo group compared to the DFP group (25%). The safety and tolerability profile of DFP administered for up to 12 months in infants and young children was comparable to the profile established in older age groups and there were no instances of iron depletion.

### Table 1. Summary of Adverse Events

| Parameter, n (%) | DFP (n = 32) | Placebo (n = 32) |
|------------------|-------------|-----------------|
| Patients experiencing ≥1 AE | 29 (90.6%) | 29 (90.6%) |
| Total ADRs | 11 (34.4%) | 11 (34.4%) |
| ADRs in ≥5% of patients | | |
| Neutropenia | 4 (12.5%) | 1 (3.1%) |
| Vomiting | 1 (3.1%) | 2 (6.3%) |
| Decreased neutrophil count* | 6 (18.8%) | 6 (18.8%) |
| Serious AEs | 5 (15.6%) | 2 (6.3%) |
| Neutropenia | 4 (12.5%) | 1 (3.1%) |
| Agranulocytosis | 1 (3.1%) | 0 |
| Dengue fever | 1 (3.1%) | 0 |
| Autoimmune hemolytic anemia | 0 | 1 (3.1) |
| Chronic bronchitis | 0 | 1 (3.1) |

*Adverse drug reactions (ADRs) included AEs that were considered to be at least possibly related to the study treatment.

†Decreased neutrophil count was defined as a one occurrence of absolute neutrophil count below 1.5 x 10^9/L with no confirmatory second value within 3 days.

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### Infection, autoimmunity, nutritional deficiencies

**S124 ADVERSE EVENTS FOLLOWING COVID-19 VACCINATION IN TRANSFUSION-DEPENDENT - THALASSEMIA PATIENTS**

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**Background:** Patients with transfusion-dependent-thalassemia (TDT) are considered as increased risk population for severe and/or morbid COVID-19 infection. Timely vaccination is the main preventive method for severe COVID-19. Different adverse events and reactions following vaccination have been reported, with severe ones being extremely rare. TDT patients may have altered immunity due to chronic transfusions, iron overload and chelation therapy, and splenic dysfunction. The safety profile of vaccination in chronically transfused patients with thalassemia has not been reported.

**Aim:** To evaluate the safety profile of COVID-19 vaccines in TDT patients.

**Patients and Methods:** This is a single institution’s, retrospective analysis evaluating all TDT patients, older than 18 years old, who had completed the vaccination protocol at least 30 days before data cut-off time (July 20th 2021). Adverse events were reported by patients up to 30 days post each dose. Demographic and hematological data, including mean hemoglobin levels before and up to 90 days after each dose, were recorded. T-test was performed to investigate changes in hematological profile and transfusion burden post vaccination.

**Results:** 186 patients (median age=45; range:18–61 years old; male/female=87/99) were included for data analysis corresponding to 53% of all TDT patients followed in our Thalassemia Unit. Distribution of vaccine types were: Comirnaty-BNT162b2 (Pfizer Inc. and BioNTech)90.86% (n =168), Vaxzevria (previously COVID-19 vaccine, AstraZeneca) 1.61% (n=3), Moderna (Moderna TX Inc.) 6.98% (n =13) and JNJ-78436735 (Janssen Pharmaceuticals Companies of Johnson & Johnson) 0.54% (n =2). No patients had confirmed or suspected previous COVID-19 infection.

Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The incidence of adverse events after 1st and 2nd dose were 43.5% (81/186) and 54.8% (102/186), respectively. Adverse events after 1st dose included pain at injection site 26.3% (n=49), fatigue 9.7%(n=18), fever 5.4% (n=10), headaches 4.3% (n=8), arthralgia and myalgia 2.2% (n=4), and lymphopenopahty 0.5% (n=1). Adverse events after 2nd dose included fever 28.5% (n=53), fatigue 17.7% (n=33), pain at injection site 15.6% (n=29), arthralgia and myalgia 11.3% (n=21), headaches 9.1% (n=17), lymphopenopahty 3.2% (n=6), dizziness 0.5% (n=1), tachycardia 0.5% (n=1), diarrhea/ vomiting 0.05% (n=1) and amaurosis fugax 0.5%: (n=1). No grade 4–5 events or anaphylaxis were observed. Two patients (both males, 51 years and 45 years old, respectively) presented with acute hemolytic crisis with hemoglobinuria in 3rd and 20th day after the second dose with Pfizer/ BioNTech, respectively. They are receiving treatment with corticosteroids without partial response. Both patients had a history of acute hemolysis crisis within the last 3 years. A slight decrease in patients’ mean hemoglobin levels was observed three months after vaccination compared to the mean hemoglobin levels before vaccination (mean=9.9 /sd=0.63 g/dL vs mean=9.8 /sd=0.64 g/dL, p= 0.05).

Acknowledgements: Compared to the vaccine trials, we observed some lower incidence of vaccine-related adverse events in our cohort of TDT patients. A temporary drop in hemoglobin levels may be noted. Of interest, two patients with previous history of alloimmunization, developed hemolysis. Close follow up is required in TDT patients post vaccination.

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**S125 THE ROLE OF THE MICROBIOME AS A SICKLE CELL DISEASE MODIFIER: AN EXPERT REVIEW**

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**Background:** There is evidence that the microbiome is involved in numerous human systems’ pathobiology, however, its role in sickle cell disease (SCD) remains elusive.

**Methodology:** An extensive systematic search was conducted by applying the PRISMA guidelines (2009) and using three databases (PubMed, Web of Science, and Scopus). The keywords were used separately and a combination of the following: “Microbiota” AND “Anemia” OR “Sickle Cell”. Articles included were confined to full-length articles written in English and focused on research and review articles on the contribution of the microbiome in the development of sickle cell disease (SCD)
severity. The main search was conducted, separately, by a MSc Student and a PhD student, both in Human Genetics and reviewed by a medical and human geneticist with expertise in SCD and a clinician-scientist with expertise in molecular pathology and microbiology. A total of 229 articles was compared and screened for duplications. The abstracts of the remaining articles were screened for suitability to the study. Articles were excluded based on its relevance to the scope of the review.

**Results:** This systematic review examines available data on the role of the microbiome in SCD clinical events. A total of 13 published articles were selected; most were observational human studies (n = 10), and five included SCD mouse models. Few studies performed microbiome 16S RNA analysis, to identify/classify uncultured microbes (n = 8/13). Results showed that the microbiome influences inflammation, and vaso-occlusive crises (VOC) in SCD, and is disrupted by medication and diet. This review was able to provide insight on how immunity can be maintained by the microbiome through TLRs and Myd88 mechanisms. The exploration of bacterial translocation may be regulated by an altering intestinal permeability and the microbial density, which is managed by the damage-associated molecular pattern (DAMPs). This may give insight into treating an altered intestinal microbiome in SCD patients. Wherein in SCD mouse models, neutrophil adhesion, Mac-1 activation, and heterotopic interaction in red blood cells were significantly influenced in microbiota.

**Conclusion:** Data suggest that the microbiome can be disrupted by the SCD endophenotypes, specifically by triggering inflammation pathways, which could promote a cycle of VOC. This review emphasizes the need for investigating microbiome effects on SCD throughout the lifespan of patients.

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**Health services and outcomes research including psychology**

S126 AN EU – ARISE INITIATIVE GAP ANALYSIS APPROACH TO IMPROVING THE QUALITY OF LABORATORY SYSTEMS IN SUB-SAHARAN AFRICA.

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**Background:** Accurate and reliable laboratory results are critical to diagnostics in sickle cell disease (SCD) newborn screening. In sub-Saharan Africa, due to neglect of some national health laboratories, there has been persistently high levels of laboratory error, lack of functioning quality management systems and laboratory accreditation.

**ARISE** (African Research and Innovative Initiative for Sickle Cell Education) is a research project funded by the EU. It involves a secondment across 8 work packages between institutions in EU (Italy, France, UK and Cyprus) and non-EU (Nigeria, Lebanon, Kenya and USA) countries, creating an interagency and multidisciplinary staff exchange programme to share best practices in newborn screening, diagnosis and treatment of SCD, leading to improved disease outcomes.

Secondments include medical, nursing, laboratory, administrative, academic and research professionals. Led by the RCPPath and INSERM, WP3 is tasked with improving laboratory and gut permeability in SCD newborn screening, diagnosis, treatment and monitoring of SCD through assessments, training and mentoring of laboratory health professionals. This is facilitated by baseline, interim and final gap assessments.

**Aims:**

1. To compare a baseline gap analysis at the commencement of the project in 2019 with an interim gap assessment 2 years into the project, following secondments to UK laboratories from Nigeria

2. To identify areas of increased focus and support during planned secondments, workshops, and virtual lectures

**Methods:** 6 partner organisation laboratories participated in the baseline gap assessment in 2019, while 10 laboratories participated in the interim gap assessment in 2021, due to new institutions joining the ARISE initiative.

An electronic online questionnaire (40 questions) was sent to each laboratory lead.

**Results:** Survey results of the 6 laboratories that undertook both the baseline and interim gap assessment were analysed. A sample of comparative results between 2019 and 2021 include the following:

- Working towards accreditation - 2/6 versus 3/6: There is the need for each laboratory to progress towards an application for accreditation.

- SOP’s available for tests and processes - 38 versus 32: This might suggest standardisation and rebranding of documents previously labelled as SOP’s.
The Consortium on Newborn Screening in Africa for SCD (CONSA), established in 2018, is a part of the American Society of Hematology’s broad initiative to strengthen the SCD response globally through advocacy and research generation.

CONSA Program Goals and Objectives

• Demonstrate the effectiveness of early identification and clinical interventions for newborns with SCD
• Create sustainable, expanded networks for newborn screening and clinical interventions
• Foster collaboration between African hematologists and public health services to develop an organized network of researchers for conducting quality studies and publishing results
• Increase hematology capacity throughout sub-Saharan Africa

CONSA introduces standard-of-care practices for screening and early intervention therapies (including antibiotics and malaria prophylaxis, folic acid supplements, family education and counseling, and immunizations) at participating clinical institutions, screening 10,000 – 16,000 babies per year in each country, and providing clinical follow-up for babies diagnosed with SCD. A shared registry captures data from CONSA institution sites, which will be used to estimate the prevalence of SCD in member countries and evaluate the effectiveness of the interventions for newborns to five years of age.

Currently, CONSA is working in seven countries, Ghana, Kenya, Liberia, Nigeria, Tanzania, Uganda, and Zambia. Hematologists and public health officials participating in the consortium have mobilized networks of screening laboratories, SCD or pediatric hematology clinics, teaching hospitals, regional referral hospitals, universities, and satellite clinics to screen newborns and provide clinical services protocol. Alongside the research showcasing the health outcomes of newborns screened and delivered early interventions, the consortium is working to ensure the long-term sustainability of programs through government, corporate, and other partner support.

All country sites launched screening in 2021. As of November 15, over 17,000 babies have been screened with over 150 found to be living with SCD. Despite challenges from the COVID-19 pandemic, including population concerns of going to health clinics, need to protect SCD patients from transmission, and supply chain breakdowns, CONSA looks forward to continuing to expand newborn screening efforts for the next several years.

Conclusion: The presentation will provide an overview of CONSA’s goals and current work to screen and provide care for newborns with SCD, despite challenges from the COVID-19 pandemic. The presentation will also include details from the Nigeria clinical sites, case studies of current babies with SCD, and recent work done to strengthen Nigeria’s national newborn screening and clinical efforts.

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S128 CONTINUOUS QUALITY IMPROVEMENT IN PAEDIATRIC SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is characterised by severe episodic pain requiring prompt and effective analgesia. However, SCD patients frequently experience poor quality of care due to lack of awareness of the condition among non-specialist staff, pre-conceived biases and unfounded allegation of drug-seeking behaviour. Several reports and surveys using Patient Reported Experience Measure (PREM) tools indicate widespread prevalence of ineffective pain relief in emergency department (ED), poor access to psychological therapies and poor funding for service development.

Aims: To use a validated PREM tool to survey patients or carers of sickle cell disease within the paediatric service of a Specialist Haemoglobinopathy Team. To use an established Continuous Quality Improvement (CQI) methodology (5-D’s-define, describe, design, deliver, digest) to ensure sustained improvement in patient-reported areas of service deficit.

Methods: The PREM survey was conducted as part of a network-wide initiative in 2018. The survey responses were analysed and problem scores created for specialist care, emergency care, ward-based care, information and support. These problem areas were categorised into domains where further improvement action was needed. CQI tools were used to map the patient journey within Emergency Department (ED) when presenting with pain followed by thematic analysis to identify potential improvements in the patient journey.

Results: The PREM survey analysis identified three domains for improvement:
• Domain A: To improve the effectiveness of pain relief and quality of empathic and informed care to paediatric sickle cell patients and their families in ED.
• Domain B: To improve the information presented to children and parents regarding SCD and the care services available in our trust.
• Domain C: To improve the availability of, and access to, mental health services for paediatric SCD patients.
We developed virtual parent support groups and psychological health screening for adolescent patients in clinics. We organised a ‘Tree of Life’ (ToL) patient empowerment workshop. The parent support groups were well attended. Plans are in place to continue ToL workshops and support groups on a regular basis.

Future work: A rapid improvement workshop is being planned to engage a wider multi-disciplinary team to engender a culture of empathy in line with our trust values. Further input from workshop is expected to identify and implement sustainable goals. We plan to undertake a repeat PPM and analysis using the end of this CQI project to understand the impact and the implemented improvements.

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S129 IMPLEMENTATION OF HYDROXYUREA THERAPY FOR SICKLE CELL DISEASE ON A LARGE SCALE IN GHANA
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Background: Hydroxyurea (hydroxycarbamide), has had a most profound and broad effect in ameliorating impact on the clinical course of sickle cell disease (SCD). Although relatively inexpensive, hydroxyurea (HU) has not been widely available to the large majority of people with SCD who happen to live in low-income countries.

In 2018, in preparation for the establishment in 2019 of a broad-based Public Private Partnership (PPP) in SCD involving the Ghana government and Novartis, a group of parents Novartis to provide HU at a lower price for use in Ghana. Novartis produced 500mg capsule of HU and submitted it to Ghana Food and Drugs Authority registered the medicine for the specific indication of SCD in October 2018. The Sickle Cell Foundation of Ghana (SCFG), a partner in the PPP was tasked to develop the Ghana-Novartis Hydroxyurea-for-SCD Program (“Ahodwo [pr. A-ho-jo] Program”, meaning, “Program for Relief”).

The program was conceived as an implementation study to determine whether treatment with HU, specifically registered in Ghana for SCD, can be safely implemented and monitored on a large scale through an organized treatment program within the public health service in Ghana.

Methods:
1. Treatment Protocol: A team of Ghanaian SCD experts developed an HU-for-SCD dose-escalating, maximum tolerated dose (MTD) Ahodwo Protocol adapted for Ghana. A unique feature of the protocol is the selection of Hb level of 10g/dL as the primary goal of HU therapy with of a Therapeutic Dose (TD) defined as, “the dose at which Hb 10g/dL or higher is achieved and maintained over a period of 12 weeks”.
2. Treatment Teams: Established SCD Treatment Centres (SCD TC) were surveyed for patient numbers, age groups, Hb Phenotypes, and available laboratory services. Doctor-nurse-pharmacist teams were recruited from 11 TC located in four Regions of Ghana in Phase 1 of the Program for training. A year later, 9 smaller SCD TC were added to the program, in Phase 2, extending it to two additional Regions.
3. Ahodwo Program App: In order to register and guide healthcare professionals (HCP) on the protocol, register all subjects, assist with dosing calculations, and monitor the entire program, a secure, smartphone-based mobile application, Ahodwo Program App, was developed, tested, and deployed to all HCP in the program. Recording toxicity and reporting all expected/unexpected adverse events were mandated and reportable through the App.
4. Steering Committee (ST): A ST comprising clinician leaders of the TC was established; the ST held bi-weekly online review meetings for the first year and monthly thereafter. All HCP teams met every quarter.

Results: Table, below, lists the number and characteristics of subjects registered in the Ahodwo Program.

| Data Elements | Phase 1 | Phase 2 | TOTAL |
|---------------|---------|---------|--------|
| Number of SCD Treatment Centers (TC) | 11 | 9 | 20 |
| Average, No. of Subjects at TC | 3,357 | 291 | 3,648 |
| Median, No. of Subjects at TC | 305 | 32 | 182 |
| Range, No. of Subjects at TC | 256 | 26 | 88 |
| Age >18yr, No. (%) | 1,728 (47.4%) |
| Male, No. (%) | 1,920 (52.6%) |
| Age <10yr, No. (%) | 1,561 (42.8%) |
| Age 10-18yr, No. (%) | 1,295 (35.5%) |
| Age >18yr, No. (%) | 792 (21.7%) |
| Presumed SCD-S or S/beta-zero, No. (%) | 3,526 (96.7%) |
| SCD-SC, No. (%) | 122 (3.3%) |

No one’s listening(https://www.sicklecellsociety.org/wp-content/uploads/2020/11/No-Ones-Listening-PDF-Final.pdf)

On June 19th, 2021, World Sickle Cell Day, the government of Ghana announced the provision of HU for people with SCD through the National Health Insurance Scheme. Following preparatory meetings to establish the required regulatory standards, implementation of the national program is expect

Conclusion: Our experience supports the tenet that hydroxyurea can be safely and effectively administered at population scale in a low-income country. Long-term sustainability in this setting is likely to be dependent on a government-supported access programme. The pioneering efforts of the government of Ghana to provide HU to its citizens with SCD are laudable and serve as a model to guide similar efforts in other low-income countries.

S130 PROCESSING SPEED DECLINES OVER TIME IN 4–25-YEAR-OLDS WITH SICKLE CELL DISEASE
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Background: Alongside physiological symptoms, young people with sickle cell disease (SCD) may also experience cognitive difficulties, including poorer processing speed. Processing speed develops rapidly from birth to around mid-childhood, with steady improvements thereafter into a person’s mid-twenties (Anderson, 2002). Nonetheless, little is known about the dynamic developmental trajectory of processing speed for young people with SCD.

Aims: This study, we aimed to investigate if the change in processing speed index (PSI) over time is significantly different between younger participants (aged under 8.99 years at first assessment) and older participants (over 9 years at first assessment) with SCD.

Methods: One hundred and five participants with SCD aged 4 – 18 (N = 8.99 = 47; N > 9 = 58) at recruitment consented to follow-up IQ assessments (WPPSI-R, WISC-III, WAIS-R or WAIS-III) and MRI scans

Figure 1. Processing speed index at timepoint 1 and timepoint 2 for participants under 9 (median age 6 years) and over 9 (median age 13 years) years by cerebral infarct status
over two timepoints between 1992-2003. A repeated measures linear mixed-effects regression model determined longitudinal change in PSI, examining the interaction between age (i.e., under 8.99 years and over 9 years) and timepoint, controlling for infarct status (i.e., no infarct on MRI, silent infarction, or stroke).

**Results:** Both younger and older participants experienced a decline in PSI over time, and this decline was largest for younger participants with no infarct. We found a significant main effect of age, F(1, 53) = 4.46, p = .04 and timepoint, F(1, 27) = 7.86, p < .009, but no significant effect of infarct status. The interaction between time-point and age approached significance, F(1, 27) = 2.97, p = .09.

**Conclusion:** Our findings demonstrated that young people with SCD experienced significant decline in processing speed over time, with a larger decline occurring in participants aged under 9 years, regardless of infarct status. These findings highlight the importance of researching and monitoring PSI longitudinally in young people with SCD, to better understand the impacts of SCD an individual's cognition, identify potential treatment effects and to ensure appropriate support is put in place.

**Note:** Mean processing speed index in a typically developing sample is 100. SCI = silent cerebral infarction; T1 = timepoint 1; T2 = timepoint 2.

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S131 REGIONAL ASSESSMENT OF THE EXPERIENCES OF HEALTHCARE PROFESSIONALS (HCPs) TREATING PATIENTS WITH SICKLE CELL DISEASE (SCD): THE INTERNATIONAL SICKLE CELL WORLD ASSESSMENT SURVEY (SWAY)

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**Background:** SCD has a high clinical burden, results in poor quality of life (QoL) and reduces life expectancy in many patients (pts). To improve treatment/management, it is important to gain a deeper understanding of pt and HCP experiences.

**Aims:** SWAY was a cross-sectional survey that assessed pt and HCP experiences of SCD. Here we focus on the experiences of HCPs from various regions on SCD symptoms and complications, impact of SCD on QoL, treatment goals and treatment satisfaction.

**Methods:** SWAY was an international cross-sectional survey developed by international expert physicians, pt advocates and Novartis to assess pt and HCP experiences.

**Summary:** The most frequent SCD symptoms/complications that HCPs reported were similar across all regions. However, regional differences in HCP experiences of how SCD impacts pts’ daily life exist (eg fewer HCPs reported a high impact on physical/sexual activity in the ME, on daily activities in the ME/Asia, and on education/work in Asia, vs other regions), which may be explained by cultural variations. HU was one of the three most common prior treatments in all regions except Africa, which may indicate an educational knowledge gap, particularly as the HCPs from Africa who completed the survey were primarily non-specialists. This could also reflect poor access to HU and/or its high cost in Africa. HCPs in most regions were dissatisfied with SCD treatments because of limited options, indicating a global unmet need for additional treatment choices. Improving QoL was the main treatment goal for HCPs in all regions, which may be indicative of a high negative impact of SCD on pt QoL and the ongoing need to address this.

| Region          | Most common treatment/management goal | Most common SCD symptoms/complications | Impact of SCD on QoL | Treatment goal for HCPs |
|-----------------|---------------------------------------|----------------------------------------|----------------------|-------------------------|
| Africa          | Pain                                  | Acute chest syndrome                   | Low                   | Improve QoL             |
| Asia            | Fatigue                               | Acute chest syndrome                   | Low                   | Improve QoL             |
| Europe          | Fatigue                               | Anemia                                 | High                  | Improve QoL             |
| North America   | Acute chest syndrome                   | Pain                                   | Low                   | Improve QoL             |
| South America   | Fatigue                               | Acute chest syndrome                   | Low                   | Improve QoL             |

**Figure:** Percentage of HCPs who reported a high impact of SCD on different aspects of patients' lives

- Physical activity
- Sexual activity
- Daily activities
- Education
- Work and play

**Note:** Not all regions were included in every question. All questions were asked in English, some were translated and back-translated into local languages. The translations were done by local experts. The HCPs were then asked to rate the importance of the various aspects of QoL and the impact of SCD on each of these aspects. The responses were then analyzed to determine the percentage of HCPs who reported a high impact of SCD on each aspect of a patient's life.
P101 GUT MICROBIOTA IMPACT ON ANGOLAN CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is one of the most prevalent genetic diseases, affecting between 20 and 25 million people worldwide. In the Sub-Saharan Africa, where it is more prevalent, it contributes to 50–80% of under-5 mortality. Clinical manifestations of SCD are very heterogeneous and the intestinal microbiome appears to be crucial in the modulation of inflammation, cell adhesion and induction of aged neutrophils, which are the main interveners of recurrent vaso-occlusive crisis. Enterocyte injury, increased permeability, altered microbial composition, and bacterial overgrowth have all been documented as microbial and pathophysiologic changes in the gut microbiome of SCD patients in recent research studies. Microbiota analysis in SCD populations will be essential to demonstrate the importance of specific bacteria and their function in this disease and provide new insights for attenuating symptoms and new drug targets.

Aims: Given this, our aim is to sequence by NGS bacterial 16S RNA gene in order to characterize the gut microbiome of SCD children and healthy siblings, as a control. A written informed consent was presented and explained to all the guardian participants prior to the data collection. A total of 72 stool samples were obtained from children between 3–14 years old.

Results: Our preliminary results showed that the SCD and control samples exhibit some notable differences in microbiota relative abundance, at different levels of classification. Children with the disease have a higher number of the phylum Actinobacteria (p=0.013) with a mean of sequences of 5.47% (±3.49), while the siblings have a mean of 3.25% (±2.98). As for the genus level, only Clostridium cluster XI bacteria was more prevalent in the SCD children, whereas the siblings had higher numbers of Blautia, Aestuariuspira, Campylobacter, Helicobacter, Polaribacter and Anaerorhabdus.

Conclusion: There is still much to learn before fully relying on the therapeutic approaches for gut modulation, which is why more research in this field is crucial to making this a reality. This works has been supported by FC/FCT/Aga Khan (project n°338042553) and FCT/MCTES (UIDB/05608/2020 and UIDP/05608/2020 –H&TRC.

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P102 PLASMA FREE HEMOGLOBIN AND REACTIVE OXYGEN SPECIES IN SICKLE CELL ANAEMIA PATIENTS UNDER HYDROXYUREA AND GLUTAMINE THERAPY

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Background: Sickle Cell Anemia (SCA), a quite common hemoglobinopathy in Greece, is a consequence of abnormal hemoglobin S production (HbS). When the oxygen tension is low, HbS polymerization occurs, resulting in red blood cells (RBCs) sickling that affects membrane integrity, cell deformability and rheological behavior. Thus, SCA provokes reduced RBCs survival, chronic hemolytic anemia, oxidative stress and microvascular occlusion. Currently, RBC transfusion and hydroxyurea supplementation are the major disease-modifying therapies available for SCD. In addition, L-glutamine oral therapy has been proposed as an anti-oxidative agent for SCA.

Aims: The purpose of this study is to measure the oxidative status of RBCs and hemolysis in SCA patients under simultaneous hydroxyurea and L-glutamine therapy.

Methods: Eighteen SCA patients (5±12 years old, HbS=68.0±9.4%) on average) as well as sixteen similar age-and gender-matched healthy volunteers (controls) participated in the present study. Six patients were under no therapy before glutamine intake, eight patients were under single hydroxyurea therapy and four patients were under blood transfusion therapy. After signing an informed consent, patients took a dose range of 10-30g glutamine (Glutamine DB EXTRA supplement) daily for a 4-month period. Blood sampling were taken before glutamine intake and during a period of 2–4 months after it. Intracellular RBC Reactive Oxygen Species (iROS) were measured by Flow Cytometry. Osmotic Fragility test (mean corpuscular fragility, MCF) and plasma free hemoglobin (p-F-Hb) were also determined. Statistical analysis was performed by GraphPad Prism 8.0.3 and SPSS v.27 software.

Results: All patients had significantly increased iROS levels (632,30±44,83 AU) compared to controls (443,07±69,40 AU, p<0.01), while these under transfusion therapy had only slightly increased values (506,50±31.80 AU, p<0.05). The group of hydroxyurea treatment had lower iROS levels (584,00±87,00 AU) compared to the no therapy group (614,34±23.56 AU, p<0.05). Co-administration of hydroxyurea and glutamine resulted in a 22% decrease in iROS within a two-month period, which was preserved until the end of the four-month period. All patients had decreased RBC MCF (MCF=0.337±0.040% NaCl) compared to controls (MCF=0.46±0.01% NaCl), a finding that was unaffected by hydroxyurea intake (MCF=0.338±0.044% NaCl), a two (MCF=0.331±0.034% NaCl) and four-month (MCF=0.337±0.047% NaCl) glutamine intake period and transfusion therapy (MCF=0.326±0.031% NaCl) (p<0.01). Total bilirubin (T-BIL) was increased in the no therapy group (2.46mgr/dl±0.28) compared to controls (0.63mgr/dl±0.17), while p-F-Hb was increased in all patients (24.34mg/dl±11.98 vs controls 7.12mg/dl±2.90) (p<0.01). Patients under hydroxyurea treatment showed a 19.02% decrease in T-BIL levels but not significant different p-F-Hb levels. Finally, concomitant hydroxyurea and glutamine administration seemed to cause a further decrease in T-BIL and p-F-Hb levels (T-BIL=23.24%, p-F-Hb=65.38% after a two-month period intake).

Summary-Conclusion: RBCs of patients under simultaneous hydroxyurea and glutamine supplementation scheme cope better with oxidative and hemolysis stresses. L-glutamine seems to be a candidate antioxidant supplement able to deal with basic symptoms of SCA.

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P103 THE ABNORMAL PRESENCE OF MITOCHONDRIA IN CIRCULATING SCD RED BLOOD CELLS ASSOCIATED WITH STRESS ERYTHROPOIESIS

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Sickle Cell Disease (SCD) is an inherited blood disorder that affects millions of people worldwide, and it is caused by a mutation of the β-globin gene which results in the polymerization of HbS when deoxygenated. Sickle cell patients experience severe pain, multi organ damage, and shortened life span. Changes arising from sickle hemoglobin (HbS) inside the red blood cell (RBC) leads to an imbalance of the oxidative reactions which increases reactive oxygen species (ROS) formation. Consent was obtained from people with SCD and people with SCD. Our lab discovered that SCD patients have a significant fraction of RBCs retaining-mitochondria which were associated with excessive oxidative and hemolysis stresses. L-glutamine appears to be a candidate antioxidant supplement able to deal with basic symptoms of SCA.
P104  BASE EDITING REPAIRS THE HBE MUTATION RESTORING THE PRODUCTION OF NORMAL GLOBIN CHAINS IN SEVERE HBE/β-THALASSEMIA PATIENT HEMATOPOIETIC STEM AND ERYTHROID CELLS

Background: HbE/β-thalassemia is the commonest form of severe β-thalasemia, and comprises approximately 50% of all cases worldwide. HbE/β-thalassemia is caused by the HbE codon 26 G→A mutation on one allele and any β-thalassemia mutation on the other. There is a reduction in β-globin production, resulting in a relative excess in α-globin chains that leads to ineffective erythropoiesis. Importantly, individuals with a mutation on one, but not two, alleles have β-thalassemia trait, a carrier state with a normal phenotype shared by 1.5% of the world's population. Recent gene therapy and gene editing approaches have been developed to treat β-thalassemia but do not directly repair the causative mutation in-situ. Gene replacement approaches rely on lentiviral vector-based sequence insertion or homology directed repair (HDR). HBE induction strategies rely on non-homologous end joining targeting of enhancers in-trans. These approaches, whilst variably successful, are associated with potential safety concerns.

Methods: Adenine base editors (ABEs) circumvent these problems by directly repairing pathogenic variants in-situ through deamination. ABEs catalyse A→T to G→C transitions. Conversion of the HbE codon to WT through base editing is an attractive strategy to recapitulate the phenotype normal β-thalasemia trait state without potentially harmful double-strand breaks or random vector insertions. ABEs are able to convert the HbE codon (AAG) to wild-type (GAG), but also to GGG or AGG (Fig A). GGG at codon 26 is found in a naturally occurring hemoglobin, Hb Aubenas. Heterozygotes have normal red cell indices and are phenotypically normal. We electroporated the latest generation of ABE8 editors as mRNA into 3 different severe HbE/β-thalassemia donor HSPCs with sgRNAs targeting the HbE codon.

Results: The mean conversion from the HbE codon to a normal or normal variant in unselected cells was 86.2% (SD±8.1%, Fig B). The indel rate from inadvertent on-target Cas9 cleavage was below 0.5%. Edited cells did not show any perturbations in erythroid differentiation as assessed by Immunophenotyping and cellular morphology. In differentiated erythroid cells, RT-qPCR showed a mean fall in the α/β mRNA ratio to 0.6±0.08. (unedited patient cells normalised to 1, n=5, Figure Ci), indicating a reduction in the excess α-globin gene expression. Protein analysis by CE-HPLC showed a 3.6-fold reduction in HbE levels (SD±1.3) and a 13.5-fold increase in HbA/HbAubenas (SD±2.4, Fig D & E).

In serial NSG-murine xenotransplantation experiments, base edited cells were found to persist in secondary transplants, showing editing is possible in long-term HSCs (mean editing efficiency 34.5%, Fig F). Potential off-target effects were assessed in-situ by CIRCLE-seq; most candidate sites were in intergenic and intronic regions (Fig G & H). The top 250 sites were found to persist in secondary transplants, showing editing is possible in long-term HSCs (mean editing efficiency 34.5%, Fig F). Potential off-target effects were assessed in-situ by CIRCLE-seq; most candidate sites were in intergenic and intronic regions (Fig G & H). The top 250 sites were found to persist in secondary transplants, showing editing is possible in long-term HSCs (mean editing efficiency 34.5%, Fig F). Potential off-target effects were assessed in-situ by CIRCLE-seq; most candidate sites were in intergenic and intronic regions (Fig G & H). The top 250 sites were found to persist in secondary transplants, showing editing is possible in long-term HSCs (mean editing efficiency 34.5%, Fig F). Potential off-target effects were assessed in-situ by CIRCLE-seq; most candidate sites were in intergenic and intronic regions (Fig G & H). The top 250 sites were found to persist in secondary transplants, showing editing is possible in long-term HSCs (mean editing efficiency 34.5%, Fig F).
P105  BLOOD MICROVESICLES AS BIOMARKERS TO PREDICT VASO-OCCULSIVE CRISIS IN SICKLE CELL ANEMIA

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Background/Aims: Sickle cell anemia (SCA) is a monogenetic disorder caused by a mutation that results an abnormal hemoglobin (HbS) with a susceptibility to polymerize and deform erythrocytes which leads to complications such as Haemolysis, chronic infections and vaso-occlusive and pain crises (Williams et Thein, 2018). The polymerization of HbS inside red blood cells leads to complex interactions with the cell membrane and other molecules which triggers the apoptosis of different blood cells and the release of microvesicles (MV) that are derived from the cytoplasm of cells submitted to stress conditions that result in apoptosis or activation. The generation of MVs in SCA could serve as a potential biomarker to predict serious cardiovascular complications (Olatunya et al, 2019). Therefore, our study suggests the research of MVs as potential cellular biomarkers and the implementation of a new strategy of innovative predictive diagnosis in order to avoid the serious complications of sickle cell anemia.

Methods: Clinically diagnosed homozygous SCA patients from the Tunis national bone marrow transplant center and healthy donors were sampled for hematological and cellular assays. Flow cytometry was performed in order to quantify apoptotic MVs derived from erythrocytes, platelets and endothelial cells using specific fluorescent antibodies and dyes.

Results and Discussion: Our results showed a statistically significant increase in the number of apoptotic MVs which results a high apoptosis rate in patients' cells comparing to healthy donors. We also found that MVs derived from erythrocytes, platelets and endothelial cells were clearly elevated in SCA patients which suggests their potential contribution in thrombotic risk and chronic hemolytic anemia. Our findings suggest that microvesicles can be considered as hemolytic biomarkers for a predictive diagnosis so that disease complications could be avoided.

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P106  EARLY PREVENTIVE DIAGNOSIS OF HEMOLYTIC ANEMIA IN SICKLE CELL PATIENTS BY DETECTING THE TRIGGERING OF ERYPTOSIS.

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Background/Aims: Sickle cell disease (SCD) also known as sickle cell anemia is one of the most worldwide disseminated hereditary hemoglobinopathies. It is caused by a single amino acid substitution at the sixth residue of 3 globin gene (GluVal), which results in an abnormal hemoglobin called hemoglobin S (HbS). The acceleration of HbS polymerization induces rigid and dysfunctional erythrocytes that play a central role in acute and chronic clinical manifestations of SCD (Conran et al, 2009).

Vaso-occlusion and hemolytic anemia are the hallmarks of SCD. We aim to explore the cellular environment of red blood cells to explain the pathophysiology of SCD. In fact, the life span of circulating erythrocytes in healthy individuals vary from 100 to 120 days. In SCD, red blood cells undergo a form of cell death, namely, eryptosis before they reach their full life span. Eryptosis is triggered by a wide variety of factors as hyperosmolarity, oxidative stress and energy depletion. It is characterized by the presence of membrane blebbing, cell shrinkage, and phosphatidylserine (PS) exposure (Lang et al, 2012). In this study, we will explore the mechanism of triggering of eryptosis in Sickle cell disease.

Methods: Following clinical diagnosis, 50 homozygous SCD patients and 30 healthy donors were identified for hematological and cellular assays. Flow cytometry was performed in order to determine the viability parameters of erythrocytes. The morphology of red blood cells and the externalization of phosphatidylserine was detected by labeling red blood cells with Annexin V. Moreover, we had identified intracellular calcium concentration and ceramide level by labeling erythrocytes with Fluo-3-am and anti-ceramide antibodies. Finally, we had quantified reactive oxygen species (ROS) by labeling red blood cells with CM-H2DCFDA.

Results and Discussion: Eryptosis in sickle cell patients is accelerated. In fact, PS (+) red blood cells are more present in patients than in healthy subjects. Therefore, eryptosis is triggered by oxidative stress, which stimulates the increase of calcium activity and subsequent externalization of PS and red blood cells shrinkage in sickle cell patients. However, the pathway of ceramide can also be considered a potential stimulating factor of eryptosis in SCD. Eryptosis ensures healthy erythrocyte quantity in circulation, whereas excessive eryptosis is the cause of acute anemia and may contribute to vaso-occlusive crisis in SCD patients.

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Clinical and epidemiological studies

P107  A PHASE 2/3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MITAPIVAT IN PATIENTS WITH SICKLE CELL DISEASE

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Background: The key pathology in sickle cell disease (SCD), a life-threatening, hereditary hemoglobin (Hb) disorder, is red blood cell (RBC) sickling due to polymerization of deoxygenated sickle Hb (HbS), which can be exacerbated by increased levels of the glycolytic metabolite 2,3-diphosphoglycerate (2,3-DPG), and decreased ATP.1–3 Sickled RBCs are rigid, not deformable, and fragile, resulting in vaso-occlusion triggering pain and chronic hemolysis.4–6  SCD treatment options are limited, with an unmet need for safe and effective therapies to improve anemia and reduce pain. Mitapivat is an oral, activator of RBC pyruvate kinase (PKR), a key glycolytic enzyme. PKR activation decreases 2,3-DPG and increases ATP, which may reduce HbS polymerization, RBC sickling, and hemolysis in SCD.7,8 Data from the phase (ph) 1 National Institutes of Health multiple ascending dose study of up to 100 mg mitapivat twice daily (BID) in SCD (NCT04000165) showed that mitapivat was safe and tolerable, increased ATP, and decreased 2,3-DPG in a dose-dependent manner, and improved anemia and hemolysis.9–12

Aims: To report the study design of RISE UP (NCT05031780, EudraCT: 2021-001674-34), a ph 2/3, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of mitapivat in patients (pts) with SCD.

Methods: Eligible: pts aged ≥16 yrs with documented SCD (HbSS, HbSC, HbSβ0thalassiemia, other SCD variants), ≥10 sickle cell pain crises (SCPCs; acute pain needing medical contact, acute chest syndrome, priapism, hepatic or splenic sequestration) in the prior 12 months, and Hb 5.5–10.5 g/dL. If taking hydroxyurea (HU), the dose must be stable for ≥90 days before starting study drug. Ineligible: pts receiving regularly scheduled blood transfusions, with severe kidney disease or hepatobiliary disease, currently receiving SCD therapies (excluding HU) or who have received gene therapy, bone marrow or stem cell transplantation. In the double-blind ph 2 part, 69 pts will be randomized (1:1:1) to 50 mg or 100 mg mitapivat, or placebo BID for 12 weeks (wks). The primary objective of ph 2 is to determine the recommended ph 3 mitapivat dose by evaluating anemia and safety vs placebo via the following endpoints: Hb response (≥1.0 g/dL increase in average Hb concentration over Wks
10–12 vs baseline [BL]), and type, severity, and relationship of adverse events and serious AEs.

In the double-blind part, 198 pts who did not participate in ph 2 will be randomized [2:1] to the selected ph 3 mitapivat dose or placebo BID for 52 wks, stratified by number of SCPCs in the prior yr (<5, ≥5) and HU use. The primary objectives of ph 3 are to determine the effect of mitapivat vs placebo on anemia, measured by Hb response (≥1.0 g/dL increase in average Hb concentration over Wks 24–52 vs BL), and the effect of mitapivat vs placebo on SCPC, measured by annualized rate of SCPC. Key secondary endpoints include average change from BL in Hb concentration, indirect bilirubin, percent reticulocyte, and Pt-Reported tests and Hydroxyurea.

Conclusion: This ph 2/3 study will investigate the efficacy and safety of mitapivat in the open-label extension period in each ph. Pts who complete the double-blind period will be eligible to receive mitapivat in the open-label extension period in each ph.

Results: Not yet available.

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P108 ASSESSMENT OF HEALTHCARE WORKERS’ KNOWLEDGE AND RESOURCE AVAILABILITY FOR CARE OF SICKLE CELL DISEASE AT HEALTH FACILITIES IN DAR ES SALAAM, TANZANIA

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Background: Sickle cell disease (SCD) is a global public health priority due to its high morbidity and mortality. In Tanzania, SCD accounts for 7% of under-five mortality. Cost-effective interventions such as early diagnosis and linkage to care have been shown to prevent 70% of deaths but require knowledge among healthcare workers and availability of resources at healthcare facilities. In Tanzania, data on these critical determinants is currently lacking.

Aim: To assess healthcare workers’ knowledge and resource availability for care of SCD at Health Facilities in Dar es Salaam, Tanzania.

Methods: A facility-based cross-sectional study was conducted between December-2020 and February-2021 among 490 nurses and clinicians at Temeke, Amana, MWananyamala and Muhimbili National Hospital in Dar es Salaam. Data was collected using structured questionnaire (knowledge) and inventory checklist (resources). Pearson’s Chi-square was used to determine association between level of knowledge and demographic factors. Multivariate logistic regression was used to ascertain the strength of associations. P-values < 0.05 were considered statistically significant.

Results: Of the 490 participants (28 years [IQR=26–35]), only 25.1% had good knowledge on SCD. The odds of good knowledge was 82% lower in nurses than clinicians (AOR= 0.177; 95% CI: 0.090, 0.349; p = 0.000); 95% lower in diploma than Master degree holders (AOR = 0.049; 95% CI: 0.008, 0.300; p = 0.001) and 4.6 times higher in those with 5 – 9 years than ≥ 10 years of experience (AOR=4.564; 95%CI: 1.341, 15.525; p=0.015). The regional-level hospitals lacked diagnosed tests and Hydroxyurea.

Conclusion: There was a general lack of knowledge on SCD among healthcare workers and limited availability of critical resources for the diagnosis and care of SCD, especially at regional-level hospitals. Efforts are needed for their improvement in order to enhance care to patients, thus reducing the morbidity and mortality due to SCD in Tanzania.

P109 CLINICAL CATEGORIZATION OF CHILDREN WITH SICKLE CELL DISEASE USING SEVERITY SCORE AT A TERTIARY CARE CENTER

Daftar Isi

1. Introduction and Aim:
2. Literature Review:
3. Objective and work plan:
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5. Results:
6. Discussion:
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70 with mean ± standard deviation of 27.69 ± 24.51. Approximately 63.7% had mild disease, 13.2% moderate disease, and 35.7% severe disease, according to our severity score grading system. Comparison of international score with our score was done with a matching of 64.9%. Some minor modifications were done in a validated score due to local factors and clinical diversity. Present samples cohort (171) was divided randomly into two groups; Discovery group (N=100) and Validation group (N=71). Validation was done with overall matching of 81.5% after including parameters which was not present in an international score. Score matching increased from 65% to 82%. All weightings demonstrated a significant difference between the scores of mild, moderate, and severely affected patients, as classified by a subjective rating or with an existing index (P < 0.01).

**Conclusion:** Routine evaluation of disease severity in children with SCA will help to prospectively identify children at higher risk for a turbulent clinical course who may need more active management and monitoring. Assessment of patients objectively after any type of intervention like counselling, treatment (prenatal and post hydrouxypure) can be done by score.

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**PI110 CLINICAL CHARACTERISTICS OF COVID-19 IN SICKLE CELL DISEASE (SCD) PATIENTS**

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**Introduction** SCA is a common genetic disorder in Saudi Arabia with estimate of 1.4 % of population\(^1\). The prevalence of SCD in Jazan region is around 24 per 10,000 which consider the second region with high prevalence of SCD after eastern province. COVID-19 infection outbreak has affected SCD with different outcome.

**Objectives:** This research aims to determine the clinical picture of COVID-19 in patients with sickle cell disease SCD. The study represented the risk factors for severe COVID-19 presentation and predictors for poor prognosis in this group of patients.

**Methods:** This study is a retrospective, descriptive, observational study of SCD adult and pediatric patients in Prince Mohammed Bin Nasser Hospital, Jazan, Saudi Arabia, who were diagnosed with COVID-19 virus infection at the study center from March 2020 to September 2021. To describe clinical presentation of SCD patients of different severities, who got COVID-19 during the study, socio-demographic data, clinical presentations, laboratory parameters, medications use, as well as COVID-19 symptoms and severity were extracted and analyzed from the medical record files.

**Results:** 43 medical records for adult and pediatric sickle cell patients with COVID-19 were collected, in order to determine the impact of COVID-19 on the clinical presentation of SCD patients. (53%) were females, (47%) were males with a mean age of 24 years (±1.9), (37%) of the sample suffered from major comorbidities, out of which 44% had ACS, and 11.6% have pulmonary embolism. The most prevalent clinical symptoms were fever (56%) and Shortness of Breath (37%). (16%) of included patients were admitted to the ICU with an average length of stay equals to 3.9 days (±0.6).

CBC showed normal parameters of PLT with a mean equal to 327 K/μL (±21.6), Basophils 0.05 K/μL (±0.01), Lymphocytes 3.6 K/μL (±0.4). High averages were found for WBC 13.8 K/μL (±1.1), Neutrophils 8.8 K/μL (±0.9) and PT 14.2 seconds (±0.3). The only laboratory parameter that showed low average reading was Hemoglobin, with a mean equal to 8 g/dl (±0.2). Out of the 41 patients who undergone CRP tests, results were positive. The main CT chest finding were ground glass appearance in 30% of the patients 88% of the studied patients were on Hydroxyurea, 76% were on 1000 mg dose. For COVID-19 management, majority of patients were on Antibiotics 93%, 70% of patients started Anticoagulants, 51% of the patient has received antiviral treatment. 32.5% of the patient were treated with steroids. 70% of the patients have received blood transfusion, 5 patients 12% were managed at home. One patient underwent surgery with falciparum malaria. Total deaths was 2 patients represented 4.6 % out of total SCD patients with COVID-19 who were included in the study.

**Conclusion:** After exploring the impact of COVID-19 on SCD patients, the main presenting symptom were fever and shortness of breath. The major complication were acute chest syndrome 44% and pulmonary embolism in 12%. The overall prognosis was excellent and most of the patient have recovered. The death was reported in 2 patients only. Outpatient treatments were feasible in 12% of the patients.

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**PI111 COVID-19 IN PATIENTS WITH THALASSEMA AND SICKLE CELL DISEASE: A SINGLE CENTER EXPERIENCE**

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**Background:** Thalassemic patients present complications such as iron overload, cardiac disease or diabetes that are expected to make them more vulnerable to COVID-19. Acute complications of SCD triggered by a viral infection include painful vaso-occlusive episodes, acute chest syndrome (ACS) and venous thromboembolic disease (VTE). Published data report variable rates of severe COVID-19 in thalassemia whereas for SCD more robust data exist suggesting a strong association with severe disease and mortality.

**Aims:** The aim of the present study was to report the severity and mortality of COVID-19 in thalassemic and SCD patients of a Greek Center and investigate possible risk factors for severe disease.

**Patients and Methods:** The patient population of our Center includes 200 thalassemic patients and 320 SCD (of which 73 and 53 transfusion dependent, respectively). Baseline clinical and laboratory data and manifestations, clinical course, treatment and outcome of COVID-19 were collected from medical files for all the patients that had a PCR-documented COVID-19 infection since the pandemic initiation. Association of characteristics with severe disease or hospitalization was investigated with Fisher’s exact test.

**Results:** Since August 2020 until November 2021 34 patients (21 thal and 13 SCD) were infected by SARS-CoV2 corresponding to 10.5% and 4% of our patient population, respectively. Their median age was 47 yrs (±17), 52% of them were males, (47%) were females with a mean age of 24 years (±1.9), (37%) of the sample suffered from major comorbidities, out of which 44% had ACS, and 11.6% have pulmonary embolism. The most prevalent clinical symptoms were fever (56%) and Shortness of Breath (37%). (16%) of included patients were admitted to the ICU with an average length of stay equals to 3.9 days (±0.6).

CBC showed normal parameters of PLT with a mean equal to 327 K/μL (±21.6), Basophils 0.05 K/μL (±0.01), Lymphocytes 3.6 K/μL (±0.4). High averages were found for WBC 13.8 K/μL (±1.1), Neutrophils 8.8 K/μL (±0.9) and PT 14.2 seconds (±0.3). The only laboratory parameter that showed low average reading was Hemoglobin, with a mean equal to 8 g/dl (±0.2). Out of the 41 patients who undergone CRP tests, results were positive. The main CT chest finding were ground glass appearance in 30% of the patients 88% of the studied patients were on Hydroxyurea, 76% were on 1000 mg dose. For COVID-19 management, majority of patients were on Antibiotics 93%, 70% of patients started Anticoagulants, 51% of the patient has received antiviral treatment. 32.5% of the patient were treated with steroids. 70% of the patients have received blood transfusion, 5 patients 12% were managed at home. One patient underwent surgery with falciparum malaria. Total deaths was 2 patients represented 4.6 % out of total SCD patients with COVID-19 who were included in the study.

**Conclusion:** After exploring the impact of COVID-19 on SCD patients, the main presenting symptom were fever and shortness of breath. The major complication were acute chest syndrome 44% and pulmonary embolism in 12%. The overall prognosis was excellent and most of the patient have recovered. The death was reported in 2 patients only. Outpatient treatments were feasible in 12% of the patients.

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thalassemic red blood cells (RBCs), despite increased energy demands. Mitapivat is an oral activator of RBC pyruvate kinase (PKR), a glycolytic enzyme that regulates ATP production. In a phase 2 study of patients with α- or β-non-transfusion-dependent thalassemia (NTDT), twice-daily (BID) dosing with mitapivat increased hemoglobin (Hb) levels by ≥1.0 g/dL in 80% of patients, supporting the broadening of mitapivat’s development in thalassemia.

**Aims:** To report the study designs of ENERGIZE (2021-000211-23) and ENERGIZE-T (2021-000212-34), two phase 3 trials to assess the efficacy and safety of mitapivat in adults with α- or β-NTDT or transfusion-dependent thalassemia (TDT), respectively.

**Methods:** Both studies are phase 3, multicenter, randomized, double-blind, placebo-controlled trials (Figure). In ENERGIZE, approximately 171 eligible adults with NTDT will be randomized (2:1) to receive 100 mg mitapivat BID or placebo for 24 weeks. Upon completion, eligible patients can transition to a 5-year, open-label extension. Key inclusion criteria: documented diagnosis of thalassemia (β-thalassemia ± α-globin mutations, Hb E β-thalassemia, or α-thalassemia [Hb H disease]), Hb concentration ≤10.0 g/dL, and NTDT defined as ≤5 RBC units during the 24-week period before randomization and no RBC transfusion ≤8 weeks prior. The primary endpoint is an Hb response defined as ≥1.0 g/dL increase in average Hb concentration from Week 12 through 24 compared with baseline. Secondary endpoints include patient-reported outcomes, changes in Hb, markers of hemolysis and erythropoiesis, and safety. In ENERGIZE-T, approximately 240 eligible adults with TDT will be randomized (2:1) to receive 100 mg mitapivat BID or placebo for 48 weeks. Upon completion, eligible patients can transition to a 5-year, open-label extension. Key inclusion criteria: documented diagnosis of thalassemia (same genotypes as detailed for the ENERGIZE study), and TDT defined as ≥20 RBC units transfused and no transfusion-free period ≥8 weeks during the 24 weeks before randomization. The primary endpoint is a transfusion reduction response, defined as a ≥50% reduction in transfused RBC units with a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. Secondary endpoints include additional measures of transfusion burden, changes in iron markers, and safety. **Results:** Not yet available. **Conclusions:** ENERGIZE and ENERGIZE-T are the first pivotal studies to assess a potential treatment across a broad spectrum of patients with thalassemia (ie, patients with TDT and NTDT; α- and β-thalassemias). ENERGIZE and ENERGIZE-T will evaluate the efficacy and safety of mitapivat, a novel, first-in-class oral activator of PKR. Both studies are actively recruiting.

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1. Taher et al. Lancet 2018; 391:155–67.
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Background: The paper presents results of a 27-year epidemiological study of screening and follow-up haemoglobinopathies in Slovakia.

Aims: The incidence of haemoglobinopathies in Slovak Republic

Methods: Between 1993 – 2020, in two centres in Bratislava and in one centre in Kosice, carriers of beta-thalassaemia genes or other haemoglobinopathies were searched for. Patients with a probability of having a haemoglobinopathy were sent to the research facilities. Diagnosis was performed by haematologists, whereby the family history was evaluated, together with overall clinical condition, blood count and blood smear, iron and haemolysis parameters, mutations of hereditary haemochromatosis, and haemoglobin electrophoresis testing.

Results: A clinical suspicion of the haemoglobin form of beta-thalassaemia or other haemoglobinopathies was documented in 694 patients. Of them 25 (6.04%) patients were foreigners. 415 (59.85%) patients were genetically examined. In 385 (92.99%) of them heterozygote beta-thalassaemia was confirmed (in 98 families). Five patients (1.21%) were diagnosed for delta-beta-thalassaemia, 4 patients (0.97%) for delta-beta-gama-thalassaemia or persistent hereditary fetal haemoglobin. In total we diagnosed 20 mutations of beta-globin gene. The most frequent mutations were IVS 1.110 (G-A), IVS II-1(G-A) and codon 39. Evidence of haemoglobin S (heterozygote sickle cell anaemia) was also notable in two non-relative children, whose fathers were of African origin, in one patient of Ghana and in one patient from Nigeria. One female patient was followed up for haemoglobin Santa Ana (mutation de novo), one family for haemoglobin Bishopstown and one patient for mutation KLF1 gene.

In our group were 14 patients (3.14%) diagnosed for alpha-thalassaemia. All patients were heterozygotes, only one female patient from Macedonia was a double heterozygote for beta-thalassaemia. Clinically all of the patients had a minor or intermedia form. In the years 2012–2019 we observed 12 pregnant patients with beta-thalassaemia. One of them had multiple pregnancies, all deliveries were without haematological complications.

Conclusions: The study showed that in the west and eastern Slovakia there is a higher number for thalassaemia and other haemoglobinopathies. Mutations are of historical origin or over the past years we have recorded an increase number of mutations from areas with high incidence of haemoglobinopathies.

Key words: thalassaemia – sickle cell disease – prevention - epidemiological study – Slovakia

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P114 NEWBORN SCREENING FOR HAEMOGLOBINOPATHIES IN BIDA, NORTH CENTRAL NIGERIA.

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Background: The global annual population of newborns with structural haemoglobin disorders is estimated at five million. Nigeria accounts for more than 30% of these in Sub-Saharan Africa with under-five mortality from haemoglobinopathies reaching 50–90%. Despite this huge burden and a 15-fold reduction in deaths from haemoglobinopathies in countries that conduct newborn screening, most sub-Saharan Africa countries do not have a screening program. Haemoglobin electrophoresis is also not sensitive for newborn screening.

Objectives: This study was carried out to determine haemoglobin phenotype patterns and frequency in neonates attending routine immunization clinics in Bida, and to identify factors associated with the occurrence of haemoglobinopathy.

Methods: It was a descriptive cross-sectional study that recruited 254 neonates by multi-staged sampling technique from nine immunisation centres. Heel prick blood sample collected on Guthrie cards were tested using High-Performance Liquid Chromatography (HPLC). The relationship of various risk factors with the occurrence of an abnormal haemoglobin variant was analysed with the Statistical Package for Social Sciences.

Results: The Ha phenotype found in this study were HbFA - 73.6% (187/254), HbFAS - 23.2% (59/254), HbFAC - 1.6% (4/254), HbFS - 4.2% (10/254), and HbFAD-0.4% (1/254). There was an almost equal normal haemoglobin occurrence in both genders. The majority (89%) of mothers did not know their HB phenotype, one-quarter of these had a newborn with an abnormal phenotype and 20% married in consanguineous marriages. Wrong perception of sickle cell disease was common.

Conclusion: Abnormal haemoglobin variants were present in more than one-quarter (26.4%) of the neonatal population studied in Bida. Most parents were not aware of their haemoglobin phenotype and had a wrong perception of sickle cell disease. Consanguinity though common in the population did not significantly affect the occurrence of an abnormal haemoglobin phenotype.

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P115 REAL-WORLD DATA ON THE EFFICACY OF PHARMACEUTICAL-GRADI L-GLUTAMINE IN PREVENTING SICKLE CELL DISEASE-RELATED ACUTE COMPLICATIONS AND HEMOLYSIS IN PEDIATRIC AND ADULT PATIENTS.

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Background: Oxidative stress is a key contributor to the pathophysiology of sickle cell disease (SCD) and related complications including acute pain (vaso-occlusive crisis VOC) and acute chest syndrome (ACS) [1-3]. L-glutamine (L-Gln), a precursor of nicotinamide adenine dinucleotide (NAD), has been shown to play a key role in the regulation of oxidative stress [4]. In a pivotal Phase 3 trial, L-Gln demonstrated significant
reduction in VOCs, hospitalizations, and ACS events compared to placebo in patients with SCD, or with no hydroxyurea (HU) use, over a 48-week period [4]. In September 2021, a re-analysis of the trial data revealed that L-Gln decreased the number of VOCs by 45% [5].

**Aims:** To confirm the efficacy of pharmaceutical-grade L-glutamine in pediatric and adult patients with SCD at follow-up time points of 24, 48 and 72 weeks.

**Methods:** In a retrospective study conducted from October 2019 to April 2020, 19 patients (4 patients from Qatar and 15 patients from France) were treated orally with L-Gln (0.3mg/kg) twice daily. Laboratory parameters (hemoglobin levels (Hg), hematocrit proportion (Ht), WBC counts, reticulocyte counts, and LDH levels) were measured at baseline and follow-up time points. Clinical parameters (number of VOCs, hospitalizations, days hospitalized, ACS events, and blood transfusions) were documented for the year prior to treatment initiation as baseline values. These parameters were also collected at 24, 48, and 72 weeks from treatment initiation. Adverse events (AEs) were also collected during the treatment period. The data values at 24, 48, and 72 weeks have been annualized. Statistical analysis was performed using MedCalc Version 20.015.

**Results:** 19 patients (68±5 years old; 53% patients <18 years) were retrospectively analyzed. 63% of the patients were receiving HU at baseline and 47% received concomitant HU during the study. Compared to baseline, patients had significantly fewer VOCs at 24, 48, and 72 weeks following L-Gln therapy (median change from 3.0 to 0; P=0.00001). Compared to baseline, there were fewer hospitalizations (median change from 3.0 to 0; P=0.00001) and patients spent fewer days in hospital (median change from 15.0 to 0; P=0.00001). Moreover, at 24, 48, and 72 weeks, the number of blood transfusions was considerably lower than at baseline, with a significantly reduced number of transfusions (3.0 to 0; P=0.00001). In the year prior to treatment initiation, 2 patients reported a single ACS event, but, no such events were observed during therapy. Following treatment with L-Gln, the mean Hg level increased significantly from baseline to 72 weeks (8.2 to 8.9g/dL; P=0.001) with peak mean increase from baseline of 11.2% at 48 weeks. A similar increasing trend was observed for Ht from baseline to 72 weeks (24% to 27%; P=0.001) with highest mean improvement from baseline of 15.5% at 48 weeks. Conversely, mean reticulocyte counts and LDH levels were significantly reduced at follow-up time points compared to baseline (P=0.003 and P=0.001, respectively). Only few AEs occurred and were mild. No compliance issue was reported.

**Conclusions:** This study demonstrated that L-Gln therapy in SCD patients from Qatar and French Guyana resulted in significant and sustained improvements in clinical outcomes (number of VOCs, number and duration of hospitalizations, and number of blood transfusions) and an increase in Hg and a reduction of hemolysis. 2 patients with a history of ACS did not experience any of those events during L-Gln therapy.

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**P116 THE IMPACT OF COVID19 PANDEMIC ON SICKLE CELL MANAGEMENT: EXPERIENCE OF A SINGLE PEDIATRIC CENTER**
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**Background:** COVID19 pandemic has put an incompressible pressure on all health services—including those offered to hemoglobinopathy patients. Sickle cell disease management, although not routinely requiring inpatient facilities, is dependent upon hospital based services on a great extent.

**Aims:** Aim of the present study was to evaluate the impact of COVID19 pandemic on medical management of sickle cell disease patients followed at a single pediatric center in Northern Greece.

**Methods:** Patient records were reviewed in order to assess changes reflecting limited access to specialized care, i.e. number of disease related complications, number of hospital routine visits and number of disease related hospitalizations, during the 18month pandemic in Greece.

**Results:** The study included 23 patients, 17 female (74%) and 6 male (26%). Age range was 2 to 19 years. Eighteen (18) patients (78.3%) were double heterozygotes for sickle cell and beta thalassemia, 4 (17.4%) were sickle cell homozygotes and 1 patient (4.3%) was double heterozygote for sickle cell disease and hemoglobinopathy D. Out of 23 patients, 4 were on regular blood transfusions due disease related issues (primary prophylaxis for cerebrovascular disease or hypersplenism in 2 cases, severe anemia or repeated pain crises in 2 other cases). No significant difference was recorded in number of hospital visits during the 18month period before and during the pandemic (5.45 visits/year and 6 visits/year, respectively—p = 0.49), reflecting a stable course for patients not receiving regular transfusions and an unaffected by blood shortage or limited hospital access course for regularly transfused patients. To that end, no significant changes were recorded in non-COVID related hospitalizations between the two groups (0.57/year before the pandemic and 0.39/year during the pandemic, p = 0.32). In addition, no difference was noted between the number of patients with a history of hospitalization (0.63 episodes per year vs 0.63 episodes per year, p = 1.0). An otherwise unremarkable overall clinical and laboratory course was recorded for all patients during the two time periods compared. No changes in regular monitoring was noted and no changes in drug prescription or drug availability for patients on hydroxyurea were recorded.

**Summary-Conclusions:** Although sickle cell disease patients require close monitoring, mostly dependent upon hospital based services, the COVID19 pandemic does not seem to have limited access to recommended care in this patient group.

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**P117 THE INTERNATIONAL HAEMOglobinOPATHY RESEARCH NETWORK (INHERENT): AN INTERNATIONAL INITIATIVE TO STUDY THE ROLE OF GENETIC MODIFIERS IN HAEMOglobinopathies**
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**Background:** Haemoglobinopathies, including sickle cell disease (SCD) and thalassemia syndromes, represent the commonest monogenic diseases in the world. Although the haematoglycitics is well established, the diverse clinical manifestations and the varying degree of severity are less understood and are thought to be governed, in part, by genetic modifiers. Despite the identification and characterisation of a few genetic modifiers by previous studies, these are yet insufficient to guide treatment recommendations or stratify patients reliably. Larger, multi-ethnic studies are needed to identify and elucidate further genetic modifiers that can be used for patient stratification and personalised treatment. There is a growing need for deeper insight with the availability of novel targeted therapies and potentially curative options like gene therapy in both SCD and thalassemia.
Aims: The International Haemoglobinopathy Research Network (INHERENT) is a recently established network with the aim of investigating the role of genetic modifiers in haemoglobinopathies, through a large-scale, multi-ethnic genome-wide association study (GWAS).

Methods: INHERENT brings together nine existing international or regional consortia in the field of haemoglobinopathies, namely ITHANET, RADeep, ARISE, SPARCO, SADaCC, REDAC, the HVP Global Globin Network, the International Health Repository, and the ClinGen Haemoglobinopathy VCEP. The activities of INHERENT are currently divided into five working groups, as follows: clinical, genotyping, data management and analysis, ethics, and knowledge translation. Participation in INHERENT is open for any group that can submit a minimum number of samples with their core phenotypic description. INHERENT membership is international and interdisciplinary and, currently, includes over 160 experts from 89 organisations, spanning 36 countries worldwide (Figure). INHERENT aims to recruit over 30,000 haemoglobinopathy patients, which is over one order of magnitude larger than any previous GWAS in the field.

Summary: We demonstrate that the current membership of INHERENT has the potential to reach this sample size target. The large increase in the sample size and the diversity in the studied populations will enable novel discoveries and expand knowledge on haemoglobinopathy genetics, thus paving the way for advancing the science of personalised diagnosis and treatment.

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P118 THE ROLE OF HEMOGLOBIN AND HEMOLYSIS ON TRANSCRANIAL DOPPLER VELOCITIES IN CHILDREN WITH SICKLE CELL DISEASE: DATA FROM A NATURAL HISTORY COHORT
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Background: Children with sickle cell disease (SCD) are at increased risk of cerebrovascular events that can impact neurocognitive development and quality of life (Colombatti 2016). Transcranial Doppler ultrasound (TCD) is a validated screening tool to identify pediatric SCD patients with the highest risk of stroke, to start on a preventive chronic blood transfusion regimen (Estcourt 2020; Inusa 2019). We aimed to evaluate the distribution of TCD velocities in a pediatric natural history cohort and investigate their correlation with hematological variables and treatments.

Methods: We performed a retrospective analysis on data from a prospective pediatric cohort followed from January 1, 2009, to December 31, 2020 (censoring date). We used transcranial Doppler imaging (TCDi) and classified results according to STOP criteria, considering terminal internal carotid artery (TICA) and middle cerebral artery (MCA) time-averaged maximum mean velocities (TAMMVs). Hematological, clinical, and treatment variables were available from the natural history cohort database.

Two-sample and Welch t-tests for unequal variances were used to compare mean hemoglobin (Hb) values and hemolysis markers in patients with and without abnormal/conditional TCDi results. Fisher and chi-square tests were used to compare categorical variables. Linear regression models were used to assess the effects of MCA and TICA TAMMVs as continuous variables on Hb. Odds ratios (ORs) for neurological events at different Hb levels were estimated using generalized estimated equations (GEE) with a binomial distribution, logistic function, and exchangeable correlation structure, allowing for correlation among repeated observations for the same patient. Multivariable GEE including characteristics and treatments variables were used to evaluate the association between neurological events and Hb.

Results: Of the 182 SCD patients in the cohort, 169 had assessments of cerebral vasculopathy, and 155 had evaluable TCDi (583 exams). The median follow-up of the entire cohort was 79.8 months (range: 2.1–298.6 months) (interquartile range [IQR]: 36.9–126.3 months). The median age at the censoring date was 13.4 years (IQR: 9.1–17.5 years). Patients with abnormal/conditional TCDi results had lower Hb (8.4 vs 8.9 g/dL,
and AOUI Verona, Verona, ITALY; Albert Einstein College of Medicine, Bronx, New York, NY, UNITED STATES; Roche Products Limited, Welwyn Garden City, UNITED KINGDOM; Cochrane Database Syst Rev. 2020;4(4):CD012389. 3. Inusa BPD, et al. J Clin Med. 2019;9(1):44.

P119 TRIAL IN PROGRESS: THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B CROSSWALK-A TRIAL EVALUATING THE SAFETY OF CROVALIMAB FOR THE MANAGEMENT OF ACUTE UNCOMPROMICED VASCO-OCCULSIVE EPISODES (VOES) IN PATIENTS (PTS) WITH SICKLE CELL DISEASE (SCD)

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Background: SCD is a group of autosomal recessive red blood cell (RBC) disorders caused by a single point mutation in the β-globin gene, resulting in the production of hemoglobin S (HbS). HbS polymerizes within RBCs under certain conditions, leading to the distortion of the RBC membrane and generation of dense and sickle RBCs. These pathologic RBCs contribute to microvascular occlusions, which may present as acute, painful episodes called VOEs. Although most VOEs are managed in the acute uncomplicated setting with parenteral opioid analgesics, vaccinations against Neisseria meningitidis, Hemophilus influenzae type B, and Streptococcus pneumoniae must be current. Eligible pts will be randomized 2:1 to receive either a single intravenous weight-based tiered dose of crovalimab or placebo. All pts will continue with pain management and other supportive care for their VOE, and may continue concurrent SCD-directed therapies. Pts will be followed during hospitalization until discharge and will also be followed post-discharge during an observational period. The maximum total study duration for an individual pt, including the hospitalization and observational periods, will be 12 weeks. The primary objective is to evaluate the incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0, incidence and severity of infusion-related reactions and hypersensitivity, and change from baseline in targeted vital signs and clinical laboratory test results. Efficacy, pharmacokinetics, pharmacodynamics, immunogenicity, and exploratory biomarker endpoints will also be evaluated.

Results: CROSSWALK-a is scheduled to be completed in September 2023. Summary: CROSSWALK-a is enrolling pts with SCD in 5 countries.

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P120 TRIAL IN PROGRESS: THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2A CROSSWALK-C TRIAL EVALUATING THE EFFICACY OF CROVALIMAB AS ADJUNCT TREATMENT IN THE PREVENTION OF VASCO-OCCULSIVE EPISODES (VOES) IN PATIENTS (PTS) WITH SICKLE CELL DISEASE (SCD)

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Background: SCD is a group of autosomal recessive red blood cell (RBC) disorders caused by a single point mutation in the β-globin gene, with either homozygous inheritance or heterozygous co-inheritance with other pathogenic variants of the β-globin gene. Hemoglobin S, produced as a result of this point mutation, polymerizes within RBCs under certain conditions, distorting them and generating dense and sickle RBCs. These pathologic RBCs contribute to microvascular occlusions, which may present as acute painful episodes called VOEs. Pts with SCD may also have severe chronic anemia, chronic pain, immune dysfunction, and progressive multi-organ damage. Current therapies for SCD include hydroxyurea, as well as newer treatments such as L-glutamine, crizanlizumab, and voxelotor. Despite these treatments, considerable morbidity and mortality among pts with SCD represents a significant unmet medical need. Complement pathway activation has been reported in pts with SCD at baseline, in acute pain crises, and in delayed hemolytic
transfusion reaction. Accumulating nonclinical data suggest the poten-
tial multimodal role for complement dysregulation in the pathophys-
iology of SCD, including vaso-occlusion, hemolysis, inflammation, thrombogenesis, endothelial activation, and end-organ damage. The complement pathway can be targeted by crovalimab, a novel anti-C5 monoclonal antibody that allows for small-volume subcutaneous (SC) self-injection. In a Phase 1/2 paroxysmal nocturnal hemoglobinuria (a complement-mediated disorder) study, crovalimab showed rapid, double-blind, placebo-controlled, Phase 2a study evaluating the efficacy and safety of crovalimab as adjunct therapy in preventing VOEs in pts with SCD.

Methods: Patients aged 12 to 55 years, weighing ≥40 kg to <100 kg and pts >100 kg). The primary objective is to evaluate the efficacy of crovalimab vs placebo based on the annualized rate of medical facility VOEs. Key secondary efficacy objectives are the annualized rate of acute chest syndrome, the annualized rate of home VOE, and change in urinary albumin-creatinine ratio, tricuspid regurgitant jet velocity, and Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue score in adults, from baseline to Week 49. Safety, pharmacokinetics, immunogenicity, and exploratory biomarker objectives will also be evaluated. Results: Primary results for CROSSWALK-c are expected in July 2024. Summary: CROSSWALK-c is enrolling pts with SCD and chronic VOEs in 6 countries.

Figure: CROSSWALK-c study schema

| Patients aged 12 to 55 years and weighing ≥40 kg | Placbo | Crovalimab |
|-----------------------------------------------|--------|-----------|
| N=50                                          |        |           |
| Follow-up up to 49 weeks                      |        |           |

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Infection, autointimunity, nutritional deficiencies

P121 PREVALENCE OF VERTEBRAL COMPRESSION FRACTURE AND HYPOVITAMINOSIS D IN CHILDREN WITH THALASSEMIA MAJOR

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Background: Thalassemia major has various complications that can increase morbidity and mortality. Osteoporosis is a common complication in thalassemia major and has a multifactorial pathogenesis. Osteoporosis can cause vertebral compression fractures and lead to disability. In TIF recommendation, a DEXA-scan is used to measure bone density in thalassemia patients. However, most patients in Indonesia could not afford the DEXA-scan examination because it is not covered by insurance. The 2019 ISCD Pediatric Positions Task Forces stated that the diagnosis of pediatric osteoporosis included the presence of a nontraumatic vertebral compression fracture (VF), without the need for BMD criteria. In Indonesia, there has been no study for the prevalence of hypovitaminosis D and vertebral compression fractures in children with thalassemia major and its correlation.

Objectives: To describe the prevalence of VF and hypovitaminosis D in children with thalassemia major.

Methods: A cross-sectional study design was conducted in children with thalassemia major aged 7–18 years at the Thalassemia Center at Cipto Mangunkusumo National Hospital. Detection and evaluation techniques for vertebral fractures were used plain radiograph from Siemens Healthcare – Ysis Max – X-ray. The classification is based on Global Consensus Recommendations on Prevention and Management of Nutritional Rickets, whereas <30 nmol/L or <12 ng/mL are deficient, 30–50 nmol/L or 12–20 ng/mL are insufficient. Results: This study obtained 165 subjects (50.1% boys, 66% homozygous beta-thalassemia). Fifty-two subjects (31.5%) have VF, and three of them have both thoracal and lumbar fractures. The most common sites of VF were lumbar five and thoracic 11–12. The youngest subject who has VF is seven years old. Osteopenia was found in 67.3% of patients. There were no subjects with fractures who had complaints of pain or a history of previous trauma. Vitamin D levels [25(OH)D] were measured in 122 subjects, and hypovitaminosis D occurred in 77.9% of the subject (32.8% deficiency, 45.1% insufficiency). Our study found no significant relationship between vitamin D levels on the incidence of vertebral compression fractures (p>0.05).

Conclusion: To our knowledge, this is the highest prevalence of VF among various studies that have been conducted. Vertebral X-ray is beneficial to detect bone density from osteopenia to fracture in children with thalassemia major. Hypovitaminosis D is common in thalassemia, requiring regular vitamin D administration. Further research is needed to consider the other contributing factors.

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Ageing and end organ damage

P122 DEEP LEARNING-BASED ALGORITHM FOR AUTOMATIC SPLEEN LENGTH MEASUREMENT

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Background: In Sickle Cell Disease (SCD), spleen enlargement happens frequently in children. Acute splenic sequestration occurs when the red pulp of the spleen filtering action is exaggerated and the red blood cells are trapped, which causes the spleen sudden enlargement. If left untreated, this condition can be life-threatening. The spleen length is typically measured in the clinic, including manual palpation and following ultrasound examination. However, the common clinical workflow is non-quantitative (manual palpation) and suffers from inter- and intra- experts’ variability (ultrasound examination). In the developing area, where there is a high prevalence of SCD, there is often a lack of experienced sonographers to conduct the length measurement while ultrasound examination. To address this problem, we set out to use a deep learning-based strategy to develop a full pipeline, which consists of a quality control system and an automated length measurement for spleen assessment.

Methods: We investigated the use of deep learning to automate the process of spleen length measurement. A deep learning model based on the ResNet was developed to classify whether the input ultrasound image could be used to measure the length. A U-net based network was trained to automatically segment the spleen. The principal components analysis was then applied to the segmentation to find the longest axis of the spleen, and the splenic length was computed based on the projection of the points within the segmentation to the axis.

References
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Figure: SPLEEN LENGTH MEASUREMENT

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Results: 475 ultrasound images of the spleen were used in this study. 475 images were used to train the quality control network (420 good quality images and 55 bad quality images), and 420 images (good quality images) were used in developing the automated spleen length measurement system. These images were obtained from SCD patients and were acquired as part of routine examinations at the Evelina Children’s Hospital, London. 108 images were manually measured by three experienced sonographers to compute the inter-expert variability as a comparison to our methods. The mean percentage error of our length measurement has reached 4.58% on good quality images which was within the human expert error (5.78%). Our quality control system has reached 0.964 sensitivity and 0.636 specificity. After incorporating bad quality images and the quality control system, the full pipeline reached 4.88% percentage length error, which is still within the human expert variability.

Conclusion: We have demonstrated that deep learning can be used for automating the length measurement for the spleen from ultrasound images. The performance of the developed pipeline has reached the human expert level. This can be potentially used in a real clinical scenario.

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Health services and outcomes research including psychology

P123 A SYSTEMATIC REVIEW OF THE BARRIERS TO UPTAKE AND ADHERENCE TO HYDROXYCARBAMIDE FROM THE PERSPECTIVE OF CHILDREN AND ADULTS WITH SICKLE CELL DISEASE, PARENTS AND CLINICIANS.

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Aim: The aim of this study was to identify the reasons for the poor uptake and adherence to hydroxyurea from the perspective of people with sickle cell disease, parents of children with sickle cell disease and clinicians of people with sickle cell disease.

Background: Children and adults with sickle cell disease have health related complications which impact on their health, quality of life and life expectancy. Hydroxyurea has been demonstrated to offer clinical benefits with minimal toxicities but uptake and adherence to hydroxyurea remains poor.

Method: This study was a systematic review. A search strategy covered several databases including Academic Search Complete, Medline, CINAHL Complete, SocIndex, PubMed, Psych Info, British Nursing Index, Cochrane and Science Direct. An inclusion and exclusion criteria was applied and 9 studies were then critically appraised using validated appraisal tools. Data was extracted, themes identified and results and findings synthesised.

Results: Four key themes and further subthemes were identified.

- Safety of hydroxyurea, subthemes: side effects, long term side effects, still experimental
- Knowledge and Understanding, subthemes: knowledge of hydroxyurea, knowledge of sickle cell disease, perceived effectiveness of hydroxyurea, perception of disease severity, perception of therapeutic effect in the community
- Clinician/healthcare, subthemes: clinician choice, clinician relationship trust in medical system
- Burden of taking, subthemes: remembering to take, aversion to taking pills, clinic reviews (missed work, school), number of blood tests, obtaining prescriptions/refills, costs, transport

Conclusions: Whilst scientific evidence suggests that the benefits of hydroxyurea far outweigh the risks, the participants in the nine included studies report barriers that effect its utilisation. Whilst many of the concerns have been reported previously this systematic review confirms that these barriers still exist. Clinicians and healthcare professionals must explore barriers with their colleagues, patients and families and need to make provisions to help reduce the burden of treatment with hydroxyurea. Continuing discussions and education throughout childhood, transition and into adulthood will enable patients and families to make informed decisions. Further qualitative studies would enhance the findings of this research.

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this topic is heterogeneous and we urgently require an evaluation of the evidence supporting efficacy of non-pharmacological interventions in reducing the frequency and intensity of sickle cell related pain in children with SCD.

**Aims:** The aim of this systematic review is to evaluate the evidence on the efficacy of non-pharmacological interventions in reducing the frequency and intensity of sickle cell related pain in children with SCD.

**Methods:** We performed a literature search through October 2021 using the terms ‘sickle cell’, ‘pain’, ‘psychotherapy’, ‘analytic’, and ‘health service’. We included randomized controlled trials and quasi-experimental studies that investigated the efficacy of non-pharmacological interventions on (1) pain frequency and intensity, and (2) analgesic and health service use in children with SCD.

**Results:** Eleven articles including 441 participants were included. Nine studies performed in the outpatient clinic investigated the efficacy of cognitive behavioral therapy, biofeedback, and massage. Two studies performed during hospital admission included virtual reality and yoga. Five studies reported significant reductions in the frequency and/or intensity of pain. One study reported a significantly reduced analgesic use. The remaining six studies did not report a reduction in pain related outcomes.

**Conclusions:** The evidence for non-pharmacological interventions to reduce pain in children with SCD seems promising, but due to heterogeneity of the included/published studies no firm conclusions can be drawn. To target SCD related pain in children, a multidisciplinary approach focusing on the physical, psychological and social aspects seems most appropriate, but the clinical implementation of non-pharmacological interventions first needs further exploration.

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**P125 EMPOWERING YOUNG ADOLESCENTS ON THE TRANSITION BY THE EDUCATION METHOD ORBIS SENSUALIUM PICTUS - THEIR OWN IMPROVING BLOOD CELL MORPHOLOGY AND MEDICAL RESULTS ON ACTIVE TREATMENT**

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**Background:** The transition from childhood to adulthood is an important part of a journey of people with inherited haemoglobinopathy and their families. The most difficult part is to find the way of motivation, so children and young adolescents can comply with their medications and attending their appointments even without the support of their families to achieve desirable targets and to maintain their good health.

**Method:** We started regular education of young adolescents on the transition in adult haematology department by an efficient and powerful method ORBIS SENSUALIUM PICTUS developed by Jan Amos Komensky, Czech teacher, living in the Netherlands in 17th century - teaching with images. We educate and motivate our clients by morphological, psychological and social aspects using image therapy.

**Results:** We are presenting improvement in compliance of the attendance and taking regular medication of young adolescents empowered by imagination education in our transition clinic.

**Summary:** Empowering young adolescents by visualising technique of reviewing their own blood cells under microscope and understanding the purpose of each medication and medical result is very powerful method of motivation. It can help them to engage better in regular consultations and to find the new meaning on their journey with inherited haemoglobinopathy. It can open the way of understanding their own disease with consideration of therapeutic options including hydroxyurea, voxelotor, crizanlizumab and gene therapy and allogeneic transplant.

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1. Brandow et al, Blood advances 2020; 4:12.
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Background: Despite a reduction in morbidity and mortality associated with the use of disease modifying therapies, sickle cell disease (SCD) remains associated with high healthcare resource utilization (HRU), primarily attributed to vaso-occlusive crisis (VOC). (1, 2) There are limited national estimates on HRU, cost of medical care, and treatment expenditures for patients with SCD in Lebanon. A better understanding of these estimates may provide new perspectives to improve access to high-quality cost-effective health care services.

Aims: We aimed to evaluate patterns of HRU and related cost in a cohort of patients with SCD receiving care in a Comprehensive SCD referral center at NINI hospital in North Lebanon.

Methods: A retrospective non-interventional observational study was conducted among 136 patients (54.4% females) with confirmed diagnosis of SCD in North Lebanon. Data on HRU including emergency department (ED) visits, ambulatory visits and hospitalizations collected in a patient health information (PHI)-anonymized format during the period 01 May 2018 - 30 Apr 2020 were obtained from patients’ paper and electronic medical files, as well as hospital and ED files. Uncomplicated VOCs were defined as pain crises, whereas complicated VOCs were defined as acute chest syndrome, acute splenic sequestration, acute hepatic sequestration or priapism. The annual rate of HRU visits was calculated as a ratio of the total number of visits to the total number of years of follow-up across all patients. The average annual cost was similarly calculated as the ratio of total cost of these visits to the total number of years of follow-up, based on available data.

Results: In the present study, the median age of patients at the time of study was 10.8 years (IQR 5.3 to 19.6 years). Majority of patients were diagnosed with SS (72.1%) and Sβ0 (21.3%) genotype across all age groups. Pain crisis (90.4%), fever (43.4%), acute chest syndrome (33.1%), and acute splenic sequestration (22.8%) were the most common SCD-related complications. The annual rate of HRU visits (per patient) was 5.7. Uncomplicated VOCs led to majority of hospitalizations, ICU and ED visits in adult patients (age >16 years). The average annual costs of HRU were $8,270,920 Lebanese pounds (LBP) amounting to $5,514 USD (per patient per year) of which 92.1% was for hospitalizations, 4% for ED visits and 3.9% for ambulatory visits. Annual costs for ED, ICU and hospitalizations were highest for uncomplicated VOC. Costs related to medications, diagnostics, non-hematologist medical consults, uncompensated care and lost productivity are not included in this analysis. Analgesics, folic acid and hydroxyurea were the most frequently administered medications across all age groups with 84% of patients being treated with hydroxyurea.

Conclusion: This real world study reveals that SCD and its related complications resulted in significant acute HRU. VOCs remain the primary factor for resource use, ICU admission and costs with the largest proportion of annual cost being attributed to hospitalizations. Despite the high HRU rate in this relatively young SCD cohort, the cost of HRU in a comprehensive setting with effective outpatient management as that in North Lebanon appears affordable for the health care system. However when additional SCD related and non SCD related costs of care are included, the economic burden of SCD care is likely to be significantly higher than the figures reported.

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P129 NARRATING SICKLE CELL DISEASE: THE EXPERIENCES OF PATIENTS AND CARRIERS

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P130 PROVIDING ADEQUATE HEALTHCARE TO PEOPLE WITH HEMOGLOBINOPATHIES DURING THE PANDEMIC (COVID-19)

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Background: Countries around the world were dealing with an increase in demand for COVID-19 healthcare, which was exacerbated by fear, confusion, and mobility restrictions, all of which impacted the provision of health care for all conditions. Patients with severe diseases, such as hemoglobinopathies, seem to pose additional challenges.

 Aim-Methods: An anonymous questionnaire was developed and given to 130 patients from four Thalassemia and Sickle Cell Disease Units of the National Health System of Greece Hospitals using stratified random sampling technique. To perform statistical analysis on the questionnaires, the MedCalc 2018 application was used.

Results: There were 130 participants (51 % women, 49 % males) with transfusion-dependent thalassaemia (84%), transfused sickle cell disease (15%), and other conditions (1%). During the pandemic, patients’ main concern was a lack of blood for transfusions (64 percent). The consistency of scheduled transfusions was not impaired (72 %) during the lock-down, while they were occasionally delayed (21 %) or did not appear at all (7 %). Similarly, when it came to systemic iron chelation therapy, 82% were consistent, whereas 6 % stopped taking the drug on a regular basis because of worry of not having enough. The pandemic and lockdown had an impact on the annual follow-up of basic disease comorbidities, with 42% postponing the standard cardiac evaluation, 30% postponing magnetic resonance imaging of the liver-heart, and 23% cancelling major assessments or treatments such as biopsies or in vitro fertilisation (IVF) therapeutic interventions. Finally, 6% of scheduled surgeries had to be rescheduled.

Conclusion: Patients with hemoglobinopathies received their scheduled transfusions without delay during the pandemic. A small percentage of patients modified their home medications because they were concerned about not being adequate during the pandemic. The significant consequence of the pandemic on our patients was the postponement of scheduled assessments and medical procedures required for chronic complications of their underlying condition.

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P131 REAL-TIME VACCINATION IMPACTS IN SICKLE CELL DISEASE: A REAL-WORLD PATIENT CASE STUDY FOR INFLUENZA AND COVID-19 VACCINATION

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Background: Sickle Cell Disease (SCD) comprises a group of red blood cell (RBC) disorders, with a diagnosed global population of ~20 million1. It is a chronic disease characterised by morphological RBC abnormalities in low oxygen due to β-globin mutation, causing vascular obstruction and complications including pain crisis and stroke2. The pandemic has seen patients with SCD face a higher risk of severe forms of COVID-19 infection and mortality3. Despite the approval of

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COVID-19 vaccinations, there is limited understanding of their impact in SCD. Evidence suggests that this has led to poor vaccine uptake due to patients feeling uncertain of their safety, potentially putting patients with SCD at risk, in addition to negatively impacting quality of life.

**Aims:** To improve understanding of the real-world impacts of COVID-19 vaccination on both patient-reported outcomes and automatically recorded biometric datapoints in real-time, specifically in the context of Sickle Cell Disease, in order to support the improvement of patient confidence and vaccine uptake, thereby reducing COVID-19 risk.

**Methods:** An FDA approved, CE marked smartwatch was provided to a 37 year old male with diagnosed HbSC following informed consent. This device was worn day and night over a 15-month period, automatically recording key biometrics including sleep quality, heart rate, and activity levels. This was supplemented by manual patient self-recording of SpO2 levels and ECG traces through the device, as well as self-reported pain scores (0–10, low-high), psychological scores (0–10, low-high), and symptoms entered via a patient-reported outcomes (PRO) portal. Metrics were compared as a 7-day pre-vaccination average, day of vaccination snapshot, and post-vaccination 2-day and 5-day average, in order to track any changes in patient wellbeing across the period following vaccination with reference to their baseline.

**Results:** Live monitoring of day-by-day indicators of patient health showed an initial spike post-COVID-19 vaccination, physiological and psychological wellbeing metrics, as well as real-time biometrics such as sleep quality and activity levels, returned to pre-vaccination levels within 5 days.

While pain scores remained statistically significantly high following influenza vaccination, this had returned to pre-vaccination levels over the 5-days following COVID-19 vaccine (Dose 1). Notably, while no significant difference was seen after 2-days of the second dose, pain scores had dropped significantly lower than even pre-vaccination levels post-Dose 2 in regards to the 5-day average. No significant changes were seen following the combined COVID-19 booster and flu vaccinations.

**Summary – Conclusion:** Our data identifies trends in the temporary impact of COVID-19 vaccination upon both PROs and real-time biometric datapoints. However, PROs highlighted a lesser impact in comparison with more traditional influenza vaccination. Furthermore, these impacts were seen to resolve within 5 days following vaccination, with post-vaccination SpO2, activity levels, sleep quality, and PRO averages returning to pre-vaccination levels following this initial spike. No ECG abnormalities were recorded pre- or post-vaccination. In conclusion, this work indicates a visible but short-term impact of COVID-19 vaccination upon a patient with SCD, suggesting no heightened risk with COVID-19 vaccination in a previously poorly explored disease.

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**P132 REVIEW OF THE INTEGRATED PSYCHOLOGICAL INPUT AT ANNUAL REVIEW CLINICS FOR PEOPLE WITH SICKLE CELL**

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**Background:** At Guy’s and St Thomas’ NHS Foundation Trust, the Haematology Health Psychology Service (HPS) is embedded within the Clinical Haematology Department. As a centre of excellence for the care of people with Sickle Cell, HPS has been forward-thinking in its endeavour to find ways to provide integrated person-centred care since it was founded in 1997. This includes working alongside other healthcare professionals as part of a multi-disciplinary team on ward rounds and specialist clinics. A twice-weekly annual review clinic is held at Guy’s Hospital for people with Sickle Cell in line with national guidelines.

**Aims:** This poster presents the findings from a recent evaluation of the long-standing integrated psychology input at the Sickle Cell annual review clinic. The aim is to explore the outcomes of the annual review clinic for people with sickle cell and consider the benefits and limitations of this holistic model of care.

**Methods:** This evaluation explores whether a need for further support was identified during the annual review appointment and what kind of support was offered. This could include a referral for psychological therapy in the service, a briefer intervention offered during or post the review or being signposted or referred to alternative sources of support. Clinical risk is also examined.

**Results:** The analysis is currently still in progress.

**Summary/Conclusion:** Although the analysis is still ongoing, the benefits of an increased presence of psychology in traditionally medical-only clinics will be discussed and the implications of a ‘catch-all’ approach will be explored; that many patients may have been seen for appropriate psychological support who might otherwise have not known it was available, or may have been reluctant to reach out for support. This will highlight the importance of holistic care when striving for excellence in person-centred Sickle Cell care.

**P133 TEENAGE WELL-BEING -- A VIRTUAL SUPPORT GROUP**

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The pandemic in 2020 and measures to control the COVID-19 virus led to many teenagers and Young People (YP) isolated from their friends, through shielding and extended home schooling. It has affected their mental health and wellbeing, with an increasing demand upon mental health services (BMJ 2021, Millar et al 2020, Jeffery et al 2021). In the Thames Valley we look after approx 200 YP with haemoglobinopathy disorders, a third between the ages of 13 & 18 years. A low prevalence area, a very wide geographical spread, making access to specialist services challenging. Access to technology and virtual connections, and a newly appointed psychologist led us to look at provision of an online wellbeing support group for teenagers.

**Aims:** To invite teenagers between 13–18 years to a weekly ‘drop in’ group, where they would be able to access strategies and resources to support with varying aspects of well-being, as well as the opportunity to ask questions, in a safe supportive environment.

**Method:** The group initially ran on a weekly basis for one hour at the end of the school day, led by 2 specialist nurses and a clinical psychologist. We covered subjects such as: stress, anxiety, low mood, fatigue, as well as more media related content like vaccinations and navigating social media. We used the Zoom platform, but then moved to Microsoft Teams, as this was the Trust’s preferred platform. Our YP and their parents were contacted and asked if they would like to join and then they would be sent an invite via email. A reminder was also sent the day before the next meeting. Parents would be included in any email communication and resources; however, they were not encouraged to join the meeting. Meeting etiquette and ground rules were explained at the beginning of the meeting and with each new attendee, in order to establish trust and
inclusion. Following the meeting, a summary and any material used was circulated to the whole group.

Results: 13 meetings January-November 2021 (initially weekly, however this was changed to monthly over the summer as demand dropped off). Subjects covered include: COVID-19 & dealing with anxiety, stress, Low mood/dealing with sadness, Vaccine safety, fatigue, returning to school, Pain talking to people about your diagnosis. Attendance was variable – with the maximum being 6 young people. A short survey was circulated to try and identify what was working, what needed to change and to have input from the YP on content. As a result of this feedback, we moved to a different day of the week and a later session time.

Summary: small numbers YP would regularly attend, parents commented they looked forward to this group, which we took to be a sign of success. Other attendees, joined sporadically on 1 or more occasions. We found the YP to be engaged. Most were happy to say hello and introduce themselves on camera but would then prefer the camera off. We didn’t have anyone comment on difficulties with access, many used their smartphone devices. Session preparation was time consuming, but as we progressed, we became more efficient at re-using material and needing less ‘team brief’ time as we understood how the sessions ran. It is an expensive service, professional time wise. However, we haven’t compared to using a clinic environment or education room on site, which would take more organising and possibly less availability. There are no transport cost or travel time, so equitable for all.

Conclusion: This has been a valuable service for a small cohort

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P134 THE AREAL PROJECT: A VIRTUAL REALITY APPLICATION TO SUPPORT THE THERAPEUTIC EXPERIENCE AND THERAPY EDUCATION OF ADULT PATIENTS WITH THALASSEMIA AND SICKLE CELL DISEASE

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Background: The chronic transfusion regimen consists of procedures that take time and that significantly impact the quality of life of patients with thalassemia or sickle cell disease; sometimes these procedures are carried out in uncomfortable environments where the patient tries with his own means to get distracted or “estranged”.

Therefore, the need to pay attention not only to the strictly physical needs but also to the psychological, emotional and social needs of patients emerges with the aim of recovering valuable time “monopolized” by therapy through enriching the therapeutic path with activities capable of involving more the person.

Aims: From this need and the opportunities offered by the digital technologies available today, the AREAL project was born, developed by the Italian startup Softcare Studios in partnership with the pharma company Novartis. AREAL consists of a gaming experience enjoyed in virtual reality thanks to the use of suitable VR viewers, designed in collaboration with medical staff to enhance the time spent in the hospital during the transfusion routine of young adult and adult patients.

Methods: AREAL consists of three gaming activities developed to immerse the patient in a sensorially stimulating scenario different from the hospital one in which the user is forced to spend time, and designed to stimulate cognitive skills (memory, reflexes, attention, auditory processing and visual, logic and association, spatial navigation), providing added value to the patient’s engagement/entertainment and compensating for the near physical immobility required during the transfusion / medical procedure (Figure 1). AREAL also integrates elements of patient education in therapy and recommended lifestyle habits to promote their well-being, and is equipped with a social functionality thanks to which patients can play together with other patients in the same hospital or between hospitals. different, laying the foundations for building a delocalized patient community.

Results: AREAL is currently in use in 3 pilot hospital centers in Italy, Padova, Genova, Napoli, where, over a period of 4 months, evidence will be collected on its impact on the therapeutic experience of patients, usability will be assessed and the integration in the staff work routine will be refined. doctor, with the ultimate goal of extending the concept of “care” not only to clinical but also emotional and psychological aspects during all the time spent in the hospital.

Figure 1. Example of different scenarios of the virtual reality

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P135 THE CLINGEN HEMOGLOBINOPATHY VARIANT CURATION EXPERT PANEL

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Background: Accurate and consistent interpretation of sequence variants is integral to the delivery of safe and reliable diagnostic genetic services. To standardize the interpretation process, in 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published a joint guideline based on different lines of evidence for the classification of sequence variants in Mendelian diseases. The generality of this guideline necessitates the application of expert judgment when evaluating and weighing evidence for variant interpretation. The Clinical Genome Resource (ClinGen) assembles Variant Curation Expert Panels (VCEPs) to perform gene- and
In this audit, we examined the records of 64 patients with sickle cell disease (SCD). Minimal research exists in this area, despite being long identified as a compelling issue for patients [1], and highlighted as a “Top 10 Priority” in a workshop during ASCAT 2019. In response, we conducted a series of workshops to explore how race and racism impacts the quality of care in the SCD community and to identify actionable areas of change. This comprised three 90 minute sessions held over Zoom in May, June and July 2021. Attendees included people living with SCD, doctors, nurses, medical students, and members of the local community.

Outcomes broadly centred around the themes of medical education; public education; and ways of better supporting the SCD patient community. However, we were struck by a rich discussion on how the name ‘Sickle Cell Disease’ may, in itself, influence the mindset of caregivers and perpetuate stigma in both clinical and social settings. The term ‘Sickle Cell Anaemia’ traditionally refers to HbSS only, though OMIM uses it to cover all genotypes [2]. Meanwhile the ICD-10 classification code D57 refers to ‘Sickle Cell Disorders’, with sub-categories for sequence variant classification based on evidence criteria that assess variant frequency, variant types and disease causality, protein domains and mutational hotspots implicated in disease, clinical manifestations, segregation, in silico predictions and functional evidence.

Conclusions: For the first time, the Hemoglobinopathy VCEP will provide a standardised classification of the pathogenicity of variants related to hemoglobinopathies. The Hemoglobinopathy VCEP specifications were approved by ClinGen in April 2021 (Step 2 approval), which initiated the process of further validation and adaptation with known globin gene variants in a pilot study (toward Step 3 approval).

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4. From the workshops, the patient group shared a strong consensus view that Sickle Cell Disorder, rather than ‘Disease’, would be preferable as a more neutral term of reference.
5. To verify the results of the workshop in an independent sample, a questionnaire was circulated to a small SCD patient support group (12 individuals) to assess their preference for one or other label. 9/12 (75%) preferred ‘Disorder’, one preferred ‘Disease’ and two expressed no preference. Which label was used by patients themselves, their families and friends, and their medical teams was important to patients, with 67% expressing a wish that this issue be pursued further. Interestingly, the acceptability of Disorder/Disease showed some variation by the patient’s country of birth. These findings point towards a pressing need for increased sensitivity around the language used to talk about illness, particularly where the condition has been historically stigmatised.

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Sickle cell disease (SCD) is a common genetic condition defined by abnormalities in hemoglobin, an oxygen carrying protein in red blood cells. About 5% of the world’s population carries genes for hemoglobin disorders, with the highest prevalence in countries in Subsaharan Africa (SSA). SCD causes significant morbidity, mortality, and economic burden in the countries and populations affected. Various countries have established national guidelines for SCD management, which serve to standardize care and improve patient outcomes. Ten such guidelines were identified for compilation and analysis in this paper as of summer 2021. Qualitative analysis of the guidelines has identified the priorities of each government and medical institutions’ stance on best practices across high-, middle-, and low-income countries. The analysis identified that care for acute complications of SCD is more frequently endorsed in the guidelines of low-and-middle income countries (LMIC), which also have higher disease burden, over high-income countries (HIC). Chronic preventative care for SCD disease, which is shown to be an evidence-based effective approach to improve patient outcomes, is more frequently recommended in guidelines of HIC over LMIC. Furthermore, national newborn screening guidelines are scarce in the countries with high prevalence rates and adolescent mortality. While most countries recommend screening programs, LMIC have limited recommendations for newborn preventative measures. Incorporation and prioritization of preventive care guidelines in LMIC may serve as a path to inform sustainable nationwide interventions to improve patient outcomes for SCD. Implementation of these guidelines would contribute to preventing acute complications and improving morbidity and mortality for individuals with SCD. In addition, prioritization and inclusion of preventive and chronic care measures in healthcare services may mitigate the economic burden of SCD in LMIC.

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