Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Results From Phase 1 Studies of GBT021601: A Next-Generation HbS Polymerization Inhibitor for Treatment of Sickle Cell Disease

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Disclosures

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- Associate Professor of Pediatrics, Emory School of Medicine
- Consultancy: Global Blood Therapeutics, Imara, Novartis, Novo Nordisk
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- Nothing to disclose

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Introduction

SCD is an inherited, lifelong disorder characterized by HbS polymerization.[1]

Voxelotor is a first-in-class HbS polymerization inhibitor that improves anemia and reduces hemolysis. Voxelotor is approved by the US Food and Drug Administration for the treatment of SCD in adult and pediatric patients aged ≥4 years and by the European Medicines Agency and the Ministry of Health and Prevention in the United Arab Emirates for patients aged ≥12 years.[2-4]

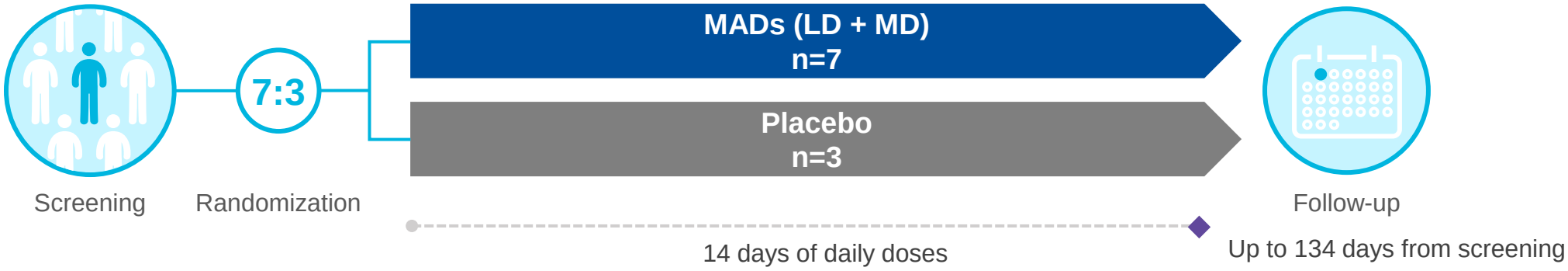
GBT021601 is a next-generation HbS polymerization inhibitor with improved PK properties. GBT021601 has the potential to achieve higher Hb occupancies at lower doses than voxelotor, potentially reducing treatment burden and improving clinical outcomes for patients with SCD.[5]

Here we explore the safety, tolerability, PK, and pharmacodynamics of GBT021601 in healthy volunteers and patients with SCD.[6]

HbS, sickle hemoglobin; PK, pharmacokinetics; SCD, sickle cell disease.

1. Kato GJ, et al. *Nat Rev Dis Primers*. 2018;4:18010. 2. Estepp JH. *Am J Hematol*. 2018;93:326-329. 3. Oxbryta. Prescribing information. Global Blood Therapeutics; December 2021. 4. Global Blood Therapeutics. Accessed February 17, 2022. https://ir.gbt.com/news-releases/news-release-details/european-commission-approves-oxbrytar-voxelotor-treatment. 5. Dufu K, et al. Poster presented at: 25th European Hematology Association Congress; June 9-17, 2021; virtual. Poster EP1198. 6. ClinicalTrials.gov identifier: NCT05036512. Accessed April 21, 2022. https://clinicaltrials.gov/ct2/show/NCT05036512.

Study Design for GBT021601-011 MAD in Healthy Volunteers[1,2]



Patient population

- Healthy volunteers aged 18-55 years
- Body mass index ≥18.0 to ≤30.0 kg/m^2
- Body weight ≥50 kg at screening and day –1

Cohort 3 and Cohort 4[1]

- LD administered on days 1-3
- MDs at days 4-14 for CH 3 and CH 4 were 50 mg and 75 mg, respectively

Endpoints[a]

- Safety and tolerability
- Pharmacokinetics

[a]GBT021601 was assayed in blood and plasma by liquid chromatography with tandem mass spectrometry methodology. The lower limit of quantitation was 0.1 ng/mL for plasma and 20 ng/mL for blood.
CH 3, cohort 3; CH 4, cohort 4; LD, loading dose; MAD, multiple ascending dose; MD, maintenance dose.

1. Data on file. Global Blood Therapeutics, Inc. South San Francisco, CA. 2. ClinicalTrials.gov identifier: NCT05036512. Accessed May 2, 2022. http://clinicaltrials.gov/ct2/show/NCT05036512.

Healthy Volunteers MAD Cohorts 3 & 4: Demographics and Safety

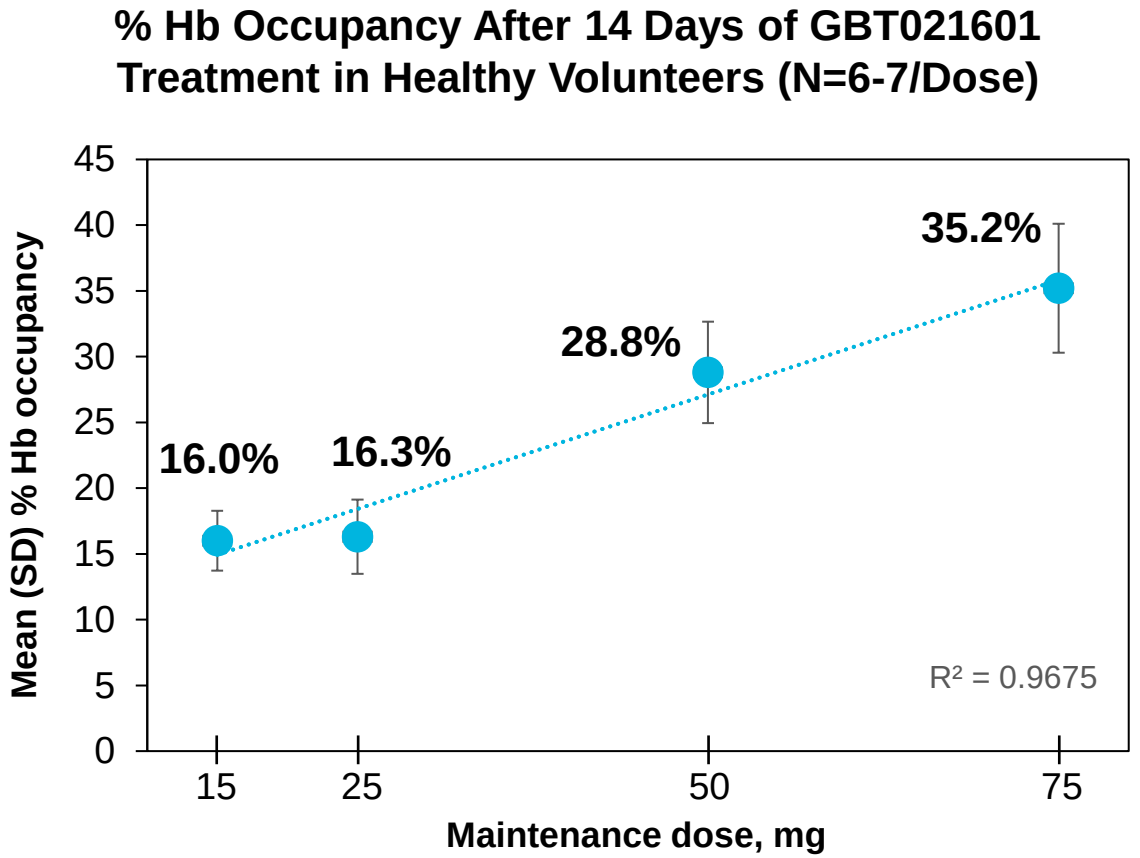
Demographics	50 mg maintenance (n=10)	75 mg maintenance (n=10)
Mean age, years (SD)	36.1 (9.4)	38.6 (10.5)
Male, n (%)	7 (70)	9 (90)
Race, n (%)		
White	8 (80)	3 (30)
Black or African American	2 (20)	7 (70)

Overview of TEAEs[a]	50 mg maintenance (n=10)	75 mg maintenance (n=10)
Number of TEAEs	16	2
Number of participants with ≥1 TEAE, n (%)	7 (70)	2 (20)
Number of TEAEs grade ≥3	1	0
Number of drug-related TEAEs	2	0
Number of participants with at least 1 drug-related TEAE, n (%)	1 (10)	0
Number of TEAEs leading to study drug discontinuation	0	0
Number of SAEs	0	0

[a]As the study is currently ongoing, data presented are still blinded.
MAD, multiple ascending dose; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.
Data on file. Global Blood Therapeutics, South San Francisco, CA.

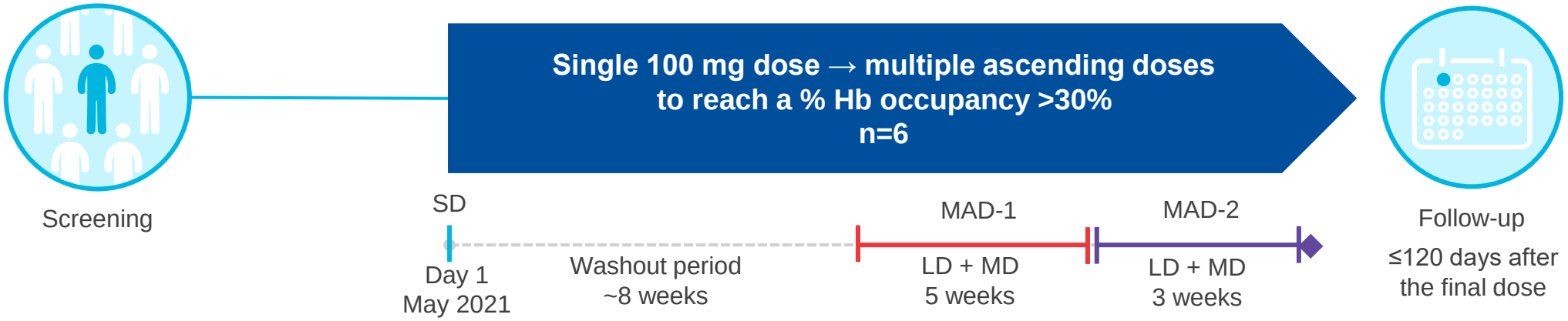
GBT021601 PK Parameters and Demonstration of Dose Proportionality With Increasing Doses in Healthy Volunteers

- GBT021601 demonstrated linear, dose-proportional PK among cohorts with multiple ascending doses in healthy volunteers



Hb, hemoglobin; PK, pharmacokinetics; SD, standard deviation.
Data on file. Global Blood Therapeutics, South San Francisco, CA.

Study GBT021601-012: Phase 1 Study in Patients With SCD



Patient population

- Patients with HbSS or HbSβ^0, aged 18-60 years
- Baseline Hb ≥5.5 g/dL and ≤10.5 g/dL
- No recent VOCs[a] or transfusions[b]
- Background HU allowed if dose has been stable for ≥90 days[c]

Dosing

- SD: 100 mg
- MAD-1: LD and 50 mg daily maintenance
- MAD-2: LD and 100 mg daily maintenance

Endpoints

- Safety and tolerability (primary)
- PK
- Relationship between time-matched GBT021601 concentrations and the changes in clinical measures of anemia and hemolysis from baseline

[a]No hospitalizations for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF or within 28 days before day 1 of study treatment.
[b]No transfusions within 60 days of signing the ICF or at any time during the screening period. [c]The HU dose must be stable for at least 90 days before signing the ICF and with no anticipated need for dose adjustments during the study in the opinion of the investigator. Hb, hemoglobin; HbSβ^0, double heterozygote for HbS and β^0 thalassemia; HbSS, homozygous for SCD; HU, hydroxyurea; ICF, informed consent form; LD, loading dose; MAD, multiple ascending dose; MD, maintenance dose; PK, pharmacokinetics; SAD, single ascending dose; SCD, sickle cell disease; SD, single dose; VOC, vaso-occlusive crisis
ClinicalTrials.gov identifier: NCT04983264. Accessed May 2, 2022. http://clinicaltrials.gov/ct2/show/NCT04983264.

SCD Cohort: Demographics and Baseline[a] Characteristics

Parameter	SCD (N=6)
Mean age, years (minimum, maximum)	20.2 (18.0, 23.0)
Male, n (%)	4 (66.7)
Race, n (%)	
Black or African American	5 (83.3)
Hispanic or Latinx	1 (16.7)
HbSS genotype, n (%)	6 (100)
Hb level, g/dL, mean (SD), range	8.2 (0.4), 7.6-8.7
Current hydroxyurea use, n (%)	6 (100)
Number of VOCs within 12 months of screening, n (%)	
0	2 (33.3)
1	1 (16.7)
2	3 (50.0)
Number of transfusions within 12 months of screening, n (%)	
0	4 (66.7)
1	2 (33.3)

[a]Baseline is defined as ay 56 visit.
HbSS, homozygous for SCD; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
Data on file. Global Blood Therapeutics, South San Francisco, CA.

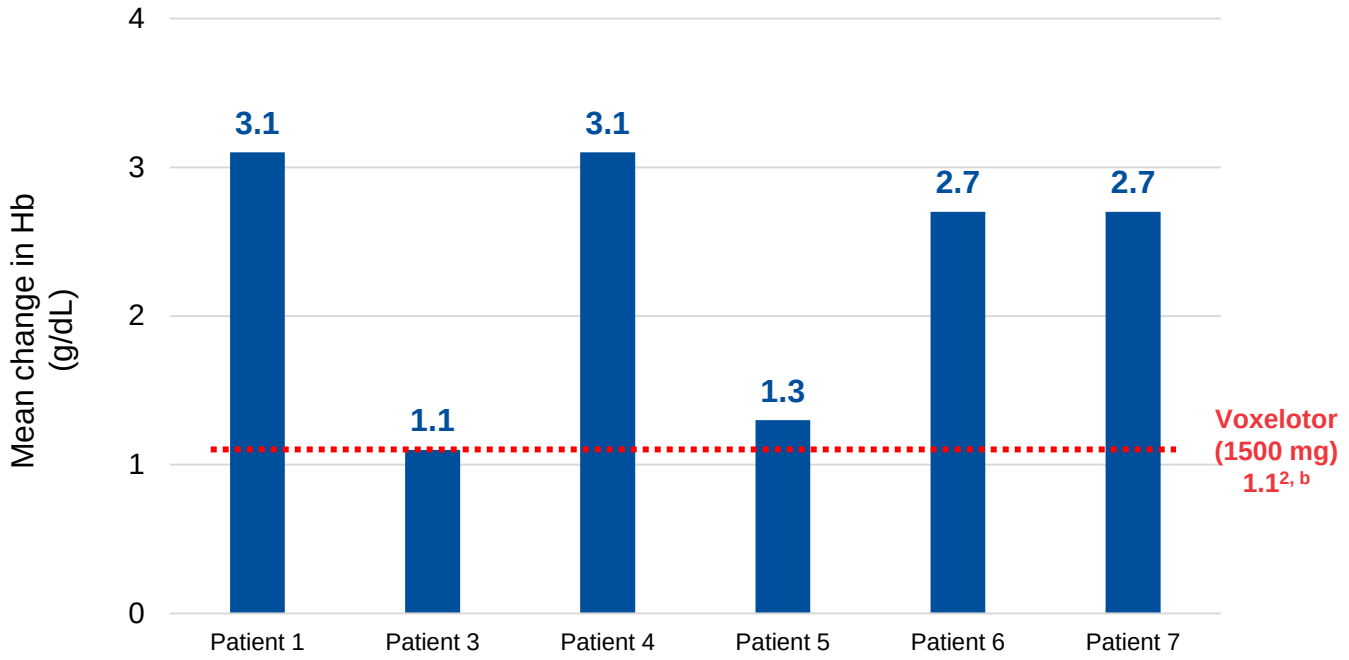
Preliminary Analysis of Single-Dose PK of GBT021601 in Whole Blood

Parameter,[a] mean	HV 100 mg[d]	SCD 100 mg[e]
$t_{1/2}$, days (CV%)	29.8 (0.9)	9.8 (0.6)
C_{max}, µg/mL (CV%)	17.4 (12.1)	16.7 (23.3)
t_{max},[b] h (range)	24 (8-48)	8 (6-36)
$AUC_{0-\infty}$, µg·h/mL (CV%)	16200 (19.7)	5070 (27.4)
B:P ratio[c]	214.4	69.3
% Hb occupancy (CV%)	1.9 (13.3)	3.3 (26.1)

[a]Calculations based on nominal (anticipated) collection times, not actual. [b]t_{max} reported as median. [c]B:P = mean $AUC_{0-\infty}$-blood:mean $AUC_{0-\infty}$-plasma. [d]PK analysis at day 98. [e]PK analysis at day 42.
$AUC_{0-\infty}$, area under the curve from time 0 hours to infinity; C_{max}, maximal observed concentration; CV, coefficient of variation; Hb, hemoglobin; HV, healthy volunteer, PK, pharmacokinetics; SCD, sickle cell disease; $t_{1/2}$, elimination half-life; t_{max}, time of maximal observed concentration.
Data on file, Global Blood Therapeutics, South San Francisco, CA.

Mean Hb Increase of 2.3 g/dL With 100 mg Dose[1]

Change in Hb (g/dL) From Baseline to End of Treatment[a]



	Patient 1	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Baseline	8.3	8.7	8.4	8.3	7.6	7.8
End of treatment	11.4	9.8	11.5	9.6	10.3	10.5

Hb change was measured at the end of treatment, which included 3 weeks at a daily dose of 100 mg (MAD-2).

All patients had a change in Hb of >1.0 g/dL.

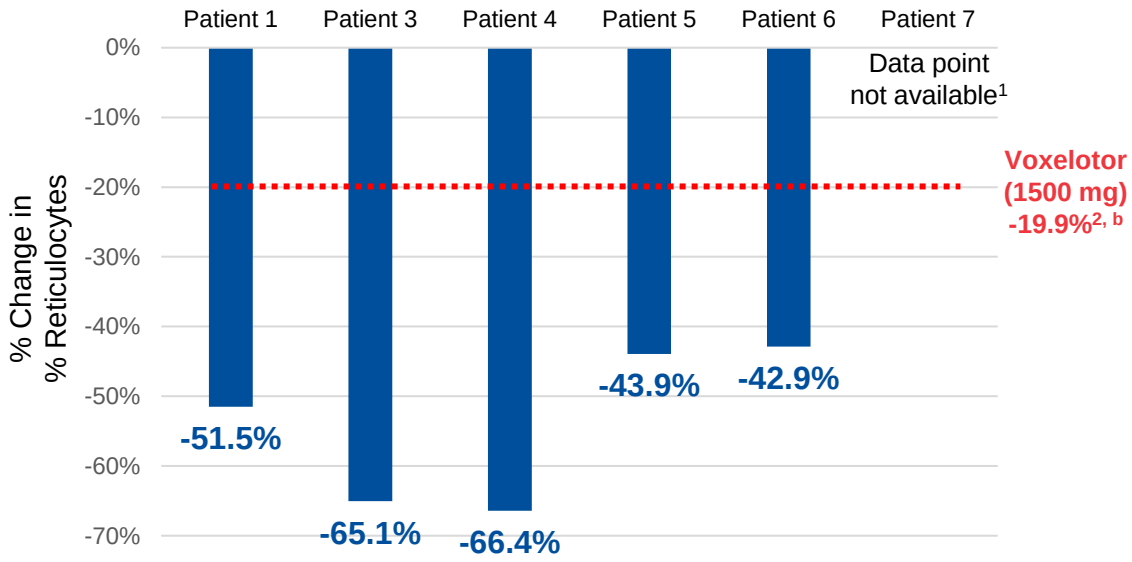
Four out of six patients had a change in Hb of ≥2.7 g/dL.

[a]Baseline was at day 56, after washout period, and at the start of the MAD period. End of treatment was measured at day 112 after 8-week MAD period.
[b]Least-squares mean change in Hb (g/dL) was assessed in 88 patients with SCD.
Hb, hemoglobin; MAD, multiple ascending dose.

1. Data on file. Global Blood Therapeutics, South San Francisco, CA. 2. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Improved Markers of Hemolysis From Baseline to End of Treatment[1,a]

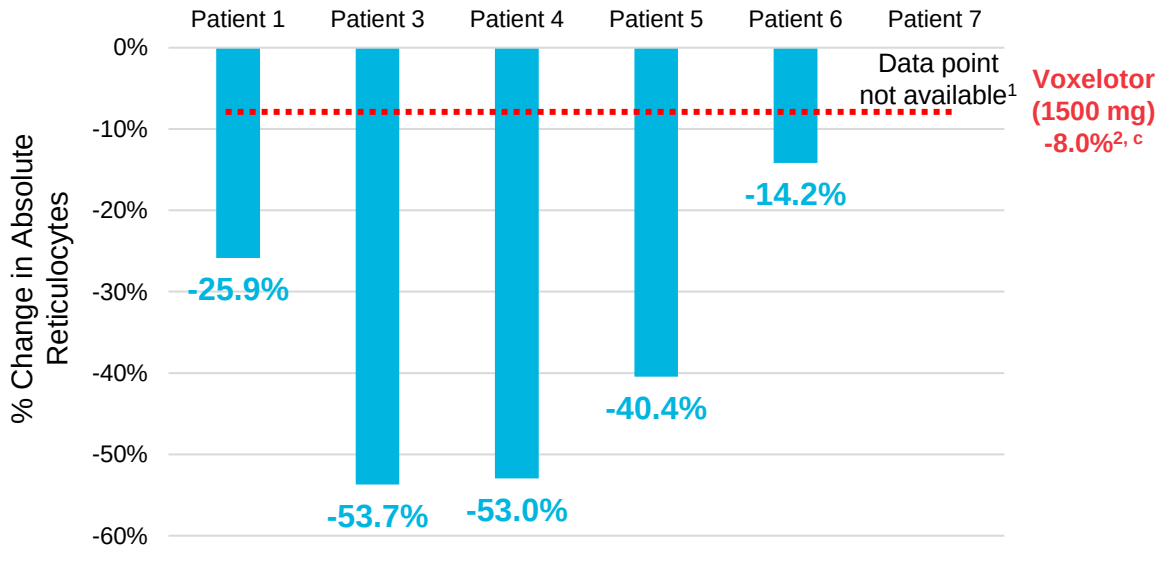
% Change in % Reticulocytes



Baseline	3.3%	8.3%	13.1%	6.6%	7.7%	N/A
End of treatment	1.6%	2.9%	4.4%	3.7%	4.4%	12.5%

Normal range of reticulocyte percentage is 0.8% to 2.2%.

% Change in Absolute Reticulocytes



Baseline ($\times 10^6$/µL)	61.5	237.4	297.4	164.2	175.1	N/A
End of treatment	45.6	109.9	139.9	97.8	150.3	385.8

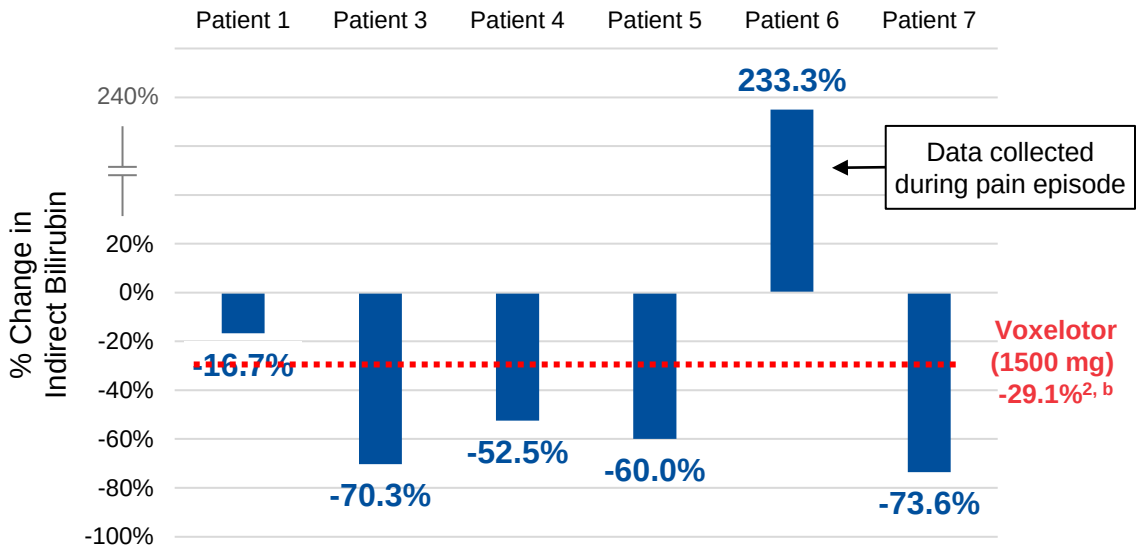
Normal range of absolute reticulocytes is 46×10^6/µL to 102×10^6/µL.

There were no clinically significant trends in the EPO levels of the GBT021601-012 patients.

[a]Baseline was at day 56, after washout period, and at the start of the MAD period. End of treatment was measured at day 112 after the 8-week MAD period. [b]Least-squares mean change in percentage of reticulocytes was assessed in 88 patients with SCD. [c]Least-squares mean percentage change in absolute reticulocytes was assessed in 88 patients with SCD.
EPO, erythropoietin; Hb, hemoglobin; MAD, multiple ascending dose; SCD, sickle cell disease.
1. Data on file. Global Blood Therapeutics, South San Francisco, CA. 2. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Improved Markers of Hemolysis From Baseline to End of Treatment[1,a] *(continued)*

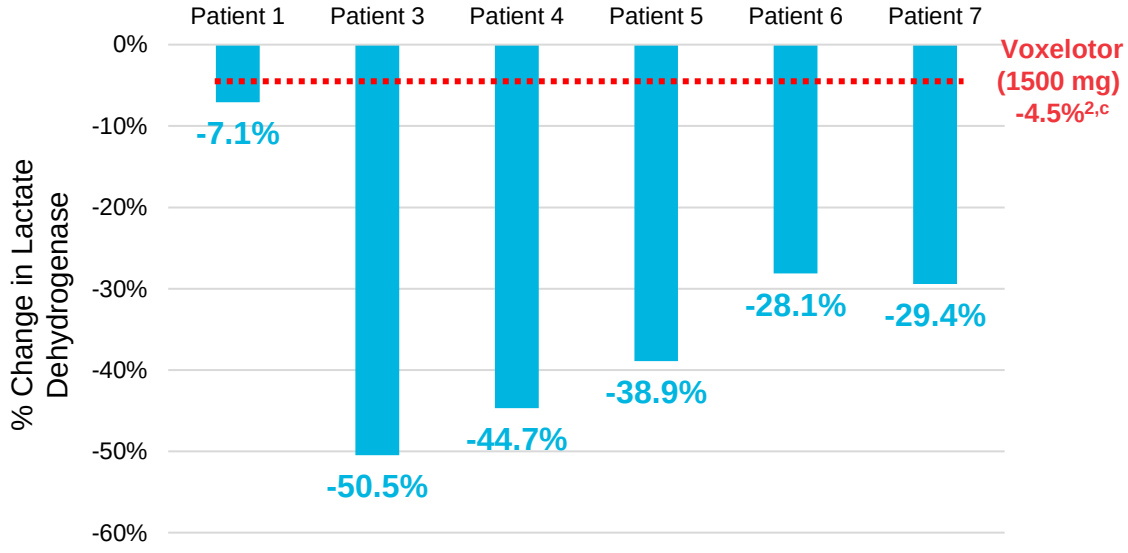
% Change in Indirect Bilirubin



Baseline, mg/dL	0.6	3.7	4.0	1.0	0.6	5.3
End of treatment	0.5	1.1	1.9	0.4	2	1.4

Normal range of indirect bilirubin is 0.1 to 1.2 mg/dL.

% Change in Lactate Dehydrogenase

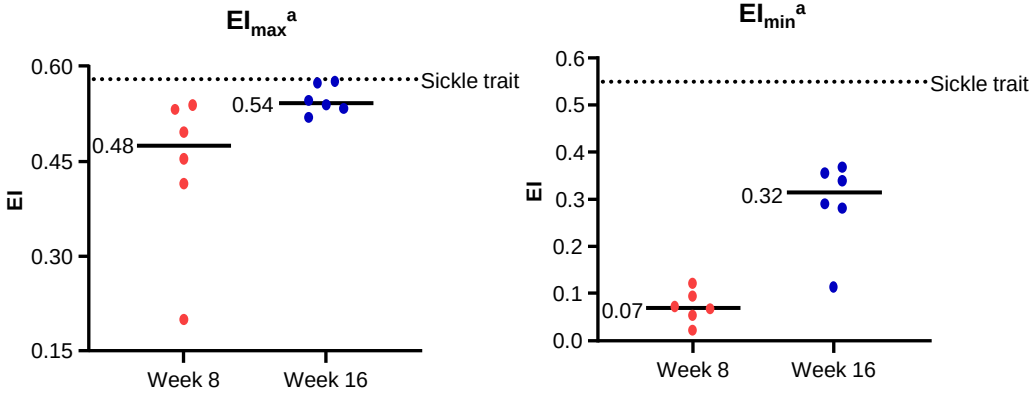


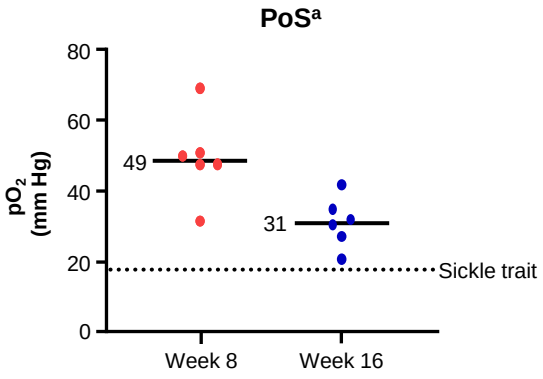
Baseline, U/L	212	555	546	329	359	843
End of treatment	197	275	302	201	258	595

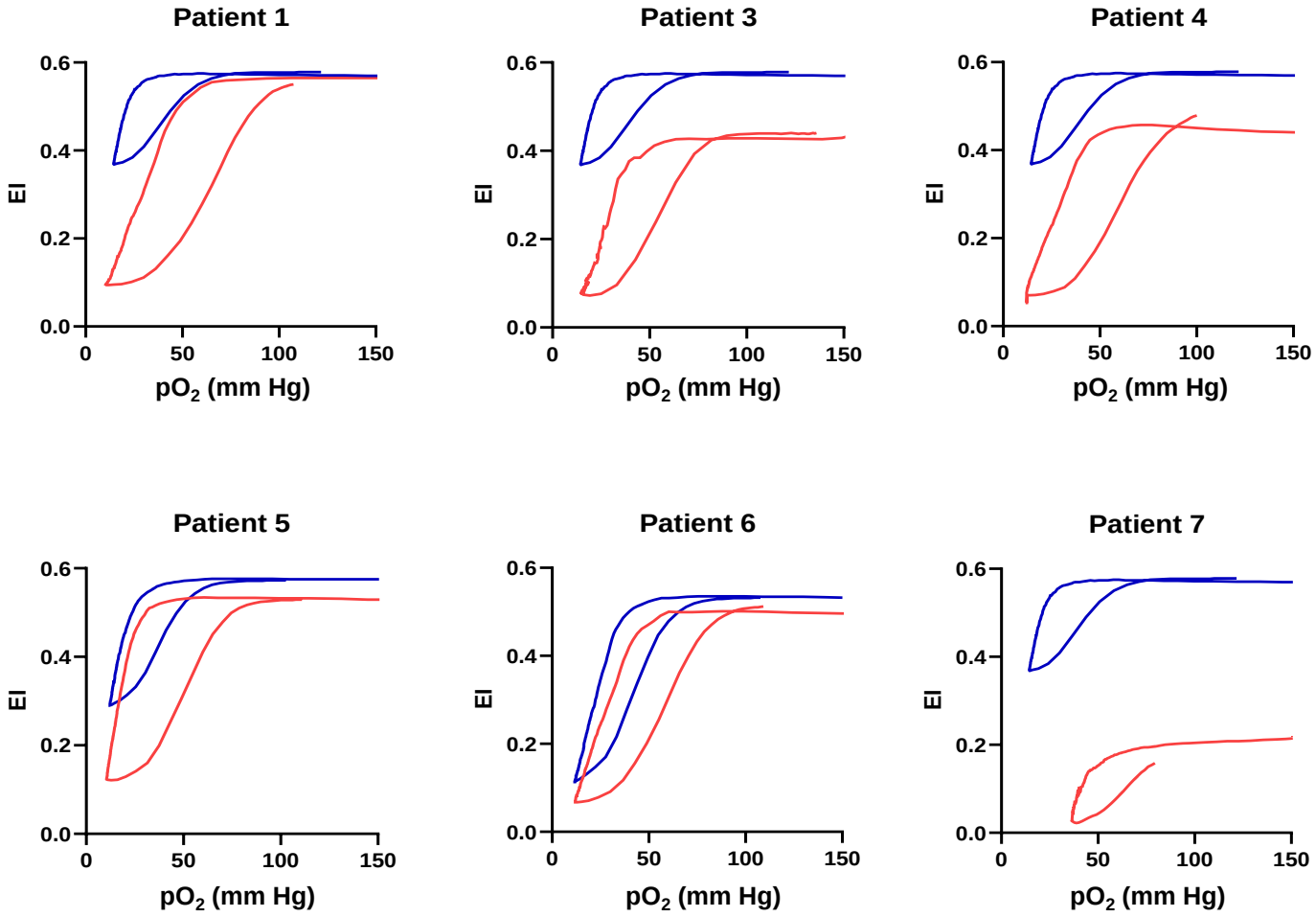
Normal range of lactate dehydrogenase is 84 to 246 U/L.

[a]Baseline was at day 56, after washout period, and at the start of the MAD period. End of treatment was measured at day 112 after the 8-week MAD period. [b]Least-squares mean percentage change in indirect bilirubin level was assessed in 85 patients with SCD. [c]Least-squares mean percentage change in lactate dehydrogenase level was assessed in 88 patients with SCD.
Hb, hemoglobin; MAD, multiple ascending dose; SCD, sickle cell disease.
1. Data on file. Global Blood Therapeutics, South San Francisco, CA. 2. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Improvement in PoS and RBC Deformability With GBT021601 in Patients With SCD



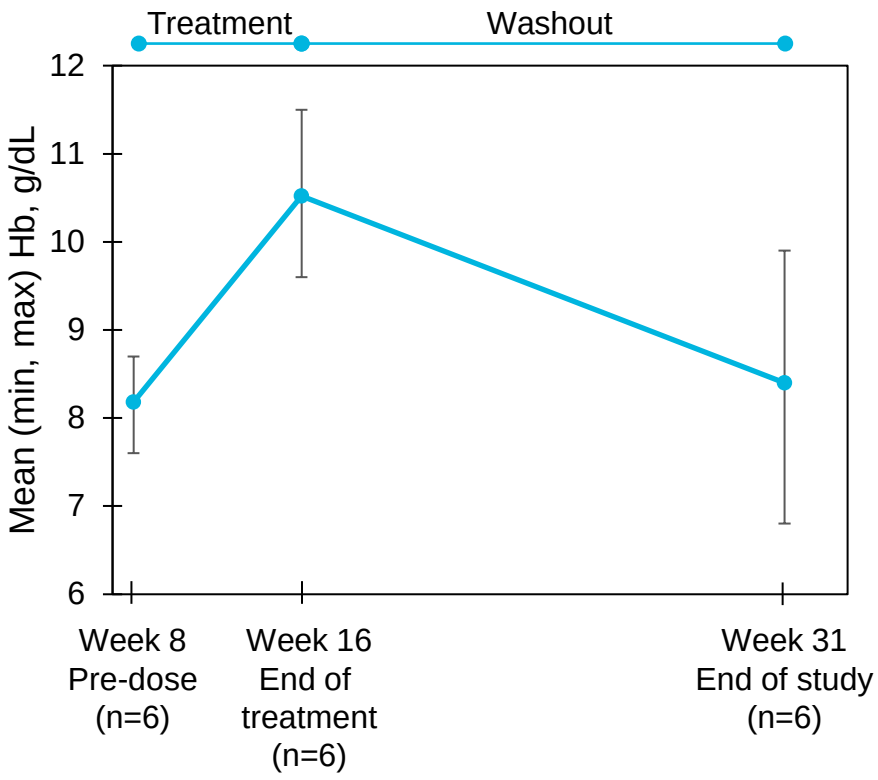




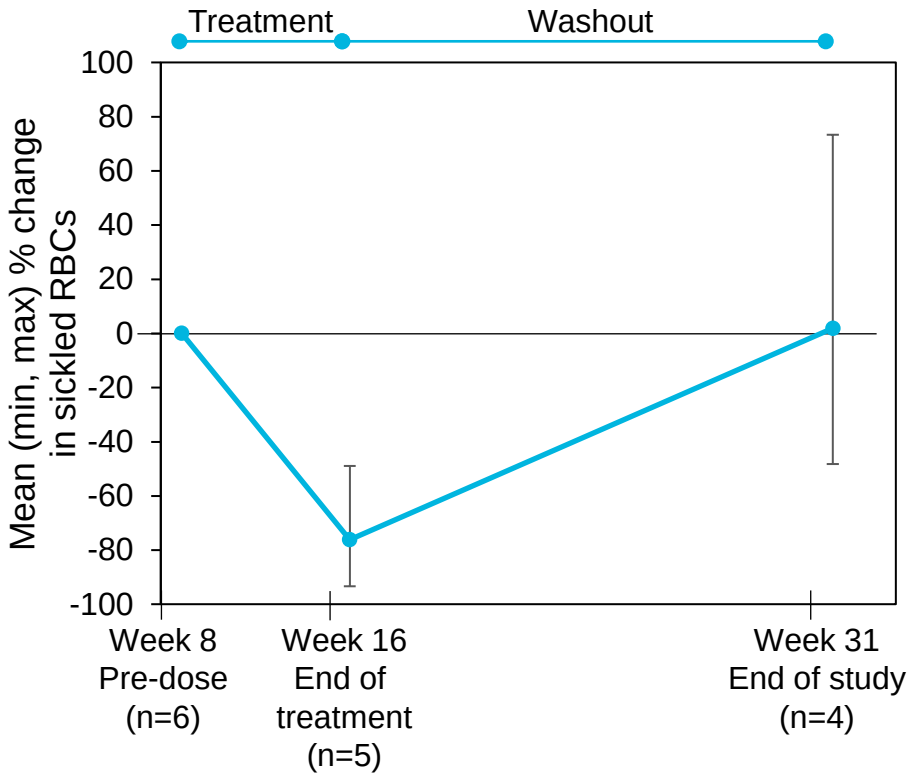
[a]Individual and median values are shown.
EI, elongation index; EI_{max}, maximum elongation index; EI_{min}, minimum elongation index; PoS, point of sickling; pO_2, partial pressure of oxygen; RBC, red blood cell; SCD, sickle cell disease.
Data on file. Global Blood Therapeutics. South San Francisco, CA.

Summary of Change in Sickled RBCs for All Patients per Timepoint

Mean Hb at Different Time Points

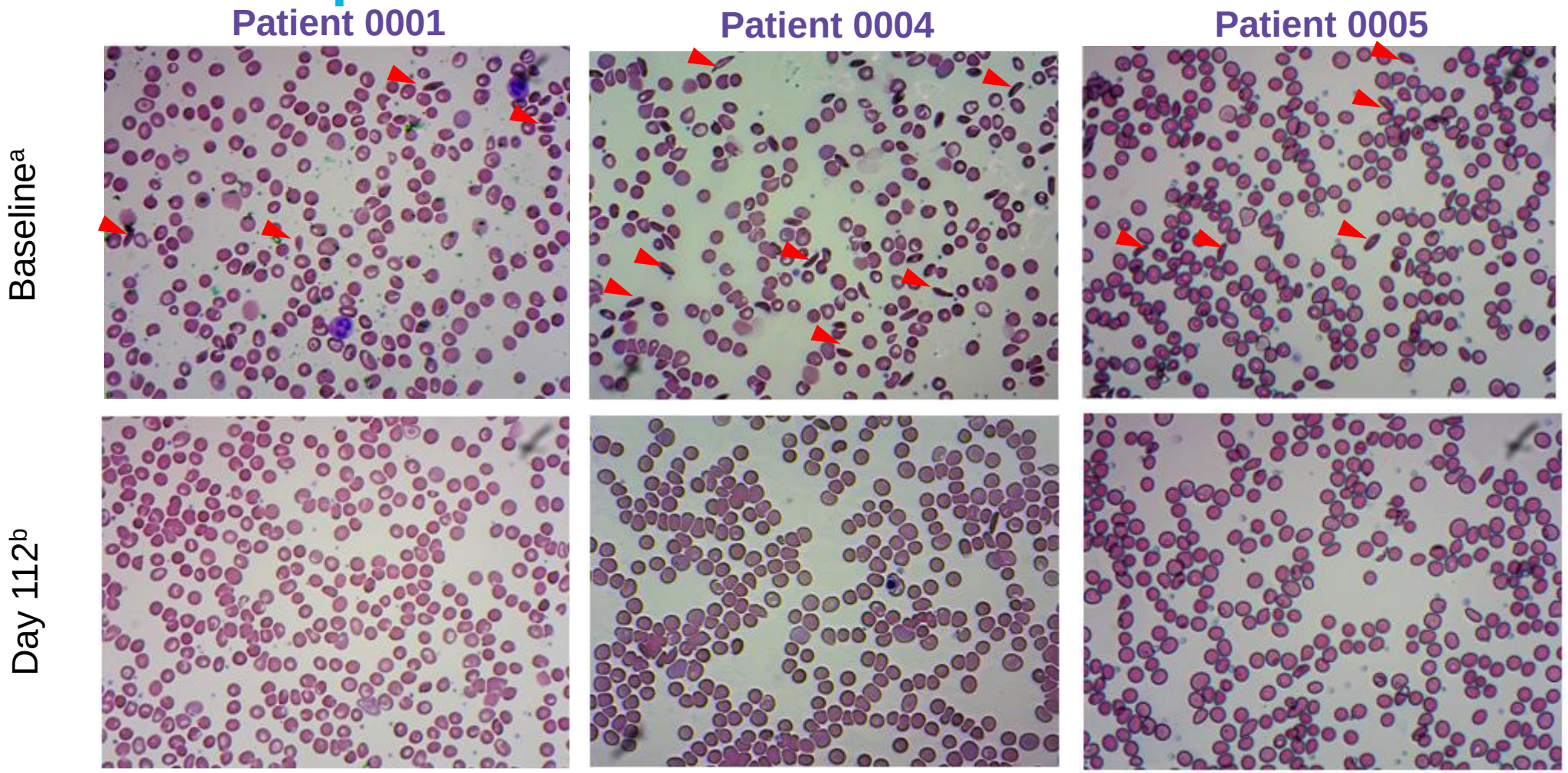


Mean % Change in Sickled RBCs



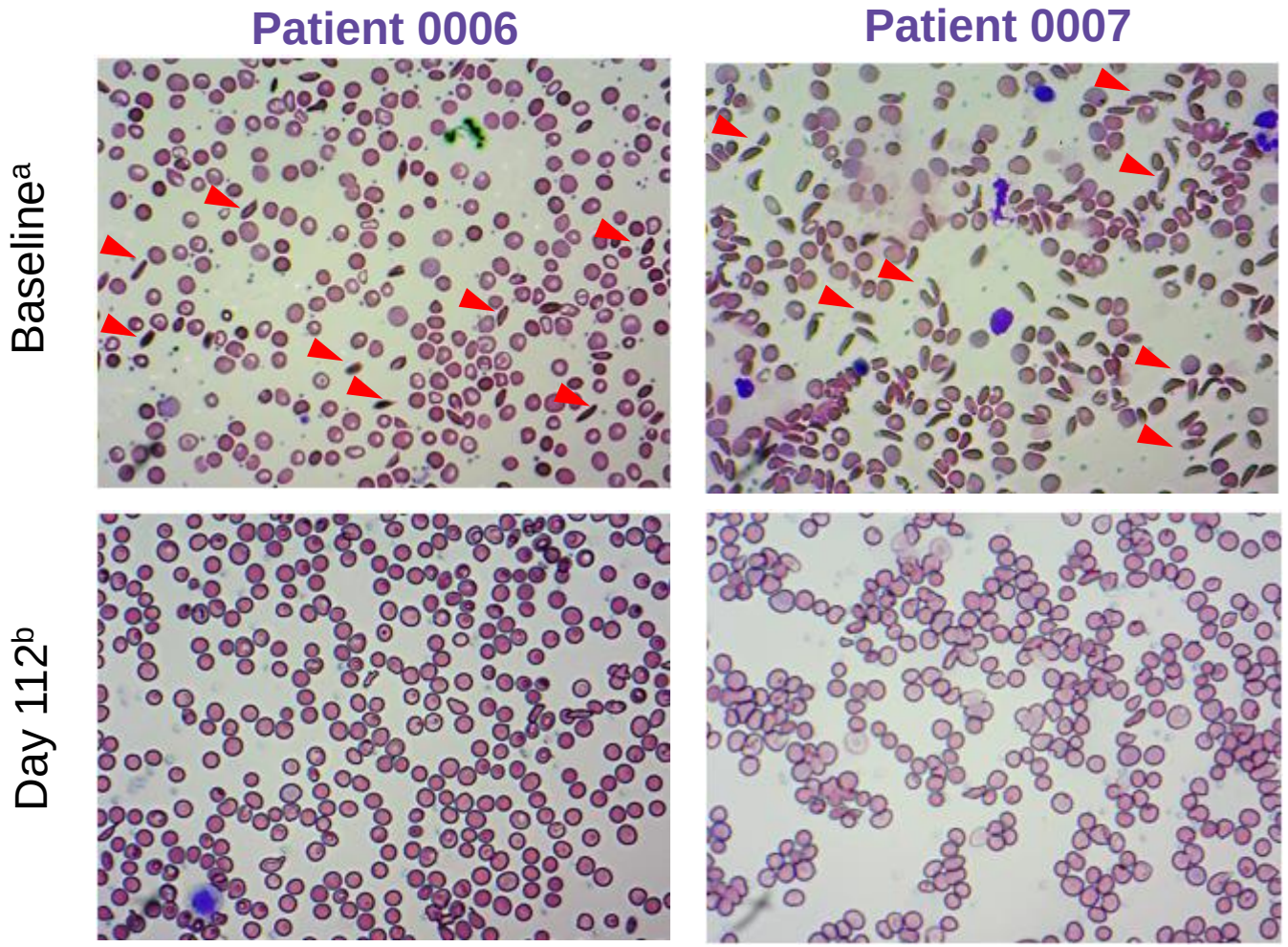
Baseline was at day 56 (week 8). Patients were not on treatment during the washout period (weeks 16-31).
Hb, hemoglobin; RBC, red blood cell.
Data on file. Global Blood Therapeutics. South San Francisco, CA.

Representative Images From Peripheral Blood Smears Before and After Multiple Doses of GBT021601 in Patients With SCD



Red arrowheads point to examples of sickled RBCs.
[a]Baseline was at day 56, after washout period and at start of MAD. [b]End of 8-week MAD treatment period.
MAD, multiple ascending dose; RBC, red blood cell; SCD, sickle cell disease.
Data on file. Global Blood Therapeutics. South San Francisco, CA.

Representative Images From Peripheral Blood Smears Before and After Multiple Doses of GBT021601 in Patients With SCD



Red arrowheads point to examples of sickled RBCs.
[a]Baseline was at day 56, after washout period and at start of MAD. [b]End of 8-week MAD treatment period.
MAD, multiple ascending dose; RBC, red blood cell; SCD, sickle cell disease.
Data on file. Global Blood Therapeutics. South San Francisco, CA.

Summary of Safety

Overview of TEAEs[a,b]	SCD (N=6)
Number of TEAEs	29
Number of participants with at least 1 TEAE, n (%)	6 (100)
Number of TEAEs grade ≥3	7
Number of drug-related TEAEs	3
Number of participants with at least 1 drug-related TEAE, n (%)	2 (33.3)
Number of TEAEs leading to study drug discontinuation	0
Number of SAEs	3

- SAEs: 3 grade 3 sickle cell pain crises (VOC, unrelated) requiring hospitalization

[a]As the study is currently ongoing, data cutoff is as of April 27, 2022. Data include the washout period. [b]Events were coded using MedDRA version 24.0; NCI-CTCAE version 4.03 was used to determine grade.
CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SAE, serious adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crisis.
Data on file. Global Blood Therapeutics. South San Francisco, CA.

Conclusions

Multiple daily doses of GBT021601 were well tolerated in healthy volunteers and patients with SCD.

In patients with SCD, the GBT021601 maintenance dose of 100 mg led to a mean Hb occupancy >30%, increased Hb, reduced markers of hemolysis, and improved RBC health.

Improved RBC health was reflected by ektacytometry results and peripheral blood smears.

Upon cessation of GBT021601, the elimination of the drug was slow (an advantage of the long half-life) with reversal of the improved hematologic parameters, with no observed rebound effect.

The intrapatient phase 1 design, which included a single dose followed by multiple doses of GBT021601, was achievable in patients with SCD.

Hb, hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

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- This study was supported by Global Blood Therapeutics.